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Headache and Comorbidities in Childhood and Adolescence

Springer

Headache

Series Editor

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The purpose of this Series, endorsed by the European Headache Federation (EHF), is to describe in detail all aspects of headache disorders that are of importance in primary care and the hospital setting, including pathophysiology, diagnosis, management, comorbidities, and issues in particular patient groups. A key feature of the Series is its multidisciplinary approach, and it will have wide appeal to internists, rheumatologists, neurologists, pain doctors, general practitioners, primary care givers, and pediatricians. Readers will find that the Series assists not only in understanding, recognizing, and treating the primary headache disorders, but also in identifying the potentially dangerous underlying causes of secondary headache disorders and avoiding mismanagement and overuse of medications for acute headache, which are major risk factors for disease aggravation. Each volume is designed to meet the needs of both more experienced professionals and medical students, residents, and trainees.

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Vincenzo Guidetti • Marco A. Arruda
Aynur Ozge
Editors

Headache and Comorbidities in Childhood and Adolescence

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Editors
Vincenzo Guidetti
Child and Adolescent Neuropsychiatry
Sapienza University
Rome
Italy

Marco A. Arruda
University of São Paulo
Neuropsychiatry, Glia Institute
Ribeirão Preto
Brazil

Aynur Ozge
Neurology, Algology and Clinical
Neurophysiology
Mersin University School of Medicine
Mersin, Adana
Turkey

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Foreword

Headache in the child and the adolescent has not received adequate scientific attention throughout the years. The prevailing tendency has been to frame this pathology as the direct consequence of personal or familiar psychological suffering. The inadequate availability of pharmacological tools assessed for primary headaches in the developmental age has eased this approach. Moreover, every decade the biological vision of primary headache changes its mechanism of action highlighting how a clear marker of illness, detectable and reliable on large populations, is still missing. Therefore, new drugs face the hard task of finding a direct application on adolescents, both for strictly regulatory reasons and for preferential rules of clinical activity in these patients.

This fifth product of the European Headache Federation Headache Book Series rigorously faces these problems and highlights the clinical and mechanistic features conjugating all the aspects related to headache in the childhood, even the ones shared with other pathologies. The common denominator, 'comorbidity', offers a comprehensive interpretation of this headache area and the renowned authors of these contributions guarantee a high, independent and trustworthy profile.

I am honoured to introduce this valuable volume edited by Vincenzo Guidetti, Marco A. Arruda and Aynur Ozge, and acknowledge the umpteenth support by the European Headache Federation to the systematization and the dissemination of the headache culture.

Rome, Italy — Paolo Martelletti

Preface

"The cure for the headache was a kind of a leaf, which required to be accompanied by a charm, and if a person would repeat the charm at the same time that he used the cure, he would be made whole; but that without the charm the leaf would be of no avail."

Socrates, according to Plato [1]

The expressive development of childhood headache knowledge can be easily visualized through a mere PubMed search. Using the keywords headache, child and adolescent, and solely the age filter, the reader can check the volume growth of publications year by year, decade by decade. The same advance can be observed by limiting the search to only clinical trials. From the first paper on childhood headache registered in this digital archive in 1948 to the early 1990s, we have a total of 1121 papers, number that doubles throughout the "Decade of the Brain" reaching 1253 at the beginning of 2010, up to now 1748. The same occurs with migraine as shown in the following PubMed publications' timeline.

PubMed Headache and Migraine in Children
Publications Timeline

	1º	1990	2000	2010	2016
Headache	1.960	1.121	1.253	2.257	1.748
Migraine	1.963	579	511	925	659

A milestone in this trajectory is the pioneering and seminal work of Professor Bo Bille of Uppsala University in Sweden who in 1962 published his thesis *Migraine in Schoolchildren* [2].

The evolution of knowledge occurred in several areas, however, in an expressive way in the classification, diagnosis, and epidemiology of childhood headache. Particularly noteworthy are the emergence of prevalence studies around the world, studies on the impact of headache in children and adolescents, and the identification of comorbidities of migraine in this age group.

The impact of this breakthrough was notable in clinical practice. From the 196 possible headache diagnoses that appear in the second edition of the International Classification of Headache Disorders (ICHD-II) [3], 113 have been described in pediatric population [4]. The studies have provided evidence that not only migraine but also other primary and even secondary headaches have a peculiar clinical presentation in childhood and adolescence.

The study of migraine comorbidities in childhood and adolescence, the reason for this book, is extremely important in clinical practice, both for diagnostic issues and for the management and treatment efficacy of these patients [5, 6].

It is critical to recognize the presence of comorbid conditions in the clinical assessment of headache patients, especially in children and adolescents, as early identification of these symptoms may lead to improved headache management [7, 8]. Moreover, the identification of comorbid disorders in headache could provide modern treatment options and improve the knowledge about causes and consequences of headache [9].

A striking and distinctive aspect of this book is the editorial norm of the authorship of chapters being entrusted to authors from different countries, often different continents, which resulted in a cooperative work that contemplates different medical realities. This experience is certainly reflected in these pages that we hope to please the reader.

Ribeirão Preto, Brazil — Marco A. Arruda
Mersin, Turkey — Aynur Ozge
Rome, Italy — Vincenzo Guidetti

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Contents

Contributors

Ishaq Abu-Arafeh, M.D., F.R.C.P.C.H Paediatric Neurosciences Unit, Royal Hospital for Children, Glasgow, UK

Marco Angriman Department of Pediatrics, Child Neurology and Neurorehabilitation Unit, Central Hospital of Bolzano, Bolzano, Italy

Marco A. Arruda, M.D., Ph.D. Child and Adolescent Neurologist, Glia Institute, Ribeirao Preto, São Paulo, Brazil

Umberto Balottin Child Neuropsychiatry Unit, C. Mondino National Neurological Institute, Pavia, Italy

Child Neuropsychiatry Unit, Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

Pier Antonio Battistella, M.D. Department of Woman's and Child's Health, Child and Adolescent Headache Center, University of Padova, Padova, Italy

Marcelo Eduardo Bigal, M.D., Ph.D. Neurologist, Teva Pharmaceuticals Research and Development, Frazer, PA, USA

Oliviero Bruni Department of Developmental and Social Psychology, Sapienza University, Rome, Italy

Roberto Canitano, M.D. Division of Child and Adolescent Neuropsychiatry, University Hospital of Siena, Siena, Italy

Michelle M. Ernst, Ph.D. Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Noemi Faedda, Ph.D. Department of Paediatrics and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, Rome, Italy

Viktor Farkas Semmelweiss University, Budapest, Hungary

César Fernández-de-las-Peñas, P.T., M.Sc., Ph.D., Dr. Scient Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain

Cátedra de Investigación y Docencia en Fisioterapia: Terapia Manual y Punción Seca, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain

Raffaele Ferri Oasi Research Insitute IRCCS, Troina, Italy

Amy A. Gelfand Pediatric Headache, Department of Neurology, University of California San Francisco, San Francisco, CA, USA

Jacob Genizi Bruce and Ruth Rappaport Faculty of Medicine, Pediatric Neurology Unit, Bnai Zion Medical Center, Haifa, Israel

Pierangelo Geppetti Headache Center, University Hospital Careggi, University of Florence, Florence, Italy

Vincenzo Guidetti, M.D. Department of Paediatrics and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, Rome, Italy

Andrew D. Hershey, M.D. Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, OH, USA

S. Ju Neuroscience Research Institute of Peking University, Beijing, China

People's Liberation Army General Hospital, Beijing, China

Omer Karadas Department of Neurology, Gulhane Education and Research Hospital, Ankara, Turkey

Kentaro Kuwabara Department of Pediatrics, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan

Marco Lamberti Child and Adolescent NeuroPsychiatry Unit, "G. Martino" University Hospital, University of Messina, Messina, Italy

Tara M. Lateef, M.D., M.P.H. Departments of Pediatrics and Neurology, Pediatric Specialists of Virginia and George Washington University School of Medicine, Washington, DC, USA

Kenneth Mack, M.D., Ph.D. Mayo Clinic, Rochester, MN, USA

Tal Eidlitz Markus Pediatric Headache Clinic, Day Hospitalization Department, Schneider Children's Medical Center of Israel, Petach Tikva, Israel

Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Marcelo R. Masruha Universidade Federal de São Paulo, São Paulo, Brazil

Kathleen R. Merikangas, Ph.D. Genetic Epidemiology Research Branch, National Institute of Mental Health, Bethesda, MD, USA

Giulia Natalucci Department of Paediatrics and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, Rome, Italy

Aynur Ozge, M.D. Department of Neurology, Mersin University School of Medicine, Çiftlikköy Kampusü, Mersin, Turkey

Antonio M. Persico Child and Adolescent NeuroPsychiatry Unit, "G. Martino" University Hospital, University of Messina, Messina, Italy

Mafalda Luce Center for Pervasive Developmental Disorders, Milan, Italy

Scott W. Powers, Ph.D., A.B.P.P., F.A.H.S. Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Headache Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Victoria Elisa Rinaldi Migraine and Neurovascular Diseases Clinic, Paris Diderot-Sorbonne-Paris Cité University, Robert Debré Hospital, Paris, France

Elisa Salvi Association of Cognitive Psychology, APC, Rome, Italy

Carmen M. Schröder, M.D., Ph.D. Faculty of Medicine, Strasbourg University, Strasbourg, France

Department of Child and Adolescent Psychiatry, Strasbourg University Hospital, Strasbourg, France

Gretchen E. Tietjen, M.D. Department of Neurology, University of Toledo College of Medicine and Life Sciences, Toledo, OH, USA

Luigi Titomanlio Migraine and Neurovascular Diseases Clinic, Paris Diderot-Sorbonne-Paris Cité University, Robert Debré Hospital, Paris, France

Irene Toldo Juvenile Headache Centre, Department of Woman's and Child's Health, University Hospital of Padua, Padua, Italy

Derya Uluduz, M.D. Neurology Department, Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey

Massimiliano Valeriani, M.D., Ph.D. Headache Center, Neurology Unit, Ospedale Pediatrico Bambino Gesù, Rome, Italy

Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark

Nathan Watemberg, M.D. Pediatric Neurology Unit, Meir Medical Center, Tel Aviv University Medical School, Kfar Saba, Israel

Marcin Zarowski Department of Developmental Neurology, Poznan University of Medical Sciences, Poznan, Poland

Chapter 1
Epidemiology of Headache in Children and Adolescents

Tara M. Lateef and Kathleen R. Merikangas

1.1 Introduction

Epidemiology is defined as the study of the distribution and determinants of diseases in human populations. Thus, epidemiologic studies are concerned with the extent and types of illnesses in groups of people and with the factors that influence the distribution of those diseases. Epidemiologists investigate the interactions that may occur among the host, the agent, and the environment (the classic epidemiologic triangle) to produce a diseased state. An important goal of epidemiologic studies is to identify the *etiology* of a disease, thereby enabling health-care providers to prevent or intervene in the progression of the disorder. To achieve this goal, epidemiologic studies generally proceed from studies that specify the amount and distribution of a disease within a population by person, place, and time (i.e., *descriptive* epidemiology) to more focused studies of the determinants of disease in specific groups (i.e., *analytic* epidemiology). Whether descriptive or analytic, the ultimate goal of epidemiologic investigations is prevention.

Table 1.1 summarizes some contributions of epidemiology to our understanding of the magnitude, risk factors, and impact of migraine. The application of the tools of epidemiology to headache has generated substantial methodological

T.M. Lateef, M.D., M.P.H.
Departments of Pediatrics and Neurology, Pediatric Specialists of Virginia and George Washington University School of Medicine,
111 Michigan Avenue, Washington, DC 20010, USA

K.R. Merikangas, Ph.D. (✉)
Genetic Epidemiology Research Branch, National Institute of Mental Health,
35 Convent Drive, MSC#3720, Bethesda, MD 20892, USA
e-mail: merikank@mail.nih.gov

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Table 1.1 Goals of epidemiologic studies

• Develop standardized assessments of headache subtypes
• Establish validity of diagnostic nomenclature
• Estimate magnitude of headache subtypes in the general population
• Identify risk and protective factors for headache subgroups
• Collect information on patterns of use and adequacy of treatment

developments designed to collect reliable and valid information on the prevalence of headaches in nonclinical samples. With these methodologies, the high prevalence of migraine in the general population has been consistently reported, and the sex- and age-specific patterns of onset and offset of migraine have been well established. Community-based studies have also demonstrated major biases in severity and comorbidity that characterize clinical samples, particularly those obtained at tertiary referral centers for headache. Finally, epidemiologic studies have provided data on the huge impact and the personal and societal costs of migraine and other headaches.

The main objective of this chapter is to summarize the magnitude and sociodemographic correlates of headache subtypes in children and adolescents as well as the long-term course of disease in this population. The impact of migraine and level of disability imposed by it on the individual and society are discussed in detail in Chap. 5.

1.2 Magnitude of Headache Syndromes Among Children and Adolescents in the General Population

The Global Burden of Disease Study conducted in 2010 identified migraine among the top ten most disabling disorders [1]. Two systematic reviews of population-based studies, published in the last 10 years, have reported the international prevalence of migraine among children and adolescents in the range of 7.7–9.1% [2, 3]. It has been difficult to summarize the rates in these studies because many studies focus on particular age subgroups, whereas few studies have examined prevalence of headache across all years of childhood and adolescence simultaneously. Abu-Arafeh et al. in 2010 [2] reported the prevalence of migraine in children and adolescents is 7.7% (95% confidence interval [CI]: 7.6–7.8), over a range of time periods between 6 months and lifetime, and the prevalence of tension/sinus headache is 58.4% (95% CI: 58.1–58.8) over a range of prevalence periods between 1 month and lifetime. In the most recent

meta-analyses conducted by Wober-Bingol in 2013 [3], an overall prevalence of migraine was reported to be higher at 9.1% (95% CI 7.1–11.1), and prevalence of headaches was 54.4% (95% CI 43.1–65.8). Variation in the prevalence rates of migraine can be attributed to sampling differences (age, sex, and ethnic composition of the sample); methodological differences, particularly related to the method of assessment of the diagnostic criteria for headache (e.g., structured diagnostic interview, questionnaire, symptom checklist); the mode of administration of headache assessments (i.e., direct interview, telephone interview, self-reported assessment); and the variation in the time frame of prevalence estimates.

The variation in estimates of childhood migraine is in part due to methodological differences, but also due to inadequacy of the current diagnostic criteria in accurately capturing migraine among youth. As demonstrated in many studies, the *International Classification of Headache Disorders-I* (ICHD-I) [4] does not adequately distinguish the primary headache syndromes in childhood. With the publication of the *International Classification of Headache Disorders-II* (ICHD-II) [5] in 2004, the sensitivity of diagnosis of migraine without aura in children improved from 21 to 53%, yet continued to miss almost half of all pediatric migraine [6]. The *International Classification of Headache Disorders-III* (ICHD-III) [7] was published by the International Headache Society in May 2013. As this version is based on a large body of research on headache, in contrast to previous editions that were mostly based on opinion of experts, it is considered a major step forward in the diagnosis and management of headache. There are no significant revisions, in terms of diagnostic criteria, in the ICHD-III that would appear to significantly impact the diagnosis of pediatric migraine or enhance the sensitivity of diagnosis over and above the ICHD-II criteria. Specific to childhood and adolescent headache sufferers, "Childhood periodic syndromes that are commonly precursors of migraine" (benign paroxysmal vertigo of childhood, cyclical vomiting, and abdominal migraine) have now been renamed as "Episodic syndromes that may be associated with migraine" and have an additional condition, benign paroxysmal torticollis. Cyclical vomiting and abdominal migraine have been grouped together as "Recurrent gastrointestinal disturbance" [7].

Chronic migraine is much less common than episodic migraine, but it is substantially more debilitating. It is well established that chronicity of migraine is facilitated by frequent attacks and closely related to disease duration; therefore, making a timely and appropriate diagnosis of migraine in childhood may prevent progression to chronic migraine in adolescence and later on in life. There are a limited number of population-based studies that have investigated the prevalence of chronic migraine among children and adolescents [8–12]. Prevalence estimates of chronic migraine based on these heterogeneous samples are approximately 1.5–1.8% [13]. Chronic migraine prevalence increases with age and especially among females after adolescence.

1.3 Risk Factors and Correlates

The evidence consistently indicates that migraine is far more common in women than in men. International studies that assessed the 1-year prevalence rates have also reported similar gender differences, ranging from 1.5 to 18.3% among women and from 0.6 to 9.5% among men [14]. The US migraine study yielded very large gender differences, with the prevalence rate of migraine being approximately 18% in women but only 6% in men [15]. The sex ratio for lifetime migraine remains stable at 2–3:1 and is generally consistent across countries. The female preponderance of headaches emerges in youth, with females having a 1.5-fold greater risk of headaches and 1.7-fold greater risk of migraine than male children and adolescents. Numerous hypotheses to explain the gender differences in migraines have been proposed, and there is abundant research on some of the mechanisms suggested as causing the female preponderance of migraine. Nevertheless, few studies have systematically reviewed the evidence for both artifactual and true causes of women's increased risk for migraine. Potential sources of artifactual causes of the sex difference include biases associated with sampling (i.e., increased detection of females in clinical samples), reporting (i.e., a greater tendency for women to report or be aware of migraine), definitions (i.e., diagnostic criteria more likely to cover symptoms expressed by women than men), or confounding with other factors that are more common in women (i.e., depression, anxiety, gastrointestinal syndromes). After exclusion of possible artifactual explanations for the excess number of cases of migraine noted in women, numerous classes of hypotheses have been considered. These include hypotheses focusing on neurobiological factors (e.g., fluctuation of reproductive hormones, increased stress reactivity in women), greater exposure or sensitivity to environmental stressors (e.g., role stress, life events associated with certain sensory stimuli), and genetic factors (e.g., greater genetic loading for migraine in women) [16]. With respect to specific headache subtypes, there is a twofold greater prevalence of migraine across the life span in women, whereas tension-type headache affects both sexes at approximately equal rates. Sex differences among migraineurs are by no means uniform across childhood and adolescence. Whereas postpubertal rates of migraine are significantly higher among females in almost all studies, the rates of migraine are equivalent among boys and girls younger than 12 years of age; notably, some studies even suggest a higher prevalence of migraine among boys aged 3–5 years when compared with girls of the same age group [17]. The American Migraine Study reported that the female-to-male gender ratio of this type of headache increased steadily from age 12 to about age 42, after which it declined [18]. The decline in the sex-based ratio at midlife may correspond with the decline in estrogen levels in women as menopause approaches. This pattern also suggests that hormonal events associated with menarche may contribute to the emerging relative increases in the migraine prevalence in females in early adolescence. Two population-based studies have analyzed the relationship between menarche and

migraine. Kroner-Herwig et al. in 2009 [19] studies a cohort of 2252 children aged 9–14 years and had them complete a questionnaire sent by mail in three consecutive years. An increased risk of headache was identified in girls who had experienced menarche during the previous 2 years compared to girls without menarche. Another population-based study by [20] found the prevalence of headache was higher in girls with menarche at age 12 or earlier compared to those with menarche after the age of 12 years (OR = 0.8, 95% CI = 0.7–0.9).

Headache and migraine prevalence reliably increase across the pediatric age spectrum. In the USA, frequent or severe headaches, including migraine, were reported in 4% of 4- and 5-year-olds, with the prevalence increasing to 25% in the next 10 years of childhood [21].

Aside from sex and age, a family history of migraine is one of the most potent and consistent risk factors for migraine. Findings from twin studies implicate genetic factors as underlying approximately one-third of familial clusters of migraine, but the mode of inheritance is clearly complex. Despite an increasing number of studies examining candidate genes associated with migraine, no replicated linkage or associations between specific genes and migraine have emerged as yet, except for hemiplegic migraine. To date, the application of genome-wide association studies in cases and controls has not identified significant associations between migraine and genetic markers. Migraine is strongly associated with a variety of medical disorders, especially asthma, eczema, allergies, epilepsy, and cardiovascular disease, cerebrovascular disease, and particularly ischemic stroke. Anxiety and mood disorders are also strongly associated with migraine. Prospective data from community studies of youth reveal that anxiety in childhood is associated with the subsequent development of headache in young adulthood.

1.4 Incidence and Course of Disease

Headaches in early childhood are not only difficult to classify but also continuously evolve over time [22]. The likelihood of migraine at puberty is practically equal among children who present with tension-type headache or migraine at 6 years of age [23].

Incidence data on migraine has been reported in one study of children [24], and several long-term follow-up studies of specific childhood headache subtypes have been conducted with school-based and clinical samples [25–27]. The incidence of migraine is low before adolescence, but then rises rapidly until middle adulthood, and finally levels off in later life. The onset of migraine may occur in childhood, when boys and girls are equally likely to suffer from migraine. Migraine in childhood is more likely to be associated with gastrointestinal complaints, particularly episodic bouts of stomach pain, vomiting, or diarrhea, and

its duration is shorter than that commonly observed in adults. In women, migraine is strongly associated with reproductive system function, with increased incidence during puberty and the first trimester of pregnancy, and is associated with exogenous hormone use. After menopause, the frequency of migraine attacks generally decreases dramatically, unless estrogen replacement therapy is administered. In general, both the frequency and the duration of migraine decrease at midlife in both men and women, and the symptomatic manifestations may change substantially over time.

What happens to a child with migraine? Longitudinal population-based studies on pediatric migraine are relatively sparse. Bille in 1997 [25] reported the first extensive study of pediatric migraine epidemiology in 1962 and subsequently followed a group of children with severe migraine for 40 years. In this study, approximately 23% of these children became permanently migraine-free as adults (34% of the boys and 15% of the girls) [25]. At the 40-year follow-up evaluation, of the initial group of migraineurs, 33% of those who had children had offspring who developed their own headaches with migrainous features. The author also showed a considerable recall bias with regard to migraine with aura: 41% of middle-aged subjects could not remember that they had aura symptoms at younger ages. This finding highlights the need for prospective follow-up studies. Other prospective studies, utilizing ICHD-II criteria, have shown that headaches remit in 17–34% of subjects, persist in 20–48%, and transform into other types of headache in 11–37% [28, 29]. Studies that use detailed headache diagnostic criteria suggest that as many as one-fourth of patients may evolve from migraine to tension-type headache and vice versa [28–30]. In terms of prognostic factors, early age at onset [31], psychosocial stressors [30], and psychiatric comorbidity [26] may be linked to a less favorable outcome.

1.5 Impact of Migraine

These recent community studies have confirmed previous evidence regarding the enormous personal and social burden of migraine in terms of both direct and indirect costs. Over 80% of those with migraine report some degree of disability. The finding that young adults with migraine suffer from migraine for an average of 1 month of every year across 30 years of prospective follow-up highlights the cumulative impact of migraine during the peak period of attainment of educational and occupational years and social milestones of adult life [32]. In the US AMPP study, one-third of those with migraine had three or more attacks per month, and more than half reported severe impairment requiring bed rest [33]. Children with migraine have been consistently shown to have more school absences, decreased academic performance, social stigma, and impaired ability to establish and maintain peer relationships [21]. In fact, the quality of life in children with migraine is impaired to a degree similar to that in children with arthritis or cancer (Table 1.2) [34].

Table 1.2 Prevalence rates of ICHD-II migraine in population or school surveys of children and adolescents

Study characteristics					12-month prevalence				Lifetime
					Age group				
Country	First author	Year	*N*	Method	<13	13–15	13–18	<18	All
Review	Abu-Arafeh	2010	131,228	All		5.8		7.7	9.8
Review	Wober-Bingol	2013	210,524	All				9.1	
Brazil	Arruda	2012	5671	Q	3.8				
China	Jin	2012	4812	Q		4.3			
Finland	Anttila	2006	1066	Q/I	10.7				
Germany	Fendrich	2007	3324	Q		6.9			
	Kroner-Herwig	2007	5474	Q/I		7.5			
	Heinrich	2009	3833	Q		13.3			
	Milde-Busche	2011	1047	Q			4.1		
India	Malik	2012	5000	Q					17.9
Japan	Ando	2007	6472	Q		4.8			
Korea	Rho	2012	5360	Q	4.9	8.8	14.2		
Nigeria	Ofovwe	2012	1679	Q			13.5		
Singapore	Chong	2010	2873	Q				8.6	
Sweden	Laurell	2004	1371	Q/I		11			
Thailand	Visudtibhan	2007	1789	Q/I					13.9
Turkey	Unalp	2007	2384	Q				9.6	
	Isike	2007	2228	Q	3.3				
	Karli	2006	2387	Q/I			14.3		
	Akyol	2007	7721	Q/I					9.7
	Alp	2012	1385	Q/I				14.3	
USA	Bigal	2007	18,714	Q			6.3		
	Lateef	2012	10,123	I			8		
New studies			94,713		6.1	7.5	7.8	10.1	12.9

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Chapter 2
Classification and Limits

Umberto Balottin and S. Ju

To keep our analysis reasonably brief, the present examination of the topic of headache classification in children and adolescents focuses only on the primary headache forms. Our main intention is to consider how the introduction of new classification criteria may lend new and possibly innovative value to research and clinical data in this field. We also consider the topic of the risks inherent in the new criteria for the classification of migraine headaches, as applied to children and adolescents.

Headache, in its various clinical forms, is very common in childhood and adolescence. The Global Burden of Disease Study 2010 rated migraine as the "seventh disabler" among 289 diseases [1, 2]. Child and adolescent headache and migraine certainly have a significant impact in terms of physical health, but they also severely affect relationships within an affected subject's family, as well as his/her mental health, relationships with peers, school attendance, educational performance and, ultimately, future prospects. Child and adolescent headache sufferers also show significant comorbidities, both with diseases typical of childhood, such as asthma and allergies, and with many neuropsychiatric disorders, such as emotional disturbances, depression and anxiety. The epidemiological picture is also rather alarming. As early as the 1960s, it was known that headache occurs with a frequency of 40% in 7 year olds and 75% in 15 year olds in the general population [3]. More recent

U. Balottin (✉)
Child Neuropsychiatry Unit, C. Mondino National Neurological Institute, Pavia, Italy

Child Neuropsychiatry Unit, Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
e-mail: Umberto.balottin@unipv.it

S. Ju
Neuroscience Research Institute of Peking University, Beijing, China

People's Liberation Army General Hospital, Beijing, China

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data emerging from a systematic review of 50 population-based studies dealing with the prevalence of migraine in childhood [4] show that 58.4% of young people under the age of 20 suffer from recurrent headache and that the risk is greater in females (OR 1.53). Migraine has a prevalence of 7.7% and, in this case, too, the risk is greater in girls (OR 1.67). Furthermore, in 40% of migraine cases, the disease has onset before the age of 18 years [5]. Tension headache and migraine feature prominently among the neurological disorders of childhood and adolescence; moreover, their highly complex pathogenesis has led some to speculate that they lie on a continuum of severity in this age group and do not necessarily constitute clearly separate disease entities [6–10]. While this view is still debated, and might indeed call into question the usefulness of a precise and detailed classification of headache in children and adolescents, it remains necessary for various reasons, including scientific purposes, to be able to refer to a complete and detailed nosographic classification of headache. Correct classification of the type of headache affecting an individual is the prerequisite for the implementation of targeted treatment. That said, it must be recognised that in the field of child and adolescent headache, targeted or precision therapy looks very unlikely (in the near future at least) to become a real clinical prospect.

The evolution of the different headache classification systems is a story that began in 1962, when the Ad Hoc Committee on Classification of Headache published its *Classification of Headache*, in which classic migraine, common migraine and other forms were defined and grouped under "vascular headache of the migraine type". This, now historic, classification system linked each form with pathogenetic mechanisms that had still not been fully clarified. For this reason, over the following years, the concepts of vascular headache and muscle contraction headache became outdated. Furthermore, the diagnostic criteria used to define each form were rather random and, in the context of a trend towards evidence-based medicine based on statistical concepts and the search for biological markers of single diseases, also rather imprecise. The decades since then have seen the development of further headache classifications by the International Headache Society (IHS), which published its *Classification and diagnostic criteria for headache disorders, cranial neuralgia and facial pain* (ICHD-I) in 1988; this classification was followed, in 2004, by its *International Classification of Headache Disorders* (ICHD-II).

In ICHD-II, the various forms of headache are set out hierarchically, according to a system of increasing levels of diagnostic complexity. At the first diagnostic level, the classification lists four categories of primary headache and eight forms of secondary headache. The four primary headache categories are (1) migraine (2) tension-type headache, (3) cluster headache and other trigeminal autonomic cephalalgias and (4) other primary headaches.

In the second edition of the IHS classification (ICHD-II), the four primary headache categories comprise, at the second diagnostic level, the following forms:

1. In the migraine category:
   (a) Migraine without aura
   (b) Migraine with aura
   (c) Childhood periodic syndromes that are commonly precursors of migraine

(d) Retinal migraine
(e) Complications of migraine
(f) Probable migraine

2. Under the heading tension-type headache (TTH):

(a) Infrequent episodic tension-type headache
(b) Frequent episodic tension-type headache
(c) Chronic tension-type headache
(d) Probable tension-type headache

3. In the third category, cluster headache and other trigeminal autonomic cephalalgias:

(a) Cluster headache
(b) Paroxysmal hemicrania
(c) Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
(d) Probable trigeminal autonomic cephalalgia

4. In the final group, other primary headaches:

(a) Primary stabbing headache
(b) Primary cough headache
(c) Primary exertional headache
(d) Primary headache associated with sexual activity
(e) Hypnic headache
(f) Primary thunderclap headache
(g) Hemicrania continua
(h) New daily persistent headache (NDPH)

As mentioned, the classification system is hierarchical, and each clinician must decide the level (from first to fourth) to which he needs to take the diagnosis. A first-digit diagnosis simply indicates the group to which the patient belongs. The subsequent levels provide further information and thus a more detailed diagnosis. The depth of information required depends on the setting and the objective. In the setting of general medicine, one- or two-digit diagnoses are generally considered sufficient, whereas in specialist clinics or headache centres, a third- or fourth-level diagnosis may be given. However, many share the view that extremely precise and detailed analysis of individual forms whose pathogenesis, aetiology and independence as clinical/nosographic entities are still far from established does not reflect the comprehensive clinical approach that is needed to address the problem of headache in children and adolescents. The fact is that none of the various classifications have specifically considered children and adolescents or included experts in headache of childhood and adolescence in their editorial boards. In a manner reminiscent of the general approach adopted by the committee that drew up and edited the various editions of the DSM classification up to DSM-V, it has always been assumed, a priori, that the classification criteria used to define the various clinical forms could be the same for all age groups and thus applied, without distinction, both to children/

adolescents and to adults. However, this assumption seems to lack adequate support from evidence-based medical data. Consequently, the classification of primary and secondary headaches continues to be a problem addressed non-specifically using a largely adultomorphic system that presents various inconsistencies and difficulties when applied to children and adolescents. Only in the field of psychopharmacology does it remain firmly established that, in view of the metabolic, pharmacokinetic and pharmacodynamic peculiarities of specific drugs, particular attention and specific caution should be exercised in the administration of substances to children and adolescents. We therefore here present the latest in the series of headache classifications—a system whose imminent presentation in its final version will coincide with the forthcoming unveiling, by the WHO, of its latest International Classification of Diseases (ICD-11).

Published in 2013 in *Cephalalgia*, the *International Classification of Headache Disorders, 3rd edition (beta version)*, hereinafter ICHD-3 beta, is the latest classification produced by the IHS. For 3 years, the members of the IHS Classification Committee worked hard in order to accomplish it, and it will soon be released in its final version.

In the extensive introduction, it is underlined that due to the complexity and analytical richness of the text, it is, with a few exceptions, impossible to memorise. Consequently, the classification remains a text that should be consulted continually in order to ensure precise and reliable diagnoses. This is particularly true in situations (frequently encountered in children as well as in adults) in which the diagnosis is ambiguous, is complex or presents overlapping characteristics between different forms. However, the classification seems to be less geared to the clinical than to the research field, where it is, instead, particularly important, especially when the aim is to conduct a pharmacological trial or study the pathophysiology or biochemistry of a specific form. This concept, explicitly stated in the text, implies that the headache forms identified by the Committee are actually different from each other and do not lie on a continuum of severity. In partial analogy with what is set out in ICHD-II, there are five diagnostic levels. At the first level, it is simply a case of identifying the diagnostic group: migraine, tension-type headache or trigeminal autonomic cephalalgias, for example. As stated in the text, “In general practice only the first- or second-digit diagnoses are usually applied, whereas in specialist practice and headache centres a diagnosis at the fourth- or fifth-digit level is appropriate”. As for the period of time considered when making a diagnosis, patients generally “receive a diagnosis according to the headache phenotypes that they currently present, or that they have presented within the last year”. The manual specifies that each distinct headache presented by an individual must be separately diagnosed, with the result that a patient may even receive as many as three separately coded diagnoses, e.g. 1.1 migraine without aura, 1.2 migraine with aura and 8.2 medication-overuse headache. In such cases, it is necessary to establish their order of importance to the patient and list the diagnoses accordingly. The manual caters for the possibility of patients presenting intermediate forms, which incidentally would seem to support the continuum concept, and suggests that in cases of diagnostic uncertainty, it is necessary to consider elements deemed useful for the

definition of the headache, such as the lifetime longitudinal headache history, the family history, the effect of drugs and the patient's age and gender, as well as other features. The manual also allows the clinician to qualify the diagnosis as "probable", even though a probable diagnosis is considered less strong than all the other diagnoses set out in the respective groups and, in the event of doubt, should be excluded in favour of the others. Similarly, it is acknowledged that some individuals may have some headache attacks that meet the criteria for one form, and others that meet other criteria. In such cases, "two diagnoses exist and both should be coded". Although the diagnostic criteria also specify the minimum number of attacks that a patient must experience in order to receive a given diagnosis, the manual does not provide for the coding of headache attack frequency and severity, despite the fact that these are very important clinical features. Furthermore, if, over time, the headache becomes chronic or worsens, it must be assigned two diagnostic codes, i.e. a primary and a secondary headache diagnosis, thus opening up important diagnostic questions. Particular attention should be paid to attacks that are similar to previous attacks but do not quite fulfil the same diagnostic criteria as these attacks. In such cases, it is necessary to have the patient describe the less typical attacks and their frequency of occurrence and to investigate their causes, also through the use of a headache diary. Headache diaries have been found to be helpful when seeking to resolve diagnostic doubts. Finally, it is specified that the Appendix has been created for research purposes and includes orphan entities some of which, if they remain insufficiently validated, will likely be deleted in the final version of the ICHD-3.

In the new classification, the first-digit codes are basically unchanged compared to the previous version, while some substantial changes are already found at the second diagnostic level. More specifically, various important changes have been made to the criteria for migraine, some of which are now particularly relevant to children and adolescents. The category "Childhood periodic syndromes that are commonly precursors of migraine" has been renamed "Episodic syndromes that may be associated with migraine" and extended to include five categories: recurrent gastrointestinal disturbance, cyclical vomiting syndrome, abdominal migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis. While on the one hand, therefore, it was decided that the periodic forms of migraine could also embrace benign paroxysmal torticollis and recurrent gastrointestinal disturbance, it was also decided to replace the "precursor" concept with a less precise one, reference now being made, more vaguely, to forms "associated with migraine". This reframing of the concept seems to be at odds with the work done, and published widely, by many research groups on periodic syndrome and its common pathogenesis and clinical continuity with migraine [8, 11–14]. This aspect, too, illustrates the essentially adultomorphic character of ICHD-3 beta.

Furthermore, the entity named basilar-type migraine no longer features in the classification, while migraine with aura is now further classified into migraine with typical aura and migraine with brainstem aura. As regards hemiplegic migraine, as many as five distinct forms have been identified: FHM1, FHM2, FHM3, FHM other loci and sporadic hemiplegic migraine. Finally, it should be noted that, apart from the extensive section devoted to the periodic syndromes, ICHD-3 beta contains only

one criterion specifically tailored to children and adolescents, namely, the duration of attacks of migraine without aura, which may last 2–72 h rather than 4–72 h. In this regard, the manual points out that "the evidence for untreated durations of less than 2 h in children has not been substantiated" and thus seems to ignore the impressive body of literature showing that migraine attacks in children can last considerably less than 2 h [1, 6, 15–18].

Generally speaking, the section on tension-type headache is unmodified and thus remains structured as in the previous classification. Instead, some important additions have been made to the section on trigeminal autonomic cephalalgias (TACs), which includes cluster headache. In detail, a sub-classification of the category short-lasting unilateral neuralgiform headache attacks has been introduced, consisting of the form with conjunctival injection and tearing (SUNCT), in turn subdivided into episodic and chronic forms; in addition, the category short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) has been added, subdivided into episodic and chronic forms. Finally, hemicrania continua (both the remitting and the unremitting subtype), previously included under other primary headaches, has been included among the TACs.

Other primary headache disorders (the last of the primary headache categories) now include many new forms, such as cold-stimulus headache, external-pressure headache and nummular headache; as mentioned, each category can now be coded as probable.

Future research data will clarify several very important issues that have already been widely discussed in the context of comparisons of the use of ICHD-II (the 2004 version) and ICHD-I (1988) in children and adolescents. According to Abu Arafeh [4], the modified IHS diagnostic criteria did not significantly change the prevalence rate for migraine, which was 7.5% using the 1988 criteria in a total population of 68,954 children and 7.8% using the 2004 criteria in a population of 64,985. On the basis of these findings, it can thus be stated that the new migraine attack duration criterion in ICHD-II did not result in a change in the prevalence of the disorder.

Clearly it has not yet been possible to apply and evaluate, systematically, the ICHD-3 beta criteria in children and adolescents. Here we consider only the most important issues relating to the most common forms of migraine and recurrent primary headache. However, it should be noted that the new classification does not include rare forms of migraine typically seen in childhood and adolescence such as acute confusional migraine of childhood and Alice in Wonderland syndrome [19].

From the paediatric perspective, the main issues remaining open following the introduction of the new headache classification are the well-known ones of migraine/headache attack duration (typically much shorter in children) and frequency of unilateral headache (lower in youngsters); added to these, there is the difficulty, in children, in reliably establishing the accompanying symptoms of migraine and headache attacks.

In fact, in ICHD-3 beta, the minimum migraine attack duration has been increased from 1 to 2 h, and the note about migraine headache being commonly bilateral in young children has been omitted, as has that on the need to infer symptoms from

children's behaviour. In some recent studies, the ICHD-3 beta criteria were shown to have a sensitivity of between 65.71 and 58% for migraine diagnoses [20, 21]; reducing the attack duration criterion to 1 h gave these same classification criteria a diagnostic sensitivity of 94% [21]. Moreover, many studies show that very high proportions of children have very short attacks, i.e. of less than 2-h or even 1-h duration. It is not rare to read of attacks lasting a few minutes in children and adolescents who then present a full migraine syndrome [15, 17]. In this regard, it is worth recalling that some authors have proposed a definition of migraine in children and adolescents that includes an attack duration of 30 min [22]. Furthermore, as mentioned above, periodic syndromes of childhood appear inextricably linked with migraine syndromes for various reasons, both pathogenetic and related to the disease course [8, 11–14, 23, 24] and therefore should not be classified in a separate section [22].

As regards the criteria for tension-type headache, the few studies conducted to date have shown that, for this form, the new criteria have a predictive value of around 62.6% after 7 months of follow-up, whereas a lower diagnostic stability (46.1%) is reported for probable tension-type headache diagnoses [20].

We have briefly examined the limits of the latest version of the *International Classification of Headache Disorders*. Although the new criteria continue to ensure that researchers are able to study the pathophysiology, biochemistry and therapeutic sensitivity of a given form and reach common positions, they nevertheless retain an essentially adultomorphic character, are still too closed to the concept of catering for juvenile forms with their own peculiarities and often have poor sensitivity. It is likely that richer and more vigorous research in the field of headache in childhood and adolescence may, in the future, help to lessen the abovementioned difficulties and problems.

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Chapter 3
Migraine Genetics

Antonio M. Persico, Marco Lamberti, and Viktor Farkas

3.1 Introduction

The existence of strong genetic underpinnings to migraine has long been suggested by its tendency to recur in families. Over half of migraine patients have a first-degree relative also affected by a similar condition [1–6], with relative risks (RRs) estimated at 4.0 and 1.4 for migraine with aura (MA) and without aura (MO), respectively [5, 6]. MZ twin concordance rates are 1.5–2.0 times higher than those recorded in DZ twins, with heritability estimated at 34–57% (on average 50%) and shared environmental factors explaining a sizable proportion of variance [1–3]. In general, these genetic underpinnings are more frequently represented by rare genetic variants endowed with high penetrance in the case of MA, whereas polygenic mechanisms with gene-environment interactions more frequently underlie MO. Environmental contributors include, among others, female sex hormones, early and recent stress, and sensory hypersensitivity to visual, auditory, and olfactory stimuli [7, 8]; suggestive evidence also points toward weather and climate conditions, electromagnetic fields, smoking, pollution, and molds [7, 8]. Finally, migraine is frequently comorbid with depression, anxiety, ADHD, sleep disorders, epilepsy, and atopic and

A.M. Persico (✉)
Child and Adolescent NeuroPsychiatry Unit, "G. Martino" University Hospital, University of Messina, Via Consolare Valeria 1, Messina 98125, Italy

Mafalda Luce Center for Pervasive Developmental Disorders, Milan, Italy
e-mail: apersico@unime.it

M. Lamberti
Child and Adolescent NeuroPsychiatry Unit, "G. Martino" University Hospital, University of Messina, Via Consolare Valeria 1, Messina 98125, Italy

V. Farkas
First Department of Pediatrics, Semmelweiss University, Budapest, Hungary

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cardiovascular diseases [9, 10]. These comorbidities can conceivably stem from shared genetic and/or environmental underpinnings to a different extent in different patients [11, 12].

The genetic underpinnings of MA and MO, encompassing syndromic, monogenic, and polygenic forms, have recently been reviewed [13] and will be hereby summarized. The importance of these studies reaches beyond the mere identification of a genetic cause for some forms of migraine, as they provide precious information on the pathophysiology of this complex condition.

3.2 Syndromic Forms

Migraine can be part of a known genetic syndrome, affecting multiple organs. Migraine-associated syndromes are typically rare, autosomal dominant genetic disorders due to highly penetrant mutations. The genetic syndromes most frequently associated with migraine include the following:

3.2.1 Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

This Mendelian disorder often begins with migraine episodes accompanied by neurological symptoms or transient ischemic attacks (TIA), ultimately yielding strokes and subcortical multi-infartual dementia in adulthood. The onset of migraine attacks in CADASIL typically occurs before 26 years of age, and females display an earlier onset of MA compared to males [14]. CADASIL stems from mutations in *NOTCH3* (chr.19q12), which encodes for a transmembrane receptor expressed in the smooth muscle cells of small brain vessels [15]. Mutations affect blood vessel stability, yielding increased pressure-induced vascular tone and a relative deficit in vasodilation [16, 17]. In particular, mutated NOTCH3 receptors accumulate in small vessels, causing granular osmiophilic deposits, decreased cell adhesion, cell loss, degeneration of smooth muscle cells in the middle layer, and fibrosis [18]. Its prevalence is 4:100,000 adults, but this probably represents an underestimation [19, 20].

3.2.2 Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS)

MELAS is characterized by epileptic seizures, stroke-like episodes, and lactic acidosis [21]. It is caused by mutations in various mitochondrial genes, most often *MTTL1* encoding for the mitochondrial tRNA for leucine. Hampered brain

oxidative metabolism seemingly plays an important role in the pathogenesis of migraine associated with MELAS [22]. Seizures are associated with radiologic evidence of cortical infarcts and with migraine-like headaches; additional features may include hemianopsia, cortical blindness, hemiparesis, episodic vomiting, and short stature. Systemic cardiac, renal, endocrine, gastrointestinal, and endothelial signs and symptoms may also be present. Ragged-red fibers are common, while a symptomatic myopathy is rare.

3.2.3 Retinal Vasculopathy and Cerebral Leukodystrophy (RVCL)

RVCL combines into a single condition three neurovascular syndromes previously named hereditary vascular retinopathy (HVR), cerebroretinal vasculopathy (CRV), and hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS) [23]. These autosomal dominant disorders are all caused by mutations in the *TREX1* gene (chr. 3p21), encoding for former DNase III (i.e., Three prime Repair EXonuclease), an autonomous non-processive 3′–5′ DNA-specific exonuclease [24]. Mutations affecting this enzyme indirectly activate autoimmunity against undigested dsDNA from dying cells [25]. *TREX1* mutations can also cause other disorders including Aicardi-Goutières syndrome, systemic lupus erythematosus, and familial chilblain lupus, through abnormal immune mechanisms [23]. Clinically, HVR is characterized by retinal microangiopathy accompanied by migraine in 70% of cases [26, 27]. CRV involves both the retina and the brain, with progressive visual loss accompanied by neurological signs, psychiatric symptoms, migraine, stroke, and death within 10 years of disease onset [23, 24]. HERNS is a multiinfartual condition characterized by retinopathy, strokes, and nephropathy [28].

3.2.4 COL4A1-Related Syndromes

Mutations in the *COL4A1* gene (chr. 13q34), encoding for the collagen type IV alpha-1 subunit, produce several autosomal dominant disorders characterized by porencephaly, perinatal hemorrhage, and small vessel disease ultimately leading to hemorrhage and hemiparesis with infantile or adult onset [29–33]. The association of *COLA4A1* mutations with migraine is still under scrutiny [32].

3.2.5 Familial Anticipated Sleep Phase Syndrome (FASPS)

FASPS is characterized by a persistent anticipation of the sleep-wake cycle, with early evening sleep onset and early awakening [34]. This autosomal dominant disorder is mainly due to a mutation in the circadian h*PER2* gene (chr. 2q37.3) [35].

A secondary cause of MA and FASPS may stem from missense mutations in the gene encoding casein kinase 1δ (CK1δ), resulting in decreased hPer2 activation [36]. Interestingly, mice carrying the CK1δ T44A mutation are prone to develop cortical spreading depression accompanied by increased spontaneous and evoked calcium signaling in astrocytes [37], an indication that CK1δ can directly contribute to the pathogenesis of migraine.

From a pathophysiological standpoint, syndromic forms underscore the role of brain vascular tone dysregulation (CADASIL and RVCL), insufficient oxidative metabolism (MELAS), and abnormal circadian variation in cortical excitability (FASPS) as important contributors to the pathophysiology of migraine attacks, regardless of whether idiopathic or immune-triggered.

3.3 Monogenic Forms of Migraine

Familial hemiplegic migraine (FHM) is a rare monogenic form of migraine with motor aura and autosomal dominant inheritance [38]. Though rare, FHM represents an interesting genetic model to study the molecular pathophysiology of migraine [39]. Parentally transmitted variants in three ion transport-related genes (CACNA1A, ATP1A2, and SCN1A) have been implicated, although de novo mutations in these same genes have also been documented in sporadic forms [40]. Moreover, especially mutations in SCN1A display pleiotropic effects, yielding epilepsy, autism, and MA/MO without typical FHM-type aura [41–43].

1. FHM type 1 (FHM1) is caused by nonsense or missense mutations in the *CACNA1A* gene (chr. 19p13), typically yielding episodic ataxia type 2 and FHM1, whereas a CAG triplet repeat expansion affecting the C-terminus causes spinocerebellar ataxia type 6, only rarely accompanied by FHM1 [44–46]. *CACNA1A* encodes the α1A subunit of the voltage-gated neuronal calcium channel, expressed with highest density in the cerebellum [47, 48]. Mutations lead to increased Ca^{2+} influx into the neuron in response to smaller depolarizations, boosting release of the excitatory neurotransmitter glutamate, because this channel is predominantly expressed presynaptically [49]. The regional distribution and functional role of this subunit may also explain why some FHM1 patients display cerebellar signs and episodic loss of consciousness.
2. FHM type 2 (FHM2) is associated with mutations in the *ATP1A2* gene (chr. 1q21–23). This gene encodes the α2 subunit of the Na^+-K^+ pump. *ATP1A2* mutations have also been very rarely encountered in basilar migraine and in common migraine, as well as in other neurological diseases, such as idiopathic cerebellar syndromes, epilepsy, benign familial infantile convulsions, alternating hemiplegia of childhood, and intellectual disability [50, 51].
3. FHM type 3 (FHM3) mutations are located in the *SCN1A* gene (chr. 2q24), encoding for the α1 subunit of the neuronal voltage-gated sodium channel, responsible for the generation and propagation of action potentials primarily in cortical neurons [52]. Indeed, *SCN1A* mutations typically lead to hypersynchronous neuronal

discharges resulting in migraine attacks, seizures, or autism, with either typical FHM course or appearing as sporadic MA or MO [41–43]. *SCN1A* mutations producing migraine only, such as Q1489K, affect not only the timing of channel inactivation, crucial to epileptogenic mutations causing generalized epilepsy with febrile seizures plus (GEFS+) or Dravet syndrome, but also on the transition from closed to the inactivated state of the sodium channel, preventing neuronal discharges from becoming epileptogenic [53, 54].

4. Other forms of typical FHM have been identified in carriers of *PRRT2* (proline-rich transmembrane protein 2) gene mutations (chr. 16p11), encoding for an axonal protein associated with the exocytosis protein complex [55], and in the *SLC4A4* gene, encoding for the Na^+-HCO_3^- cotransporter NBCe1 [56]. Lastly, other missense mutations located in the *SLC1A3* gene, encoding the glial glutamate cotransporter EAAT1, have been found to cause alternating hemiplegia, migraine, episodic ataxia, and seizures [57, 58].

In summary, familial forms of MA, and in particular FHM, are due to rare and highly penetrant genetic variants, usually inherited but at times sporadic. These mutations disrupt neuronal excitability by affecting the transmembrane electrochemical gradient and/or by enhancing extracellular glutamate concentrations. Genetic variants in FHM genes do not play widespread causative roles in common forms of MO, usually involving more complex polygenic mechanisms [13, 59].

3.4 Polygenic Forms

The vast majority of migraine cases, especially the most common forms of MO, are polygenic and have been studied using association in candidate genes, linkage in multigenerational pedigrees, and genome-wide association studies (GWAS).

Candidate genes assessed using the former approach have been schematically grouped into four gene families (for review see [13]):

1. "Neurological genes," encoding ion channels (calcium channel, voltage-dependent, P/Q type, alpha-1A subunit [CACNA1A], voltage-potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3 [KCCN3]), Na^+/K^+-ATPase subunits, and molecules involved in the synthesis, release, and effects of neuropeptides (calcitonin gene-related peptide) or neurotransmitters (glutamate, GABA, dopamine, serotonin) relevant to neuronal excitation and/or to nociception. Only three genes encoding potassium channels are associated with migraine, namely, *KCNK18, KCNG4,* and *KCNAB3*. In particular, *KCNK18* is expressed in the trigeminal and dorsal root ganglia and is related to MA.
2. "Vascular genes," involved in blood pressure regulation, endothelial cell function, vasodilation, and vasoconstriction. Many vascular genes associated with MA also confer risk for stroke and heart disease. Several common variants in vascular genes may predispose to migraine while also influencing type and frequency of the attacks. The most relevant vascular genes include angiotensin-converting enzyme (*ACE*, chr. 17q23), methylenetetrahydrofolate reductase

(*MTHFR*, chr. 1p36.22), *NOTCH3*, endothelial genes including endothelin-1 (*EDN1*), endothelin receptor types A and B (*EDNRA* and *EDNRB*), inducible NO synthase (*NOS2*), endothelial NO synthase (*NOS3*), and vascular endothelial growth factor (*VEGF*).

3. "Hormonal genes," involved in estrogen and progesterone metabolism especially relevant to menstrual migraine. These include estrogen receptor 1 (*ESR1*), estrogen receptor 2 (*ESR2*), progesterone receptor (*PGR*), androgen receptor (*AR*), follicle-stimulating hormone receptor (*FSHR*), nuclear receptor interacting protein 1 (*NRIP1*), and cytochrome P450, family 19, subfamily A, polypeptide 1 (*CYP19A1*). However, a meta-analysis of eight genetic association studies investigating these genes suggests an association only with the ESR1 c.594G>A and c.325C>G polymorphisms, with no difference between MA and MO.
4. "Inflammatory genes," especially tumor necrosis factor alfa (TNF-α) implicated in neurogenic inflammation. The immune system may indeed play an important role in the pathogenesis of migraine. CSD, for example, triggers local neurogenic inflammation, with activation of mast cells and macrophages accompanied by the release of proinflammatory cytokines ultimately inducing the sensitization of meningeal nociceptive nerves.

Meanwhile, linkage has also been used to successfully map migraine loci in monogenic forms, such as FHM. For example, a frameshift mutation in the *KCNK18* gene, encoding for the TRESK pore potassium channel highly expressed in trigeminal and dorsal root ganglia during embryogenesis, was associated with MA in a single large pedigree from Ontario [60]. The truncated TRESK protein produces abnormal neuronal excitability [60, 61], so TRESK may play a broader role in common forms of migraine considering that *KCNK18* gene variants were found associated with migraine also in a case-control study [62].

Latent class analysis (LCA) and trait component analysis (LTC) methods have been used in some migraine studies to overcome the limitations of classical linkage in the presence of genetic and clinical heterogeneity and to target more homogenous subgroups of patients [63–66].

3.4.1 Genome-Wide Association Studies (GWAS)

The genome-wide association approach allows to perform cost-effective screenings for common variants conferring sizable predisposition in complex disorders. Applying the most advanced genotyping technology to analyze large cohorts, usually of several thousand individuals, many susceptibility loci are identified, although replication remains challenging given disease heterogeneity. In the field of migraine genetics, GWAS have been performed by a large collaborative group, the International Headache Genetics Consortium (IHGC), testing for association with various migraine traits up to several million single-nucleotide polymorphisms (SNPs) that cover the entire genome ([67–72], for review see [73]).

The most recent and comprehensive meta-analysis published to date encompasses 22 GWAS involving a total of 59,674 affected subjects and 316,078 controls [74]. This combined data set included more than 35,000 new migraine cases not involved in previously published GWAS. This meta-analysis detected 38 genomic loci harboring 44 independent association signals at levels of genome-wide significance (Table 3.1). Among these loci, the majority was involved in vascular disease (PHACTR1, TGFBR2, LRP1, PRDM16, RNF213, JAG1, HEY2, GJA1, and ARMS2) or in smooth muscle contractility and regulation of vascular tone (MRVI1, GJA1, SLC24A3, and NRP1). Six loci are involved in nitric oxide (NO) signaling and oxidative stress (REST, GJA1, YAP1, PRDM16, LRP1, and MRVI1). Only two loci encode for ion channels (KCNK5 and TRPM8), while three others (SLC24A3, ITPK1, and GJA1) can be linked to ion homeostasis. The association of these 38 genomic loci is driven by MO, which is the more common form of migraine, while no association with MA was detected, due to the smaller sample size. No evidence of significant heterogeneity was detected, suggesting a partially shared genetic susceptibility underlying both MA and MO. Collectively, these results strongly point

Table 3.1 Migraine loci and genes identified by Genome-wide Association Studies (GWAS)

Chr	Index SNP (and involved genes)	Migraine subtype[a]	*P* value (odds ratio) (95% confidence Interval)	References
1	rs12134493 (near TSPAN2)	NS	6.71 × 10−14 (1.14 [1.10–1.18])	[72]
1	rs2651899 (PRDM16)	NS NS	3.80 × 10−9 (1.11 [1.07–1.15]) 3.28 × 10−14 (1.09 [1.07–1.12])	[68] [72]
1	rs10915437 (near AJAP1)	NS	2.81 × 10−8 (0.86 [0.82–0.91])	[72]
1	rs3790455 (MEF2D) rs2274316 (MEF2D)	MO NS	7.06 × 10−11 (1.20 [1.14–1.27]) 3.14 × 10−8 (1.07 [1.05–1.10])	[70] [72]
1	rs6693567 (near ADAMTSL4–ECM1)	NS	1.2 × 10−8 (1.05 [1.03–1.06])	[73]
1	rs1572668 (1p31.1[b])	NS	2.1 × 10−8 (1.04 [1.02–1.05])	[73]
2	rs7577262 (TRPM8)	NS NS MO	9.11 × 10−14 (0.87 [0.84–0.90]) 1.09 × 10−8 (0.79 [0.73–0.86]) 8.64 × 10−11 (0.81 [0.76–0.86])	[72] [72] [72]
2	rs138556413 (CARF)	NS	2.3 × 10−8 (0.88 [0.84–0.92])	[73]
3	rs7640543 (near TGFBR2) rs6790925 (near TGFBR2)	MO NS	1.17 × 10−9 (1.19 [1.13–1.26]) 2.16 × 10−8 (1.05 [1.02–1.07])	[70] [72]
3	rs13078967 (near GPR149)	NS	1.8 × 10−9 (0.87 [0.83–0.91])	[73]
4	rs7684253 (near REST–SPINK2)	NS	2.5 × 10−9 (0.96 [0.94–0.97])	[73]
6	rs9349379 (PHACTR1)	MO MO	3.20 × 10−8 (0.86 [0.81–0.91]) 2.81 × 10−10 (0.93 [0.91–0.96])	[70] [72]
6	rs10456100 (KCNK5)	NS	6.9 × 10−13 (1.06 [1.04–1.07])	[73]
6	rs13208321 (FHL5)	NS MO	1.34 × 10−11 (1.10 [1.07–1.13]) 1.58 ×10−12 (1.18 [1.13–1.24])	[72] [72]

(continued)

Table 3.1 (continued)

Chr	Index SNP (and involved genes)	Migraine subtype[a]	*P* value (odds ratio) (95% confidence Interval)	References
6	rs1268083 (HEY2–NCOA7)	NS	5.3 ×10−9 (0.96 [0.95–0.97])	[73]
6	rs28455731 (near GJA1)	NS	7.3 × 10−9 (1.06 [1.04–1.08])	[73]
6	rs140002913 (near NOTCH4)	NS	3.8 × 10−8 (0.91 [0.88–0.94])	[73]
7	rs4379368 (c7orf10)	NS MO	1.46 × 10−9 (1.11 [1.08–1.15]) 5.81 × 10−8 (1.19 [1.12–1.27])	[72] [72]
7	rs10155855 (near DOCK4–IMMP2L)	NS	2.1 × 10−8 (1.08 [1.05–1.12])	[73]
8	rs10504861 (near MMP16)	MO	1.17 × 10−8 (0.86 [0.81–0.90])	[72]
8	rs1835740 (MTDH/ AEG-1)	MA	1.69 × 10−11 (1.18 [1.13–1.24])	[67]
9	rs6478241 (ASTN2)	MO NS	3.86 × 10−8 (1.16 [1.11–1.23]) 1.04 × 10−9 (1.16 [1.11–1.22])	[70] [72]
10	rs10786156 (PLCE1)	NS	2.0 × 10−14 (0.95 [0.94–0.96])	[73]
10	rs12260159 (HPSE2)	NS	3.2 × 10−10 (0.92 [0.89–0.94])	[73]
10	rs2506142 (NRP1)	NS	1.5 × 10−9 (1.06 [1.04–1.07])	[73]
10	rs2223089 (ARMS2–HTRA1)	NS	3.0 × 10−8 (0.93 [0.91–0.95])	[73]
11	rs4910165 (MRVI1)	NS	2.9 × 10−11 (0.94 [0.91–0.98])	[73]
11	rs10895275 (YAP1)	NS	1.6 × 10−8 (1.04 [1.03–1.06])	[73]
11	rs561561 (IGSF9B)	NS	3.4 × 10−8 (0.94[0.92–0.96])	[73]
11	rs11031122 (MPPED2)	NS	3.5 × 10−8 (1.04 [1.03–1.06])	[73]
12	rs11172113 (LRP1)	NS MO NS MO	4.30 × 10−9 (0.90 [0.78–0.93]) 2.97 × 10−8 (0.86 [0.81–0.91]) 2.69 × 10−19 (0.90 [0.88–0.92]) 9.96 × 10−11 (0.88 [0.84–091])	[68] [70] [72] [72]
12	rs1024905 (near FGF6)	MO	2.1 × 10−17 (1.06 [1.04–1.08])	[73]
14	rs11624776 (near ITPK1)	NS	7.9 × 10−9 (0.96 [0.94–0.97]	[73]
16	rs77505915 (CFDP1)	NS	3.3 × 10−10 (1.05 [1.03–1.06])	[73]
16	rs4081947 (near ZCCHC14)	NS	2.5 × 10−9 (1.03 [1.00–1.06])	[73]
17	rs17857135 (RNF213)	NS	5.2 × 10−10 (1.06 [1.04–1.08])	[73]
17	rs75213074 (near WSCD1–NLRP1)	NS	7.1 × 10−9 (0.89 [0.86–0.93])	[73]
20	rs4814864 (SLC24A3)	NS	2.2 × 10−19 (1.07 [1.06–1.09])	[73]
20	rs111404218 (near JAG1)	NS	2.0 × 10−9 (1.05 [1.03–1.07])	[73]
20	rs144017103 (near CCM2L–HCK)	NS	1.2 × 10−8 (0.85 [0.76–0.96])	[73]
X	rs12845494 (near MED14–USP9X)	NS	1.7 × 10−8 (0.96 [0.95–0.97])	[73]

[a]*NS* migraine subtype is not specified, *MO* migraine without aura, *MA* migraine with aura
[b]The nearest coding gene (LRRIQ3) to this locus is 592 kb away
Abbreviations: *Chr* chromosome, *SNP* single-nucleotide polymorphism

toward the vascular component of migraine pathophysiology as playing a primary role in the cascade of events leading to its clinical expression. Other components highlighted by previous smaller-scale GWAS, seemingly playing relevant, yet secondary roles, include glutamatergic and serotoninergic neurotransmission, NGF signaling, and neuroimmune interactions [13].

3.5 Conclusions

Genetic studies of migraine have come a long way in identifying the rare and common variants involved in triggering the onset and/or determining the progression of this disorder. Even more importantly, they have provided pivotal contributions to our understanding of the three main pathophysiological components involved in migraine: the vascular, neural, and nociceptive domains [75]. The advent of GWAS has partly overcome the lack of replication previously afflicting candidate gene association studies. Next-generation sequencing has dramatically improved our capacity to identify rare variants in enriched pedigrees, as compared to linkage analysis. As genetic knowledge grows, its translation into effective therapies, its complex interactions with environmental factors and with epigenetic regulation of gene expression, and its overlap with the genetic underpinnings of frequently comorbid conditions, such as depression, represent challenging tasks to be addressed by future investigations with enhanced confidence.

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Chapter 4
Epigenetics

Andrew D. Hershey, Vincenzo Guidetti, and Noemi Faedda

4.1 Introduction

The pathophysiology of migraine is far from resolved. The current theory regards migraine as a complex multifactorial disorder, with both predisposing genetic factors and environmental factors contributing to the attacks [1]. Twin studies have reported that over half of the variation in migraine is attributable to a genetic component, while the remainder is attributable to unshared environmental factors [2–4]. Several studies have identified the role of some genes in the pathophysiology of migraine [5]; however, epigenetic mechanisms may play an important role in the etiology and phenotypic expression of migraine disorders, and these mechanisms may explain how non-genetic factors (such as female hormones, stress, and inflammation) may modulate the severity and frequency of the attacks [1].

The term "epigenetics" was first coined in the 1940s by Conrad Waddington to describe "the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being" [6, 7]. Thus, epigenetics is the science that studies the environmental factors that do not change the DNA coding sequence, but that turn genes "on" and "off," affecting how cells "read" genes [8]. Indeed, external factors are able to change gene expression through several processes, such as DNA methylation, histone modification, and RNA-associated silencing [9]. Furthermore, these changes, although not encoded

A.D. Hershey, M.D.
Division of Neurology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, OH 45229-3039, USA
e-mail: Andrew.hershey@chmcc.org

V. Guidetti, M.D. • N. Faedda, Ph.D. (✉)
Department of Pediatric and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, Rome, Italy
e-mail: vincenzo.guidetti@uniroma1.it; noemi.faedda@gmail.com

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in the DNA, are heritable and may persist for multiple generations, with huge impacts on biological processes and on cardiovascular, reproductive, mental, and metabolic disorders [10].

4.2 Basic Mechanisms of Epigenetics

As the concept of epigenetics and its observed effects have been identified and refined, the processes underlying its mechanisms have been established. According to the latest interpretation of epigenetic changes, the key requirements are that the DNA sequence is not changed, but that the DNA is modified in such a way that the gene expression, and thus the resulting phenotype, is altered by modification of the DNA. Furthermore, this modification can be inherited by both mitotic and meiotic mechanisms, such that the changes can be passed on from one cell to the next, as well as from parent to child. Changes that are currently accepted as epigenetic include alterations of histones and chromatin remodeling, and therefore chromosomal compaction and available genes for expression; post-translational modification of histone amino acids; and covalent modification of DNA, including DNA methylation, non-coding RNAs (ncRNAs), and RNA and DNA editing (reviewed in [11–13]). In general, these processes will alter the expression of mRNA and thus alter the resulting protein or transcript.

DNA methylation has been the most widely studied mechanism of epigenetics. This process involves the attachment of a methyl group to the 5-position of the DNA base, where a cytosine nucleotide is followed by a guanine nucleotide. This CG sequence can often occur in promoter regions of a gene; when methylation occurs, expression of the gene is promoted. When methylation occurs in one of the two alleles of a gene, it can result in selective paternal or maternal expression of the gene. This expression may be regulated across generations, resulting in a mixed inheritance pattern.

This CG sequence can also occur elsewhere in the genome, and when it is located in chromatin binding regions, it can alter the folding of chromosomes and histone wrapping, resulting in some genes being unavailable for transcription. Additionally, the histones themselves can be modified, and this results in the same altered pattern of transcription.

When the human genome was sequenced, the number of protein-encoding areas was much lower than expected and there were many areas of DNA that seemed to be available for transcribing, but not for encoding protein. It has been proposed that additional epigenetic modifications that rely on this ncRNA contribute directly to the expression of coding regions. These ncRNAs include small segments of RNA (micro RNA or miRNA), and when these miRNAs bind specific DNA sequences they can alter the RNA expression of mutliple genes and thus impact a whole cascade of genes [11].

Other ncRNAs include small nucleolar RNA (snoRNA), small Cajal body-specific RNAs (scaRNAs), and others (reviewed in [11]). Many brain-specific

snoRNAs have begun to be identified and their reported role in neurological diseases is growing; they may underlie the mechanism of imprinting and environmental alterations in gene expression.

4.3 Epigenetic Mechanisms in Migraine and Headache

The current theory of migraine suggests that it is a complex multifactorial disease caused by both predisposing genetic variance and environmental factors [1]. The International Headache Society [14] classifies migraine in two categories: defined migraine without aura (MOA) and migraine with aura (MA). However, a diagnosis of one type does not exclude the other; indeed, a patient can often suffer from both types of headache, or the headache may switch from one type to the other during the course of the illness [15].

Familial and twin studies have detected a heritability of 42% for migraine [16]. First-degree relatives of patients with MOA carry a recurrence risk for MOA that is nearly twice that of any random member of the general population, and the recurrence risk for first-degree relatives of patients with MA is nearly four times that in the general population [2]. Of note, a very recent meta-analysis of 375,000 individuals identified 38 susceptibility loci for migraine [5] involved in vascular and smooth muscle tissues.

Although genetic associations are found in migraine disorder, the biological, neural, and molecular mechanisms that underlie the pathophysiology of migraine are far from known. MOA would seem to be caused by a primary brain dysfunction, leading to the activation and sensitization of the trigeminovascular system and to the release of vasoactive neuropeptides [15], while MA has been associated with a reversible, transient cortical event called cortical spreading depression (CSD) [17–19]. CSD is a slowly propagating wave (2–6 mm/min) of neuronal and glial depolarization followed by a prolonged inhibition (15–30 min) of cortical activity [19]. These factors alone are not enough, however, to explain the complexity of the disease: environmental factors, differences in lifestyle, and epigenetic mechanisms must also be involved.

In this vein, interesting new research has detected the impact of several epigenetic mechanisms on the pathophysiology of migraine. Park et al. [20] analyzed epigenetic modifications that allow enhancer activation, in glia, of neuropeptide calcitonin gene-related peptide (CGRP) expression, which has an important role in migraine. *CGRP* gene expression involves an enhancer that is active in neurons, but not active in glia. Park et al. [20] found that DNA methylation and histone deacetylation, well-established mechanisms of epigenetic modifications, induced the *CGRP* gene in glia. Likewise, elevated CGRP levels observed in acute migraineurs could result from these epigenetic mechanisms [21].

Several studies have found elevated plasma homocysteine (Hcy) levels and some variants of enzymes involved in folate metabolism in migraine patients [22]. It would seem that complex epigenetic interactions among folate-related enzymes,

sex, and Hcy levels predict the MA phenotype. Indeed, genetic factors explain only a minor proportion of the variance for both Hcy plasma levels and for predicting MA phenotype [23].

Furthermore, it appears that valproic acid, which is effective in treating migraine, acts through epigenetic mechanisms: valproic acid increases the levels of gamma-aminobutyric acid (by blocking gamma-aminobutyric acid transaminase), modulates the release of excitatory neurotransmitters, and blocks certain calcium channels [21, 24–26].

Additionally, research has found evident epigenetic chromatin modifications in rats 24 h after the induction of CSD [27]. This finding shows that epigenetic mechanisms, in particular DNA methylation and histone acetylation, have roles in the regulation of long-term synaptic plasticity, in the modulation of basal synaptic transmission, and in the balance between excitation and inhibition in various brain regions [28]. Thus the increased neuronal activity in migraine could alter the brain epigenome, promoting subsequent migraine attacks and creating a feed-forward loop and the development of chronic migraine [1].

4.4 Epigenetics, Environmental Factors, and Comorbidities

Environmental factors have an important role in the development of migraine; they may directly trigger migraine attacks or lower the attack threshold by making the brain more susceptible to trigger factors [1]. Some often associated with migraine attacks are stress, hormonal changes, sleep deprivation, and the skipping of meals [29].

Research suggests that migraine is a nervous system disorder characterized by altered synaptic transmission and/or altered neuronal excitability [30], and through epigenetic mechanisms female sex hormones are able to change the balance between inhibitory and excitatory neurotransmission, increasing excitatory neuronal activity [1].

Stress, in particular, may produce long-lasting changes in the threshold for migraine attacks by inducing epigenetic changes throughout the brain [1]. Stress affects neuroendocrine (hypothalamic-pituitary-adrenal [HPA] axis), autonomic, immune, and metabolic functions [31]. Adverse experiences in childhood, in particular abuse, may have long-term effects on the function of the HPA axis and on immune system activity, with these effects being mediated by epigenetic changes [32]. Several studies have found an association between adverse childhood experiences, in particular abuse, and adult pain, including headache [31, 33]. A recent study showed that early life stress changed stress reactivity by reducing resting state functional connectivity between the amygdala and the prefrontal cortex [34]. It has also been shown, by Maizels et al., that patients with headache, have altered functional connectivity between brainstem pain-modulating circuits and limbic centers [35]. To explain the features of the disorder, these authors [35] described a “neurolimbic” pain network model. Thus, stress-related changes in the limbic system, following adverse childhood experiences, could predispose a person to migraine

headaches and psychiatric disorders [31]. Indeed, patients with migraine headaches not only show a high prevalence of childhood abuse, but they also have a greater risk of developing comorbidities, including organic diseases such as vascular, metabolic, and epilepsy disorders, and psychiatric disorders such as depression, increased risk of suicide, anxiety, learning disorders, and post-traumatic stress disorder [24, 25, 36, 37]. Epigenetic mechanisms have been found to play a role in almost all of these comorbid disorders.

Epigenetic regulatory mechanisms are implicated in the neurobiological processes of neural development, homeostasis, stress responses, and neural network function that are responsible for determining complex epileptic disease states [38]. A recent study has reported that epigenetic gene regulation mechanisms, in particular histone acetylation and methylation, are associated with the pathophysiology of mood disorders [39].

Several findings support the hypothesis that changes in DNA methylation profiles may contribute to the biology of anxiety [40]. Recent studies have also shown the involvement of epigenetic factors in the development and progression of cardiovascular disease [41]; in particular, DNA methylation has been associated with changes in cardiovascular-related biomarkers, including Hcy [42] and C-reactive protein [43, 44]. These lines of evidence suggest that causal pathways shared by migraine and its comorbid disorders may be modulated by epigenetic mechanisms [1].

4.5 Conclusion

Current pharmacological treatments are ineffective in about half of migraine headache sufferers [45], while non-pharmacological interventions such as cognitive behavioral therapy may be very effective [46]. Therefore, to identify the mechanisms that predispose to migraine headache, it is necessary to understand the underlying genetics and modifications of the genetics mediated through epigenetics. This understanding could lead to the design of novel migraine drugs with specific molecular targets [1], as well as leading to possible environmental and psychological modifications. Furthermore, once the exact mechanisms underlying the disease are discovered, clinical intervention in patients showing transgenerational epigenetic inheritance could prevent or reduce the severity of migraine headaches at a very early stage of childhood development.

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Chapter 5
Headache, Burden, and Quality of Life

Michelle M. Ernst, Scott W. Powers, and Derya Uluduz

5.1 Introduction

Headache is a frequent health complaint during childhood, with increasing prevalence in adolescence, high likelihood of persisting into adulthood, and rising incidence over the past decades [1, 2]. Given the significant frequency of pediatric headache, it is important to understand the influence of headache on the functioning of children and adolescents because childhood is a time during which important developmental milestones occur via engagement in social and academic settings. This impact can be examined in terms of the specific burden that it creates for children and families as well as in terms of the effect it has on a more holistic view of quality of life (QoL).

M.M. Ernst, Ph.D.
Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

S.W. Powers, Ph.D., A.B.P.P., F.A.H.S. (✉)
Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Headache Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
e-mail: Scott.powers@cchmc.org

D. Uluduz, M.D.
Neurology Department, Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey

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5.2 Burden of Pediatric Headache

Physical symptoms. The physical burden of headache is substantial. For example, a population-based study of 1674 eight to tenth grade German students found that headache sufferers had been experiencing their headaches for an average of 4 years [3]. Average pain intensity ratings for pediatric headache often ranges between 5 and 7 on a scale of 0–10 [3, 4]. Adolescents with chronic migraine reported having approximately 18 headache days per month [4]. Relative to other populations with chronic pain, children with headache report greater pain frequency than children with juvenile idiopathic arthritis and children with sickle cell disease and greater pain intensity than children with juvenile idiopathic arthritis [5]. In addition, children with headache, particularly migraine, may be at greater risk of experiencing pain in other parts of the body [6]. Nausea, photophobia, and phonophobia are common associated features of migraines [7, 8]. Headache is also comorbid with other physical conditions including motion sickness, stomach issues, seizures, persistent nightmares, allergies, and asthma [9]. In addition, the diagnosis of migraine [but not tention-type headache (TTH)] has been shown to be associated with obesity in some studies [10]. Orthostatic issues are also noteworthy and distressing for sufferers of pediatric migraine [11]. Finally, sleep disturbances are also elevated in children with migraine compared with healthy controls [12].

Functional disability. The overall interference of headache in the daily lives of youth has been measured using both generic measures such as the functional disability inventory (FDI; [13]) and measures specific to headache such as the pediatric migraine disability assessment (PedMIDAS; [7]). Using the FDI, patients with headache show greater disability than patients with juvenile idiopathic arthritis or sickle cell anemia [5]. The PedMIDAS was developed based on an adult measure of migraine-related disability and has been shown to be a reliable and valid measurement of childhood migraine disability [7]. It has a grading scale to aid in the interpretation of disability level, and in children presenting for an initial visit to a headache clinic, 58% scored in the mild or moderate categories, and 15% scored in the severe range on the PedMIDAS [14].

School attendance and functioning. Numerous studies have shown that youth with headaches are more frequently absent from school, leave school early, or spend considerable time in the nurse's office compared to children with no headache [3, 6, 15, 16] and compared to children with other types of pain [17]. Headache severity has been found to be related to academic performance [18]. The complicated relationship between school and children may establish a negative cycle, given that teachers may not always respond favorably to children with frequent absences, and perceived "teacher unfairness" has been related to pediatric headache [19].

Psychological suffering. Childhood headache is associated with psychological symptoms. In studies using self-report or parent-report scales, some, but not all, studies indicate that children with headache demonstrate greater overall behavioral and emotional issues relative to healthy normative samples and comparable to or greater than children with other chronic conditions [5, 6, 20–23]. Studies using a

standardized psychiatric interview to establish psychological diagnoses also have mixed findings, with headache sufferers demonstrating comparable [24] or increased [25] prevelance of anxiety or depression relative to the general population. Migraine may have higher association for distress and suicide risk compared to other types of headache and no headache [25], and migraine with aura may confer even greater risk for psychiatric symptoms [26]. The nature of the relationship between headache and distress is unclear—it could be that shared genetic or psychosocial risk factors are implicated in both headache and psychosocial maladjustment, that distress predates migraine, or that the stress associated with the burden of headache leads to emotional or behavioral dysregulation [27].

Health-care utilization. Pediatric headache, particularly migraine, is associated with higher utilization of physical and mental health-care provider visits [3, 23], including emergency services [18]. Migraine is also associated with higher medication utilization [3, 4]. This utilization may result in a high financial burden of headache; while studies have not been conducted for pediatric headache, the yearly cost of adult chronic migraine in the United States is about $1000 [28]. Not only does headache increase costs to families and society due to payment for services, but headache may negatively impact parents' work performance, income, and societal contribution, with parents of children with headache having to leave work to help their child [16].

5.3 Quality of Life and Pediatric Headache

Health-related QoL is a multidimensional approach to understanding the impact of chronic illness and typically involves examining of functioning across physical and psychosocial domains. One of the most well-validated and used QoL measures, the pediatric quality of life inventory (PedsQL; [29]), has been validated in this population [30] and has been utilized to determine that the QoL of youth with headache is lower compared with the PedsQL normative sample of healthy children [30, 31] and children reporting no headache [32–34]. In addition, the QoL of children with headache is similar to that of children with other chronic illnesses such as cancer or arthritis [31]. Studies using headache-specific QoL measures [35, 36] or other general QoL measures [17, 37] have also demonstrated a negative relationship between the presence of headache and QoL.

A number of factors have been shown to be related to QoL in youth with headache. The type of headache has been investigated, with conflicting results such that in one study, migraine correspondended with lower QoL compared with TTH [18], whereas in another study, no difference between migraine and TTH was found [36]. Psychological issues such as anxiety or depression may impact QoL in headache sufferers [38], although Paschoal and colleagues found that the relationship between headache and QoL remained even when controlling for levels of anxiety and depression in the adolescents that they studied [37]. Child coping and family adherence to meaningful routines were positively related to QoL [39]. A higher degree of goal

frustration was associated with worse QoL in one sample of adolescents with headache, with this relationship particularly strong in the group with more frequent headaches [34].

5.4 Clinical Implications

Pediatric headache confers risk of significant burden of illness and reduced quality of life. The specific impact on psychosocial impairment and quality of life for each child is often difficult to predict. Assessment of functioning should consider children's variable cognitive and social development depending on age, and the important issue is to obtain better information from the child and the parent. The use of validated measures for burden (e.g., PedMIDAS) and quality of life (PedsQL) can assist in diagnosing deficits and guiding clinical intervention. Based on the current evidence-based treatment of headache in children and adolescents [40], it is clear that the goal should be both reduction of headache days and headache-related disability. Psychological intervention, particularly cognitive behavioral therapy, is known to be effective in addressing headache, disability, and quality of life outcomes [30, 41, 42] and can be as cost effective as medication [43].

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Chapter 6
Child Abuse and Headache in Children and Adolescents

Gretchen E. Tietjen and Noemi Faedda

6.1 Introduction

Headache is among the most frequent somatic complaints of persons reporting adverse childhood experiences (ACEs) such as childhood maltreatment. Childhood maltreatment is estimated to occur in over 12% of youths prior to the age of 18 years old, based on verified reports of physical, sexual, and psychological abuse [1]. Many cases of abuse are, however, either not reported or not substantiated [2], which may explain why the percentage of adults recalling abusive behaviors in childhood is two- to fourfold higher [3]. In addition to domestic maltreatment and dysfunction, bullying at school and via social media is a prominent source of early life stress [4].

In addition to differences between study sample populations and methods of ascertainment, varying definitions of childhood maltreatment likely contribute to the wide range of prevalence rates of abuse in the literature. Sexual abuse is commonly defined as being touched or made to touch another in a sexual way, being made to view sexual material, or being the victim of attempted or actual intercourse. Physical abuse includes having a parent or household adult physically attack (push, grab, slap, burn, choke, or throw something at one), as well as being hit hard enough to leave marks or cause injury. Emotional or psychological abuse includes being insulted, belittled, humiliated, or threatened with physical violence. There may be a subjective element of feeling unloved, unsupported, or having one's

G.E. Tietjen, M.D. (✉)
Department of Neurology, University of Toledo College of Medicine and Life Sciences, 3000 Arlington Ave. MS 1195, Toledo, OH 43614, USA
e-mail: gretchen.tietjen@utoledo.edu

N. Faedda, Ph.D.
Department of Pediatric and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, 00185 Roma, Italy
e-mail: noemi.faedda@gmail.com

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feelings hurt. Parental loss through divorce, death, and incarceration, as well as witnessing domestic violence, and substance abuse are additional emotionally traumatic experiences, which are less frequently studied. Emotional maltreatment outside the home in the form of bullying by peers has however been the subject of considerable interest in recent years, and there are multiple investigations of bullying and health conditions. Bullying is characterized by unwanted aggressive behavior, which may be physical, verbal, relational (e.g., efforts to harm the reputation or relationships of the targeted youth), and damage to property. There is usually an imbalance of power and repetition of behaviors. Bullying may be direct, with the targeted youth present, or indirect, such as spreading damaging rumors about the targeted youth. Surveys of bullying in North America and Europe showed an average prevalence of 16% but a range across countries spanning 5–40% [5]. Recent statistics from the USA show a 20% prevalence in high school-age adolescents [4]. This chapter examines the prevalence of childhood maltreatment in children and adolescents with headache; the evidence for the effects of maltreatment on brain development, structure, and function; the putative mechanisms by which maltreatment may be linked to headache; and treatment options in those suffering childhood abuse and headache.

6.2 Prevalence of Childhood Maltreatment in Headache Disorders

Over the past 25 years, there is accumulating evidence of an association of childhood maltreatment with headache in adults [6–13] and in children and adolescents [5, 14–19] (Tables 6.1 and 6.2). In three large population-based studies investigating the link to headache in adults [11–13], prevalence of childhood sexual abuse ranged from 10 to 21%, physical abuse from 26 to 28%, emotional abuse from 11 to 22%, and witnessed domestic violence from 8 to 13%. These study samples differed in proportion of women (54–79%) and of persons with headaches and migraines (11–85%), but mean age of the participants in these studies (47–56 years old) was similar. Variables potentially influencing the strength of the association include type of adverse experience, extent of abuse (frequency, duration, number of abuse types), age at occurrence and at interview, and sex of the abused. Most studies have focused on physical and/or sexual abuse [6–10, 14–17], but more recent studies examining the relationship of maltreatment to headache included other types of ACEs, such as emotional abuse [11, 12], witnessing parental violence [11, 13], and bullying [18]. Victims of emotional abuse may lack outer physical scars, but the stronger association with headache and migraine (i.e., odds of developing headache increase by about 50%) suggests substantial physiological changes nonetheless [11, 12]. Emotional abuse is the ACE most likely to overlap with other types of abuse, at least in the headache population [19], and the case has been made that all types of abuse involve a component of emotional abuse [20].

Table 6.1 Association of childhood maltreatment and headache in adults

Authors, year of publication	Study design	Sample	Headache diagnosis	Childhood maltreatment history	Association of headache and maltreatment	Limitations
Felitti (1991) [6]	Cross-sectional survey	231 adults, HMO sample	No specific headache diagnoses	Childhood sexual abuse	Chronic headache twice as common in abused	Retrospective Self-report Small sample size No specific headache diagnosis
McCauley et al. (1997) [7]	Cross-sectional survey	1931 women, multicenter primary care sample	No specific headache diagnoses	Childhood physical and sexual abuse	Headache more common in abused, prevalence ratio = 2.2, 95% CI 1.7–2.8	Retrospective Self-report—only 2 screening questions on abuse No specific headache diagnosis
Golding (1999) [8]	Meta-analysis	7502 pooled community-based sample of youth and adults	No specific headache diagnoses	Childhood sexual abuse	Headache more common in abused, OR = 1.9, 95% CI 1.2–3.0	Retrospective Self-report No specific headache diagnosis
Walker et al. (1999) [9]	Cross-sectional retrospective survey	1225 women, HMO random sample	No specific headache diagnoses	Sexual abuse	HA more common in abused, OR = 1.3, 95% CI 1.1–1.6	Retrospective Self-report—used validated childhood trauma questionnaire Possible response bias No specific headache diagnosis
Goodwin et al. (2003) [10]	Cross-sectional retrospective survey	3032 adults, community sample	Migraine	Childhood physical abuse	Migraine more common in frequently abused, OR = 2.7, 95% CI 1.2–5.8	Retrospective Self-report

(continued)

Table 6.1 (continued)

Authors, year of publication	Study design	Sample	Headache diagnosis	Childhood maltreatment history	Association of headache and maltreatment	Limitations
Anda et al. (2011) [11]	Cross-sectional survey	17,337 adults in HMO in San Diego, CA	Frequent headache	Childhood abuse, including emotional, physical, and sexual abuse plus other exposures per ACE questionnaire	Frequent headaches were associated with emotional abuse (OR = 1.6, 95% CI 1.4–1.7), physical abuse (OR = 1.4, 95% CI 1.3–1.5), and sexual abuse OR = 1.3, 95% CI 1.1–1.4)	Retrospective Self-report
Tietjen et al. (2015) [12]	Cross-sectional survey"	9734 adults, nationally representative sample	Migraine, episodic tension-type headache per ICHD2	Emotional abuse, emotional neglect. Sexual abuse modified CTQ	Migraine was associated with emotional abuse (OR)	Retrospective Self-report No data on physical abuse No headache-free controls
Brennenstuhl et al. (2015) [13]	Cross-sectional survey	22,996 adults, nationally representative sample	Migraine	Sexual abuse, physical abuse, witnessed domestic violence	Migraine was associated with sexual abuse, physical abuse, and witnessed domestic violence	Retrospective Self-report No data on emotional abuse

Table 6.2 Childhood maltreatment and adverse life events in children and adolescents with headache

Authors, year of publication	Study design	Sample	Headache diagnosis	Childhood maltreatment history	Association of headache and maltreatment	Limitations
Juang et al. (2004) [14]	Cross-sectional survey	4645 adolescents, 13–15 years old, community based	Chronic daily headache (CDH)	Physical abuse, neglect	Especially physical abuse (10%) is more frequent in the CDH group	Retrospective
						Small sample
						No use of ICHD2 criteria
Due et al. (2005) [5]	International cross-sectional survey	123,227 students 11, 13, and 15 years of age from schools in 28 countries in Europe and North America	Headache	Bullying victimization	The risk of high symptom load increased with increasing exposure to bullying in all countries. In particular headache:	The translation of questions
					Boys: OR 1.39 (95% CI 1.30–1.47) for bullied sometimes and 1.91 (95% CI 1.78–2.05) for bullied weekly	With more than 20 different languages, there may be an information bias
					Girls: OR 1.43 (95% CI 1.35–1.51) for bullied sometimes and 1.83 (95% CI 1.70–1.97) for bullied weekly	Self-report
						No specific headache diagnosis
Fuh et al. (2010) [15]		3955 adolescents, 13–15 years old, community	Migraine or probable migraine	Physical abuse	Physical maltreatment is associated with migraine, and it may be related to an increase in the frequency and intensity of attacks	Use self-report
						Investigated the physical abuse by being beaten only
Zafar et al. (2012) [16]	Cross-sectional survey	122 children between 10 and 17 years of age	Chronic daily headache	Physical and sexual abuse	Children with a history of abuse reported higher headache frequency and intensity and scored in the clinically significant range of impairment on the PedsQL	Formal documentation of abuse records was not available
						Small sample size

(continued)

Table 6.2 (continued)

Authors, year of publication	Study design	Sample	Headache diagnosis	Childhood maltreatment history	Association of headache and maltreatment	Limitations
Genizi et al. (2014) [17]	Cross-sectional survey	Adolescents between the ages of 15 and 16 years	No specific headache diagnoses	Physical and sexual abuse	Jewish girls who were physically abused during childhood had a higher prevalence of frequent headaches	No use IHS criteria
					Jewish students who reported being sexually abused had higher headache prevalence	No specific headache diagnosis
Gini et al. (2014) [18]	Meta-analysis	20 studies, including a total of 173,775 participants	No specific headache diagnoses	Bullying victimization	Fourteen studies reported data on the prevalence of headache, which was on average 32.7% (range: 9.1–71.7%) in the bullied group and 19.1% (range: 5.3–46.1%) in the control group	The majority of studies: – Self-report – Do not report separate effects for different ethnic groups and information on the type of headache – Individuals cannot be randomly allocated to groups so the influence of confounding variables cannot be fully evaluated

Retrospective investigation of the health effects of childhood trauma in adults involves self-report of ACEs years after the event and may be colored by the psychologically traumatizing nature of the event, the time elapsed between the event and the interview, the stigma attached to being a victim, and the current psychological state [21]. Studies of the effects of abuse in children and adolescents may lessen recall bias, but it is more difficult to identify victims of sexual, physical, and psychological abuse, especially when the perpetrator is a family member. Children may be reluctant to report accurate information about abuse because of fear of punishment or rejection.

To our knowledge, only four studies have assessed the relationship between headaches and physical and sexual abuse in children and adolescents [14–17] (Table 6.2). Juang et al. [14] compared childhood adversity in cases of chronic daily headache (CDH) between 13 and 15 years old and their age- and sex-matched controls among students in Taiwan, showing that childhood adversities, specifically physical abuse (10%) and parental divorce (17%), are more frequent in the CDH group. Fuh et al. [15] enrolled 3955 students, ages 13–15, to complete a validated headache questionnaire using International Classification of Headache Disorders (ICHD) 2 criteria for headache diagnosis [22], the Adolescent Depression Inventory (ADI), and a classification of physical maltreatment. A higher frequency of physical maltreatment was associated with a higher likelihood of migraine diagnosis. Among the students diagnosed with migraine, those reporting physical maltreatment had higher frequency of headaches and a greater proportion of severe headaches. Zafar et al. [16] evaluated the relationship between abuse and headache in headache specialty clinic patients between 10 and 17 years of age with chronic daily headache. From the sample of 122 patients, 8 (6.5%) reported a history of abuse (3 physical abuse, 4 sexual abuse, and 1 both physical and sexual abuse). Although the small sample size limited statistical power, children with a history of abuse reported higher headache frequency and intensity and scored in the clinically significant range of impairment on the pediatric measure of quality of life. Genizi et al. [17] presented a self-administered questionnaire to 2088 Jewish and Arab students, between the ages of 15 and 16 years. They found that Jewish girls who were physically abused during childhood had a higher prevalence of frequent headaches (55% vs. 33%) and Jewish students who reported being sexually abused had higher headache prevalence as well (44.4% vs. 27.3%).

We are aware of no studies of headache in children and adolescents reporting emotional abuse within the family, but there are numerous reports showing as association of somatic symptoms, including headache, in youths who have been bullied, which is an emotionally traumatizing event [5, 18] (Table 6.2).

6.3 Effects of Childhood Maltreatment on Brain Development

6.3.1 Structural and Functional Changes

Structural changes. In morphometric MRI studies of adults who report being maltreated as children, there were smaller hippocampal volumes as well as decreased thickness of the amygdala, anterior cortex cinguli, orbitofrontal cortex (OFC), dorsolateral and ventromedial prefrontal cortex, and corpus callosum [23]. MRIs of abused children showed reduced cortical thickness of the ventral anterior cingulate, superior frontal gyrus, and the OFC, as well as of the left middle temporal area and lingual gyrus [24]. Structural brain MRI studies in young women with a history of childhood sexual abuse showed volume reductions in the hippocampus at ages 3–5 years and 11–13 years, in the corpus callosum at ages 9–10 years, and in the frontal cortex at ages 14–16 years, suggesting time-sensitive responses to abuse [25]. It is hypothesized that structural changes in the limbic system are due to prolonged elevation of glucocorticoids and in turn lead to dysregulation of the HPA axis by interfering with the tightly controlled feedback mechanisms. Of note, the radiological profile described in abused persons is similar to that described in migraineurs. A 2015 meta-analysis of radiological studies from adults found that, compared to healthy controls, those with migraine had decreased gray matter thickness in the posterior insular–opercular regions, the prefrontal cortex, and the anterior cingulate cortex [26]. A recent single-center case-control MRI study of migraine found cortical thinning in areas participating in affective and cognitive aspects of pain processing (anterior cingulate cortex, medial orbital, frontal gyrus, entorhinal cortex, and pars triangularis) as well as in areas involved in multisensory integration (temporal pole and superior temporal lobe) [27]. Whether structural changes from abuse predispose to migraine or whether structural changes are a result of migraine progression is uncertain.

Functional changes. Structural limbic system changes related to alterations in neural architecture may affect brain function [28]. In a functional magnetic resonance imaging study of young men, emotional abuse predicted reduced resting-state functional connectivity between the right amygdala, which modulates pain activity and perception, and pregenual anterior cingulate cortex and predicted elevated state anxiety after acute psychosocial stress [29]. A functional study of persons with migraine showed a decrease in resting-state connectivity between the amygdala and the periaqueductal gray matter, an important site in both ascending pain transmission and the descending pain inhibitory system, suggesting migraine might be modeled as a dysfunctional "neurolimbic" pain network [30, 31].

6.3.2 Effects on Cognitive and Neuropsychology Development

Abuse-related structural and functional changes as seen on neuroimaging studies are likely related to the large impact of abuse on cognitive and neuropsychological functions (Table 6.3). Childhood maltreatment, including neglect, as well as

Table 6.3 Negative effects of child maltreatment on brain structure

Brain structure	Outcome	Function	Publication
Hippocampus	Reduced volume	Memory and learning	Riem et al. (2015) [87]; McCrory et al. (2010) [88]; Wilson et al. (2011) [46]
Prefrontal cortex	Smaller size	Behavior, cognition, and emotion regulation	Van Harmelen et al. (2010) [89]
Corpus callosum	Reduced volume	Interhemispheric communication, arousal, emotion, and cognitive abilities	Teicher and Samson (2016) [90]
Amygdala	Overactivity	Detecting fear and preparing body to defend or escape (fight or flight reaction)	Teicher and Samson (2016) [90]
Orbitofrontal cortex	Reduced volume	Emotion and social regulation	Hanson et al. (2010) [91]; De Brito et al. (2013) [24]
Cerebellum	Reduced volume	Executive function and motor abilities	McCrory et al. (2010) [88]
Cortisol levels	Altered cortisol level	Reaction to stressors	Bruce et al. (2009) [92]; Gonzalez (2013) [93]
Catecholamines	Impaired concentrations of noradrenaline and dopamine	Stress regulation and executive functions	Glaser (2000) [86]; De Bellis et al. (2011) [37]

physical, sexual, and psychological abuse, alters cognitive–behavioral, socio-emotional, and physical development of child with effects that persist into adulthood. Font and Berger [32] suggested that for children's social–emotional development, the particular type of maltreatment may be less important than whether or not a child experienced any form of maltreatment, whereas cognitive development may be more influenced by specific maltreatment subtypes.

6.3.2.1 Language

Language can be defined as a socially shared code or conventional system for representing concepts through the use of arbitrary symbols and rule-governed combinations of those symbols [33] and involves several abilities like encoding, transmitting, and interpreting a message. The child's brain is physiologically predisposed to respond to the sound of words; when a young child hears speech, a neural systems in his brain, specific for speech and language, is activated [34]. The environment plays an important role in the process of learning language. If the appropriate exposure does not occur, neural networks that allow the child to realize his/her genetic potential and to learn language rapidly and effortlessly may be discarded [35].

A growing body of knowledge shows that abused children do not globally reach the level of standard developmental in receptive, expressive, and pragmatic language [36–39], and it seems that language development is compromised, regardless of whether the child is exposed to physical abuse or neglect. In fact, pragmatic difficulties are more common in neglected children because of difficulties in parent–child interactions and the failure of the parent to provide adequate stimulation for development and to meet the child's physical and emotional needs [40–42]. Abused children show generalized language deficits, difficulty using language to articulate needs and feelings, difficulty conveying abstraction, and difficulty sustaining coherent narratives [43].

6.3.2.2 Attention and Executive Function

Executive functioning generally includes three components: working memory (being able to hold, manipulate, and process information over a short period of time), inhibitory control (filtering thoughts and impulses and resisting interference from irrelevant stimuli), and cognitive or mental flexibility (adapting to different situations and thinking about multiple mental state simultaneously) [35, 44]. Maltreatment may cause deficit in several regions that regulate such functions [44, 45]. The prefrontal cortex is at particular risk since it is still undergoing neurogenesis and synaptic pruning during childhood and adolescence [46]. Maltreated children performed more poorly than controls on measures of attention and executive functioning [47]. Maltreated adolescents also demonstrated impaired executive functioning skills, including executive-loaded working memory, fluency, and inhibition, but switching (verbal and nonverbal) was protected or even enhanced, perhaps related to increased vigilance for signs of danger [48].

6.3.2.3 Memory and Learning

A growing body of research found that maltreated children have reduced volume of and functional deficits in the hippocampus, a brain area essential for efficient memory and learning capabilities. Abuse-related damage in the temporolimbic structures leads to various learning problems [49]. The frontal lobe, involved in encoding episodic memories [50], is often impaired in abused children, leading to distorted or false memories, so that children recall the incorrect source, context, or sequence of information or events [49].

A history of childhood trauma is associated with overgeneral memory, i.e., a tendency to report memories characterized by generic descriptions, such as descriptions of extended events that lack spatial and temporal details [51]. Children, who have experienced sexual and physical abuse or neglect, can use overgeneral memory like a functional emotion regulation strategy that protects them from memory of the traumatic event [51]. Short-term verbal memory [52], memory and response inhibition [53], and verbal declarative memory [54] are common deficits in abused children and in adults with a history of abuse in early infancy.

6.4 Mechanisms Linking Maltreatment and Headache

The hypothalamic–pituitary–adrenal (HPA) axis plays an important role in the physiological stress response, maintaining homeostatic balance through negative feedback mechanisms. These mechanisms are tightly regulated by mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) in the limbic system (particularly the hippocampus) as well as by GR in the PVN and anterior pituitary. Chronic stress, such as which occurs with childhood maltreatment, may lead to loss of negative feedback control and alterations in stress responsivity. We know from animal studies that prolonged elevation of glucocorticoids leads to dendritic remodeling of limbic system structures, with the most prominent changes being atrophy of the hippocampus [55] and hypertrophy of the amygdala [56, 57]. These alterations in neural architecture may, in turn, affect brain function [28]. Stress responses are also mediated through systems involving endocannabinoids, monoamine neurotransmitters, oxytocin, and inflammation. Early life stress reduces endocannabinoid signaling and reduces serotonin levels in the amygdala and nucleus accumbens [58]. Both of these changes may predispose to painful conditions, such as migraine, fibromyalgia, irritable bowel, and interstitial cystitis [59]. Oxytocin, a hypothalamic neuropeptide, modulates the HPA stress axis, and early life stress may be a factor in the nature of its effects. For instance, emotional abuse in childhood was associated with increased amygdala–hippocampal connectivity in response to psychosocial stress. This connectivity was, however, moderated after administration of intranasal oxytocin [60]. The immune system may also play a role in linking stress and migraine, as adults abused as children have an elevated basal rate of inflammation [61], a process implicated in the pathophysiology of migraine [62]. Emotional abuse is associated with psychosocial stress-induced increases in amygdala–hippocampal connectivity, which was moderated after intranasal OXT, concurrent with negative cortisol response.

There is evidence that certain polymorphisms within genes that code for proteins affecting HPA axis function have the potential to predict vulnerability to environmental stressors, including early adverse experiences. This is referred to as a gene–environment interaction. HPA axis-related genes include *CRHR1*, *NR3 C1* (a glucocorticoid receptor [GR]), *NR3C2* (a mineralocorticoid receptor [MR]), and *FKBP5* (a GR regulator), which are highly expressed throughout the limbic system. These genes have all been studied in childhood maltreatment but not in migraine. Also of interest are polymorphisms of the serotonin transporter (5HTT) gene, which is purported to predict major depressive disorders in association with childhood maltreatment [63]. The gene–environment interaction of childhood abuse and migraine has not been studied.

Epigenetics refers to processes unrelated to alteration in the DNA sequence, which up- or downregulate gene expression. These processes include DNA methylation, posttranslational histone modifications, and gene regulation by microRNAs. Early life stress leads to epigenetic modifications, which affect neurobiology and disease vulnerability throughout the life span and even across generations.

In animal models stress-induced epigenetic changes have been shown to occur in genes directly impacting HPA axis function (*NR3C1*, *FKBP5*, *Crh*, *Avp*), as well as those genes regulating functions outside the HPA axis, including *5-HTT*, *GAD1*, *ESR1*, and *BDNF* [64]. Human studies have focused on genes for the glucocorticoid receptor and serotonin transporter. The impact of epigenetics on the pathophysiology of migraine remains largely unknown, but it is intriguing that two migraine prophylaxis agents, valproic acid and topiramate, inhibit HDAC and reverse epigenetic changes [65].

6.5 Management in Children with Maltreatment and Headaches

Several studies have shown that childhood adversity negatively affects non-pharmacological and pharmacological treatment outcomes, such as time to remission and symptom recurrence [66, 67]. Headache treatment in a child who has suffered abuse is complicated by the increased risk of developing depression, anxiety, personality disorder, and post-traumatic stress disorder, attempting suicide, and abusing drugs or alcohol [68]. Studies comparing the effects of pharmacotherapy and psychotherapy on the treatment of child maltreatment have had mixed results [69, 70], but the benefits of the psychotherapeutic approach for abused children are widely recognized. Cognitive behavioral therapy (CBT), which encompasses a variety of approaches designed to alter thinking and behavior, improves both headache and psychological well-being in abused children. Trauma-focused cognitive behavioral therapy (TF-CBT), an evidence-based psychotherapy for the treatment of children and adolescents (ages 3–18 years old) who have experienced adverse events, is particularly beneficial [71, 72]. There are several components of TF-CBT:

- Psychoeducation and parenting skills
- Relaxation
- Affective expression and regulation
- Cognitive coping
- Trauma narrative development and processing
- In vivo gradual exposure
- Conjoint parent–child sessions
- Enhancing safety and future development.

There is strong evidence supporting the efficacy of exposure therapy for children who have been abused and neglected [38, 73]. Exposure therapy facilitates the processing of trauma and helps patients react better to memory or cue of the event. This therapy involves confronting feared, but not dangerous, situations associated with a trauma and imagining exposure to the trauma [73]. Another effective practice is to

have a patient write about the trauma, and in the case of young patients, playing and drawing may help them express their emotions and describe the traumatic event. These exercises have been tested among patients with chronic medical illness and history of abuse, and it was found that expressive writing significantly improved health [74–77].

It is critical to take adherence to headache therapy into account, especially in abused children. A strong therapeutic alliance, defined as an emotional bond between client and therapist [78], is a cornerstone for the success of the treatment. A poor therapeutic alliance leads to nonadherence to treatment and affects efficacy, severity of the disorder, and the risk of relapse [79, 80]. Children who have been maltreated by an adult may form a neural template which signals to the child to be fearful of all adults, including the clinician [34]. In cases where the perpetrator is a relative, children often find it difficult to talk about what happened, and also they might hesitate to disclose accurate information regarding their abuse due to fear of parents' punishment or rejection.

In recent years behavioral treatment approaches, including CBT, have been shown to be as effective as pharmacological treatment with positive effect on severity, frequency, and recurrence of the headache disorder in children and adolescents [81, 82]. Behavioral therapy improves adherence to headache treatment, and it has a positive impact on the child's or adolescent's quality of life, disability, and emotional functioning [83]. For these characteristics the behavioral treatment could be considered the first-line therapy in the management of children with headache who have suffered from sexual, emotional abuse, or neglect.

It is very important that cases of child maltreatment are detected early and that intervention is early and effective to minimize the consequences for the child and avoid the risk that pain *becomes chronic* [84]. For some, headache or other somatic complaints may be an "alarm bell" indicating an uncomfortable situation in the child's environment.

6.6 Conclusion

Despite growing evidence of an association between maltreatment and headache, the optimal management of headache in children who have been abused is seldom addressed. Most doctors do not routinely screen headache patients for abuse [85], so many cases are not reported, and treatments may not be appropriate for child's physical and emotional needs. However, since many factors (including age, sex, genetics, and support systems) affect the response to adverse childhood events, it is not possible to accurately predict the outcome of these adverse experiences [86]. More research is needed to identify or develop efficacious treatments for headaches and other conditions which are common in children and adults suffering from abuse and neglect.

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Chapter 7
Childhood Episodic Syndromes That May Be Associated with Migraine

Victoria Elisa Rinaldi, Amy A. Gelfand, and Luigi Titomanlio

7.1 Background

Headache is one of the most common pain conditions in children and adolescents visiting a paediatrician [1], and migraine is the most common cause of primary headache in childhood [2], followed by tension headache and cluster headache.

Headache is a frequent reason for consultation at the emergency department (ED), and triage systems have been developed in order to quickly identify urgent or nonurgent patients; the differential diagnosis in these children includes primary headache disorders such as migraine and secondary headache aetiologies such as trauma, infection, inflammatory, vascular, neoplastic or epileptic disorders [3]. As in adults, migraine in children can be divided into two major subtypes: migraine without aura and migraine with aura, which is characterized by the presence of focal neurological symptoms that usually precede or sometimes accompany the headache.

Tension-type headaches (TTH) are the second most common cause of primary headache in children and adolescents [4]. A transformation between TTH and migraine has been reported [5]; however it is also possible that with growth and development, children's ability to explain their symptoms improves and clinicians are able to recognize that what they have been describing is migraine rather than tension-type headache.

V.E. Rinaldi • L. Titomanlio (✉)
Migraine and Neurovascular Diseases Clinic, Paris Diderot-Sorbonne-Paris Cité University, Robert Debré Hospital, 48 Boulevard Serurier, 75019 Paris, France
e-mail: luigi.titomanlio@rdb.aphp.fr

A.A. Gelfand
Pediatric Headache, Department of Neurology, University of California San Francisco, San Francisco, CA, USA

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Trigeminal autonomic cephalalgias are quite rare in the paediatric population [6].

The International Classification of Headache Disorders-III beta (ICHD-III beta) [7] has developed diagnostic criteria for paediatric migraine and for migraine equivalents. These were previously called "Childhood Periodic Syndromes" but are now defined as "Episodic Syndromes that may be associated with Migraine". They include cyclical vomiting syndrome, abdominal migraine, benign paroxysmal vertigo and benign paroxysmal torticollis [8]. In the latest ICHD-III beta classification, infantile colic, alternating hemiplegia of childhood and vestibular migraine were added in appendix and also classified among the "Episodic Syndromes that may be associated with Migraine". The hallmark of these syndromes is the recurrent episodic nature of the events that may occur in the absence of headache and that may precede the development of typical migraine manifestations by several years [9]. Although historically noted to occur only in childhood, they may also occur in adults. Additional conditions that may also occur in these patients include episodes of motion sickness and periodic sleep disorders including sleepwalking, sleep talking, night terrors and bruxism.

7.2 Classification and Current State of Clinical Practice in Episodic Syndromes That May Be Associated with Migraine

Childhood periodic syndromes are characterized by episodic reversible and stereotyped attacks [9]. There are many similar features between children with periodic syndromes and children with migraine, including demographic factors, triggers and relieving factors and accompanying neurologic, gastrointestinal and vasomotor symptoms [10]. Children with these disorders are neurologically normal and healthy between attacks but they often have a family history of migraine and they may eventually develop migraine in adolescence or adulthood.

The prevalence of the episodic syndromes is believed to be 1.8–4% in the paediatric population [11], and in patients with known migraine, it is as high as 9.8%. Further evidences for these periodic disorders being early-life manifestations of migraine genetics include an association between benign paroxysmal torticollis and the CACNA1A gene of familial hemiplegic migraine [12] and the observed benefit seen with certain migraine-specific drugs (e.g. triptans and dihydroergotamine) in some episodic syndromes [13, 14].

The diagnosis of episodic syndromes is one of exclusion and requires a careful history and a thorough neurologic and general physical examination. Additional neurodiagnostic studies may be required to exclude other diseases such as epilepsy, metabolic disorders, ischemic events or psychological disorders.

7.2.1 Cyclic Vomiting Syndrome (ICHD-III Beta 1.6.1.1)

This syndrome is characterized by self-limited, recurrent episodes of severe nausea and vomiting, interspersed with completely symptom-free periods in otherwise healthy children [9]. Patients usually experience a stereotypical pattern of events consisting of a prodromal phase followed by an emetic and then a recovery phase [15]. The timing of the episodes is characteristically predictable. During the prodromal phase, children experience worsening nausea and autonomic dysfunction with decreased muscle tone, pallor, lethargy and apathy. These symptoms last a few hours and are followed by intense vomiting which can often be bilious, with persistent nausea, retching, anorexia, drooling, abdominal pain, headache, pallor, photophobia and phonophobia. Attacks last typically several hours to several days [16] (mean duration of 3.4 days) and then the child returns to normal health. The onset of cyclic vomiting syndrome generally occurs before 6 years of age, and the median age for resolution of vomiting episodes is 10 years of age [17], although it has been reported to occur in all age groups from 6 months of age to adulthood [11]. Seventy-five percent of these affected children will develop migraine by the age of 18 years [15].

7.2.2 Abdominal Migraine (ICHD-III Beta 1.6.1.2)

Abdominal migraine is characterized by recurrent episodes of abdominal pain lasting from 2 to 72 h and accompanied by dysautonomic signs such as pallor, dark shadows under the eyes, flushing, anorexia and vomiting [18]. Affected children experience a dull or colicky pain generally localized in periumbilical region, but sometimes the pain can be poorly localized. Pain severity is generally high enough to interfere with normal daily activities. The onset of abdominal migraine occurs at the age of 7 years with a peak prevalence at 10 years of age [19]; according to some studies, this episodic syndrome could persist into adult life and evolve into migraine. Sometimes, a preceding aura occurs with visual disturbance, flashing lights, numbness or a tingling sensation, slurred speech or muscle weakness. Prodromal symptoms such as behaviour and mood changes or anorexia can also sometimes precede the onset of abdominal pain. Headache is usually absent during the attacks; if head pain during attacks is present, a diagnosis of migraine with or without aura should be considered [18]. Both acute and preventative migraine therapies have been reported to be effective in the treatment of abdominal migraine [10, 13, 14]. General treatment includes avoidance of triggers, acute treatment strategies, non-pharmacologic treatment and, when needed, pharmacologic management. There is a small, randomized placebo-controlled trial supporting the efficacy of pizotifen as a preventive for abdominal migraine [20].

7.2.3 Benign Paroxysmal Vertigo of Childhood (ICHD-III Beta 1.6.2)

This disorder is characterized by recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously, in otherwise healthy children. The onset is characterized by sudden anxiety and fear followed by attempting not to fall. Vertigo may be accompanied by nausea, vomiting, nystagmus, pallor, sweating, photophobia and phonophobia. The onset is between the age of 2 and 4 years, and the frequency of attacks varies from once a day to once every 1–3 months [21]. Young children with vertigo may not be able to describe vertiginous symptoms, but parental observation of episodic periods of unsteadiness may be interpreted as vertigo in the younger children. Typically, these patients have a positive family history for migraine and a positive personal history for motion sickness. Some authors suggest that benign paroxysmal vertigo may be an early-onset variant of migraine with brainstem aura [22], but this hypothesis requires further study. Moreover, it is important to exclude posterior fossa tumours, seizures and vestibular disorders in these patients.

7.2.4 Benign Paroxysmal Torticollis of Infancy (ICHD-III Beta 1.6.3)

This disorder is characterized by recurrent stereotyped episodes of head tilting to one side, sometimes with a slight rotation, that remits spontaneously and that appears commonly around the age of 2–6 months [23]. These paroxysmal attacks can be accompanied by vomiting, pallor, irritability, malaise and ataxia [7]. Torticollis is usually secondary to cervical dystonia though other areas can also be involved such as pelvic asymmetrical posturing [23]. Typically the frequency and duration of the attacks reduces gradually as the child grows older with resolution typically around age 3 [23].

7.2.5 Infant Colic (ICHD-III Beta A1.6.4)

Infantile colic affects 5–19% of babies during their first months of life, and it is characterized by inconsolable crying and fussing for more than 3 h per day, for more than 3 days per week and for more than 3 weeks in an otherwise healthy and well-fed infant [24].

A relationship between infantile colic and migraine was firstly documented in 2001 [25] and subsequently confirmed with a multicentre case-control study [26], suggesting that colic may represent one of the earliest clinical manifestations of migraine (Fig. 7.1). A prospective cohort study has demonstrated that infants with colic are more likely to develop migraine without aura, but not migraine with aura,

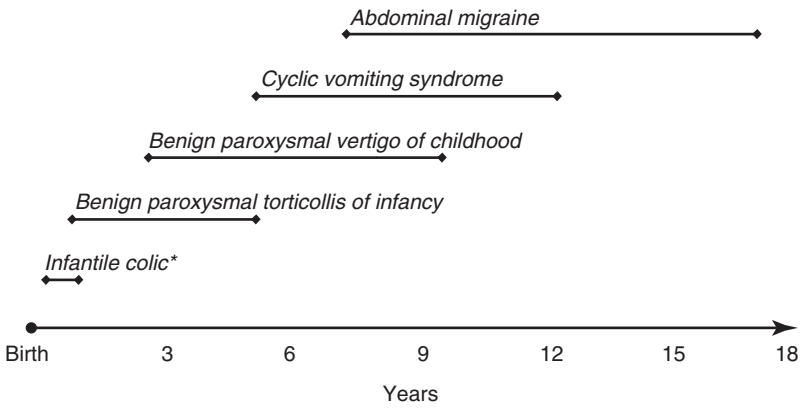

Fig. 7.1 Age-related expression of childhood episodic syndromes common precursors of migraine. *Infantile colic is actually considered as an episodic syndrome that may be associated with migraine (*From Spiri D et al. Ital J Pediatr. 2014;40:92*)

by their late adolescence [27]. Additional prospective cohort studies are needed to further detail the natural history of children with infant colic, in particular whether they are more likely to develop other childhood episodic syndromes as they grow.

Educating parents about the association between infant colic and migraine may help them understand why their baby is crying so much, hopefully minimizing the risk of Shaken Baby Syndrome [28–30] and alleviating maternal guilt or concern about diet and breast milk-related causes [31]. Effective treatments for infant colic are still lacking, though given the very young age of these infants, caution is required and migraine-specific agents have not been studied for safety in this age group. Behavioural interventions such as encouraging parents to decrease light and sound stimulation during periods of crying would be safe, and there is preliminary evidence that such strategies can help soothe colicky crying [32].

7.2.6 Alternating Hemiplegia of Childhood (AHC) (ICHD-III Beta A1.6.5)

This rare condition consists of attacks of hemiplegia that alternates sides. It is less clearly a migraine-associated disorder as while in the other episodic syndromes, children are normal between attacks, in AHC children may have a progressive encephalopathy and intellectual impairment [7]. It is thought to be a neurodegenerative disorder and in some cases may be related to a mutation in the ATP1A3 gene [7]. AHC can be either familiar or sporadic. An attack usually begins with a typical aura, often consisting of hemi-sensory symptoms, followed by motor symptoms. Occasionally drowsiness, dysarthria, aphasia and confusion may follow. Symptoms usually resolve in 12–24 h and maybe followed by headache [33]. Serious sequelae including stroke may occur.

7.2.7 Vestibular Migraine (ICHD-III Beta A1.6.6)

Previously called "Migraine-associated vertigo or dizziness" and "migrainous vertigo", this clinical entity requires that the patient meets the ICHD criteria for migraine and that migraine features (migraine headache, photophobia, phonophobia or visual aura) occur within at least half an hour of the episodes of vertigo [34]. In contrast, benign paroxysmal vertigo of childhood episodes is typically purely vertiginous in the absence of other migraine symptoms and usually resolves by age 6, while vestibular migraine can occur at any age. Duration of episodes is variable [7]. Some might argue that vertigo is such a common complaint in migraineurs that there is not necessarily a reason to distinguish those who have attacks with prominent vertigo from other with migraine, as, for example, we would not say those with prominent photophobia have "photophobic migraine".

7.3 Pathogenetic Hypothesis, Treatment and Remaining Concerns in Episodic Syndromes

Our expanding knowledge of migraine genetics and pathophysiology will hopefully lead to increased understanding of the episodic syndromes as well [9]. As the enteric nervous system and the central nervous system (CNS) may exert direct effects on each other and that they are derived from the same embryologic tissues [35], it has been hypothesized that an increased arousal in the CNS in response to triggers contributes to the pathogenesis of abdominal migraine determining a release of neuropeptides that lead to dysregulation of the gastrointestinal system [9]. This pathogenic hypothesis could also explain the association between infantile colic and migraine, though there is no direct evidence that colicky infants are experiencing abdominal discomfort. Cyclic vomiting syndrome is also believed by some to be a brain-gut disorder involving neuroendocrine pathways in genetically predisposed individuals [36]. Mutations in the CACNA1A and PRRT2 genes, which are associated with familiar hemiplegic migraine, have been reported in some patients with benign paroxysmal torticollis and benign paroxysmal vertigo [12, 13, 37], thus confirming their link to migraine.

To the present day, no clearly effective treatments have been identified for infant colic although positive results have been obtained by decreasing the infant's level of stimulation during acute episodes as it is observed in migraine [38]. There are also no known effective treatments for benign paroxysmal torticollis and benign paroxysmal vertigo, though several cases of benign paroxysmal torticollis being treated successfully with topiramate have been reported [39]. Cyclic vomiting syndrome can be treated acutely with rehydration and antiemetics. There is also uncontrolled evidence that the neurokinin-1 receptor antagonist aprepitant is effective as both an acute and preventive treatment for cyclic vomiting syndrome [40]. Abdominal migraine may respond to triptans and dihydroergotamine, and preventive treatment

with pizotifen, flunarizine or other migraine-preventive agents may be helpful if attacks are frequent or long-lasting [13, 14, 20].

Children with frequents attacks of these episodic syndromes can be very limited in daytime activities; therefore disability and quality of life in these children should be assessed using validated scales as they are in children with migraine [41]. The expanding knowledge on migraine pathophysiology may be applicable to childhood episodic syndromes as well. Familiarity with the characteristics and evolution of these syndromes may help paediatricians make a correct diagnosis, avoid unnecessary or invasive medical testing in children and facilitate timely delivery of appropriate treatment.

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Chapter 8
Comorbidity with Attention Deficit Hyperactivity Disorder

Marco A. Arruda and Marcelo Eduardo Bigal

8.1 Background

Since some primary headaches and attention deficit hyperactivity disorder (ADHD) share several clinical features, the issue of whether these conditions are comorbid is of importance. Both are prevalent chronic diseases of the childhood, affecting from 3 to 10% of children and adolescents worldwide. The burden of these conditions is severe, disturbing the child's life in many degrees and dimensions, making them major public health problems of childhood and adolescence.

Headache is the most frequent neurological symptom and one of the commonest forms of pain in childhood [1, 2]. According to the literature estimates [3] and a recent nationwide populational study we have conducted in Brazil [4], the lifetime prevalence of recurrent headaches in children is about 80%. Nearly half of children from 5 to 12 years old experience recurrent headaches in a 6-month period. Some of them have very frequent headaches. Of all children in the population, 7% have headaches from 5 to 9 days per month, 2% have headaches from 10 to 14 days per month, and 1.6% have headaches on more days than not. Among these headaches, migraine is particularly important. Episodic migraine (headaches in less than 15 days per month) affects 9% of all children, while chronic migraine (headaches on more than 15 days per month with migraine headaches on at least 8 days) affects 1% of the pediatric population. Episodic tension-type headache affects 13% of children, while 1% suffer from chronic tension-type headache.

M.A. Arruda, M.D., Ph.D (✉)
Child and Adolescent Neurologist, Glia Institute, Ribeirao Preto, SP, Brazil
e-mail: arruda@institutoglia.com.br

M.E. Bigal, M.D., Ph.D
Neurologist, Teva Pharmaceuticals Research and Development, Frazer, PA, USA

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The burden of primary headaches in childhood is best characterized for migraine, which impacts the child's quality of life [5, 6], school attendance [4, 5] and school performance [4], sometimes disrupting the family [7]. The subject is less studied for the other primary headaches [5].

For pediatric migraine, health-related quality of life can be more affected than cardiopathy and diabetes in the pediatric ages. As for school functioning, children with frequent migraines are more affected than those with cancer, diabetes, and cardiopathy [6, 8].

Migraine has several comorbidities, justifying the present book. The psychiatric comorbidity in children and adolescents with migraine has been investigated by clinical [7, 9–13] and population-based studies [14–18]. Only few studies have focused tension-type headache [5, 16].

ADHD is a neuropsychiatric condition characterized by pervasive impaired executive dysfunction with core symptoms of inattention, hyperactivity, and impulsivity [19] and is one of the most thoroughly researched disorders in medicine [20]. According to a meta-regression analysis, based on more than 9000 references and 170,000 children and adolescents involved, the ADHD worldwide pooled prevalence is 5.3% [21]. In Brazil, the estimated prevalence of ADHD is 5.1% in children aged from 5 to 13 years [22].

As with migraine, the broad range of negative outcomes of ADHD has been largely documented affecting the child development, safety, mental health, school functioning, and social performance, with burdensome consequences to families and society, which characterizes it as a major public health problem.

The high prevalence and pronounced impact of both conditions require studies on the possible association between them. Despite the importance of the subject, the comorbidity between primary headaches and ADHD in children has not been well established, and to the best of our knowledge, only one populational study has focused this hypothesis [17].

Accordingly, herein we reviewed the literature and present our experience, based on two large populational studies we have conducted in Brazil (Attention Brazil Project) where children were identified at schools and parents and teachers were directly interviewed, in order to investigate whether ADHD and/or symptoms of hyperactivity-impulsivity and inattention are associated with migraine and/or tension-type headache (TTH) (Fig. 8.1).

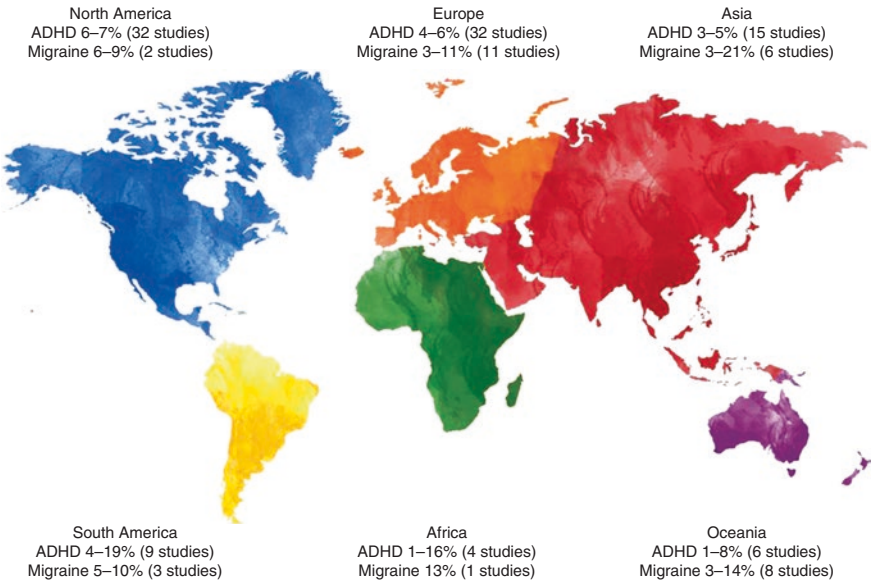

Fig. 8.1 The world map of ADHD and migraine in children and adolescents [3, 21]

8.2 ADHD Diagnosis and Prevalence

ADHD is diagnosed in clinical grounds, and Table 8.1 displays the cardinal aspects of the diagnosis according to DSM-V and ICD 10.

A large number of populational studies have been conducted in the last three decades to estimate the prevalence of ADHD in children and adolescents, with estimates ranging from as low as 1% to as high as nearly 20% [21, 23, 24]. The substantial variability of prevalence rates found in different parts of the world has raised the issue of whether cultural or social aspects can influence the prevalence of the disorder [25, 26]. A systematic review of the literature assessed by a meta-regression analysis was conducted to answer that question. The authors concluded that the heterogeneity of results is significantly associated to publication bias and other methodological issues as requirement of functional impairment as a criterion for the diagnosis, the source of information, and the adopted diagnostic criteria, the Diagnostic and Statistical Manual of Mental Disorders (DSM), or the International Classification of Diseases (ICD) [21].

Table 8.1 Comparison of ADHD diagnostic criteria according to DSM-V and ICD 10

Diagnostic criteria	DSM-V[a]	ICD 10[b]
A persistent pattern of symptoms inappropriate for developmental level and IQ	Inattention and/or hyperactivity-impulsivity	Inattention and hyperactivity-impulsivity
Inattention and hyperactivity-impulsivity symptoms	Six or more symptoms for children up to age 16 or five or more for adolescents 17 and older and adults	Does not establish a minimum number of symptoms
Symptoms were present	Before age 12 years	Before age 6 years
Duration of the symptoms	Symptoms have been present for at least 6 months	No mention
Pervasiveness of the symptoms	Several symptoms are present in two or more settings (at home, school, or work; with friends or relatives; in other activities)	Should be evident in more than one situation (e.g., home, classroom, clinic)
Impairment	Clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning	No mention
Co-occurring mental disorders	Excludes schizophrenia or another psychotic disorder	Excludes anxiety disorders, mood disorders, pervasive developmental disorders, and schizophrenia

[a]Attention deficit hyperactivity disorder (ADHD)
[b]Hyperkinetic disorder (HKD)

The vast majority of populational studies on ADHD in children and adolescents are based on DSM-IV [19] with higher prevalence rates than studies based on ICD 10 [27] because of the less restrictive criteria adopted by the former. The ADHD prevalence in studies based on the DSM-IV range from 0.2 to 26.8% (7.2%) and those based on the ICD 10 from 0.7 to 2.0% (1.3%) [28].

The studies based only on the information of the parents or of the teacher (the so-called OR rule) report prevalence rates varying from 1.4 to 23.4% (9%) and they are significantly higher than the studies based on the information from both of them (AND rule) (from 0.4 to 2.4%, 1.4%) [28].

As expected, studies that require impairment for the diagnosis show a smaller prevalence rate (3.9% vs. 9.1%) [28].

To attenuate the abovementioned methodological limitations, investigators recommend that studies require clinical impairment for the diagnosis and aggregate information from parents and teachers, mirroring the clinical diagnosis process and keeping constant the set of criteria associated with variability of estimates [28].

8.3 Migraine and ADHD: Clinical Studies

In spite of the high risk of selection bias in clinical studies, some of them found limited evidences of a possible association between primary headaches and ADHD or one of its cardinal symptoms (inattention, hyperactivity, and impulsivity) in children.

A first assessment of visual attention in children with migraine was conducted by Villa and colleagues submitting 30 children with migraine and 30 controls without headache to visual tasks (the Trail Making Test, the Letter Cancellation Test, and the Brazilian Computerized Visual Attention Test). Although the attention performance was within normal range in both groups, they found that children with migraine showed more difficulties in selective and alternate attention tasks, as well as higher levels of impulsivity than controls [29].

Applying the Conners' Continuous Performance Test in 62 children with primary headaches (14 with migraine with aura, 29 without aura, and 19 with TTH) and 52 matched controls, Riva and colleagues did not find significant differences in attention performance between headache subgroups. Compared to controls, children with headache showed a faster reaction times in tasks demanding inhibition what may indicate impulsivity [30].

A retrospective review of medical records of 243 children aged 6–18 years with primary headaches (135 with migraine and 108 with TTH) referred to an outpatient neurologic clinic, Genizi and colleagues found higher rates of ADHD and learning disabilities compared to reported rates in general pediatric population of Israel. They also found a higher prevalence of ADHD in children with TTH compared to those with migraine [31].

8.4 Migraine and ADHD: Populational Studies

In a large cross-sectional study of 9264 children aged 4–17 years accessed by the 2003 National Health Interview Survey, Strine and colleagues found that children with frequent or severe headaches (FSH) were 3.2 times more likely to have an abnormal SDQ total difficulties score than children without FSH and 2.7 times more likely to have a high level of impairment, suggesting potential mental health disorders. Children with FSH also exhibited high levels of emotional, conduct, inattention-hyperactivity, and peer problems than controls, causing a clinical significant impact in their home life, friendships, classroom learning, and leisure activities [32].

In another cross-sectional nationwide survey in the United States (1999–2004 National Health and Nutrition Examination Surveys), 10,198 children and adolescents were assessed. The authors found a twofold risk of a previous medical diagnosis of ADHD in children with FSH (odds ratio 2.03, 95% CI 1.56–2.02). Children with FSH also showed a higher risk of learning disability, stuttering, missed school days, and mental health care than children without headaches [33].

8.5 Zoom In

A pilot study (descriptive phase) was conducted by us as part of large population survey (analytical, nationwide) aiming to investigate the mental health of children and adolescents in Brazil (Attention Brazil Project). In one of the arms of this project, we tested if ADHD or its symptoms were associated with specific headache types or with headache frequency. The target sample consisted of all children aged 5–12 years (n = 1856) registered in the public school system of a city (Santa Cruz das Palmeiras, São Paulo, Brazil). Direct interviews were conducted with one of the parents and with the teacher using validated questionnaires [17].

The headache module of the questionnaire assessed headache features and frequency, associated symptoms, and consumption of analgesics and caffeine. Based on the results, the following headaches of interest were considered: episodic migraine, probable migraine, chronic migraine, episodic TTH, and chronic TTH.

ADHD was assessed according to the DSM-IV criteria using the validated Brazilian versions of the MTA-SNAP-IV scale completed by mothers and teachers [34] and the Child Behavior Checklist (CBCL) [35] completed by the mothers. The grade of impairment was defined by the CBCL.

The overall prevalence of episodic migraine was 3.8%, TTH happening <1 day per month was seen in 2.3% of the sample and between 1 and 15 days per month in 1.6%. The overall prevalence of ADHD was 6.1%. The prevalence of ADHD was not significantly different by headache category. For hyperactivity and impulsivity symptoms, the prevalence was 8.1% in children without headache, 23.7% in children with migraine (relative risk [RR], 2.6; 95% confidence interval [CI], 1.6–4.2), and 18.4% in children with probable migraine (RR, 2.1; 95% CI, 1.4–3.2). For inattention, no significant differences were seen. In multivariate analyses, ADHD or inattention symptoms were not predicted by headache subtypes or headache frequency. Hyperactivity and impulsivity symptoms were significantly associated with any headache ($p < 0.01$), TTH ($p < 0.01$), or migraine ($p < 0.001$) (Table 8.2).

In another study with the same sample and taking in account the behavioral and emotional symptoms captured only by the CBCL (not by the MTA-SNAP-IV scale), a significantly higher prevalence of inattention was found in children with migraine overall (17.1% vs. 6.4%, RR 2.6; 95% CI 1.7–4.2), episodic migraine (17.8% vs. 6.4%, RR 2.8; 95% CI 1.6–4.9), TTH overall (10.2% vs. 6.4%, RR 1.6; 95% CI 1.0–2.6), and episodic TTH (14.7% vs. 6.4%, RR 2.3; 95% CI 1.2–4.3) relative to controls [16].

Despite the fact of both instruments being based in DSM-IV, the MTA-SNAP-IV and the CBCL showed discordant sensibility/specificity concerning the inattention identification and can explain the different findings of both studies conducted in this pilot phase.

Table 8.2 Prevalence of ADHD, hyperactivity-impulsivity, and inattention as a function of headache diagnosis (pilot study)

		ADHD according to DSM-IV				Hyperactivity-impulsivity symptoms				Inattention symptoms			
	Total	*n*	%	95% CI of prevalence	RR (95% CI)	*n*	%	95% CI of prevalence	RR (95% CI)	*n*	%	95% CI of prevalence	RR (95% CI)
No headache	345	23	6.7	4.1–9.3%	Reference	28	8.1	5.2–11.0%	Reference	27	7.8	5.0–10.7%	Reference
Migraine overall	427	31	7.3	4.8–9.7%	1.1 (0.6–1.8)	85	19.9	16.1–23.7%	2.2 (1.5–3.3)	49	11.5	8.5–14.5%	1.4 (0.9–2.2)
Migraine with or without aura	118	11	9.3	4.1–14.5%	1.4 (0.7–2.7)	28	23.7	16.0–31.4%	2.6 (1.6–4.2)	14	11.9	6.0–17.7%	1.5 (0.8–2.7)
Chronic migraine	14	1	7.1	0–20.6%	1.1 (0.1–7.4)	1	7.1	0–20.6%	0.9 (0.1–6.1)	0	0.0	–	–
Probable migraine	309	20	6.5	3.7–9.2%	1.0 (0.5–1.7)	57	18.4	14.1–22.8%	2.1 (1.4–3.2)	35	11.3	7.9–14.9%	1.4 (0.9–2.3)
TTH overall	537	24	4.5	2.7–6.2%	0.7 (0.4–1.2)	73	13.6	10.7–16.5%	1.6 (1.1–2.4)	53	9.9	7.3–12.4%	1.2 (0.8–1.9)
Infrequent episodic TTH	16	0	0.0	–	–	1	6.3	0–18.1%	0.8 (0.1–5.4)	0	0.0	–	–
Frequent episodic TTH	79	3	3.8	0–8.0%	0.6 (0.2–1.9)	13	16.5	8.3–24.6%	1.9 (1.0–3.5)	8	10.1	3.5–16.8%	1.3 (0.6–2.7)
Chronic TTH	2	0	0.0	–	0	0	0.0	–	0	1	50.0	0–100%	4.6 (0.9–23.7)
Probable TTH	537	24	4.5	2.7–6.2%	0.7 (0.4–1.2)	73	13.6	10.7–16.5%	1.6 (1.1–2.4)	53	9.9	7.3–12.4%	1.2 (0.8–1.9)

8.6 Ongoing Work

The nationwide phase of the Attention Brazil Project was designed to establish inception cohorts for studying disorders that may impact learning in children. It was built from a virtual network of professionals that started in 2006 as a not-for-profit academic organization called Aprender Criança (the Learning Child). Currently about 5700 members are registered into the organization, including professionals of different areas (e.g., psychologists, medical doctors) as well as teachers from the public and private education system in Brazil [36].

The starting point for the study consisted in identifying 124 teachers, which then completed a 4-h online training provided by one of us (M.A.A.). Before conducting parental interviews, teachers completed the Brazilian-validated version of the MTA-SNAP-IV scale for each child [34] and provided information on the performance of the students according to the usual state parameters.

Mothers were then interviewed by the teachers using a standardized questionnaire with 102 questions assessing sociodemographic features, past medical history of the child, headaches, parental perspective on school performance (not reported here), and mental health. The headache module of the questionnaire consisted of 14 questions, assessing the distinguishing features required for headache diagnosis of the children according to the ICHD-2 [37]. The questionnaire is the validated Portuguese version of the questionnaire used in the American Migraine Studies and has been extensively used in pediatric and adult studies in Brazil [38]. Based on the response to the questionnaires, headache diagnoses were assigned strictly following the ICHD-2.

The mental health status was evaluated by the validated Brazilian version of the MTA-SNAP-IV scale and the Strengths and Difficulties Questionnaire (SDQ) [39, 40]. The SDQ identifies hyperactivity, inattention, emotional symptoms, peer problems, and conduct problems. The SDQ impact supplement was applied to evaluate the clinical impairment of ADHD symptoms required by the DSM-IV diagnostic criteria. The diagnosis of ADHD followed the DSM-IV operational criteria.

ADHD was modeled as a function of headache diagnosis and symptoms, frequency of headaches, and abnormal SDQ scores.

Of the 8599 children being educated by the participating teachers, parental consents were obtained from 6445 (75%) and analyzable data (complete demographic and headache information) from 5671 (65.9%). All were aged from 5 to 12 years (50.7% boys). They were enrolled from 87 cities in 18 Brazilian states, under the five national regions.

The prevalence of ADHD was 3.9 (6.0% in boys and 1.8% in girls, RR 3.33; 95% CI 2.48–4.46), episodic migraine was 9.4, and episodic TTH in 12.6% of the sample. Compared to children with no headache, the prevalence of ADHD was significantly higher in children with migraine overall (6% vs. 2.1%, RR 2.9; 95% CI 1.9–4.5), episodic migraine (6.8% vs. 2.1%, RR 3.3; 95% CI 2.0–5.3), probable migraine (5.3% vs. 2.1%, RR 2.5; 95% CI 1.6–3.4), chronic migraine (17.1% vs.

Table 8.3 Prevalence of ADHD, hyperactivity-impulsivity, and inattention as a function of headache diagnosis (nationwide study)

	ADHD according to DSM-IV			Hyperactivity-impulsivity symptoms			Inattention symptoms		
	n (%)	RR (95% CI)	*p*	*n* (%)	RR (95% CI)	*p*	*n* (%)	RR (95% CI)	*p*
No headache	26 (2.1)	Reference		37 (3.0)	Reference		43 (3.4)	Reference	
Migraine	107 (6.0)	2.9 (1.9–4.5)	<0.00	85 (4.8)	1.6 (1.1–2.4)	0.01	124 (7.0)	2.0 (1.5–2.9)	<0.00
Episodic migraine	40 (6.8)	3.3 (2.0–5.3)	<0.00	30 (5.1)	1.7 (1.1–2.8)	0.03	46 (7.8)	2.3 (1.5–3.4)	<0.00
Probable migraine	60 (5.3)	2.5 (1.6–3.4)	<0.00	53 (4.7)	1.6 (1.0–2.4)	0.04	71 (6.2)	1.8 (1.3–2.6)	0.00
Chronic migraine	7 (17.1)	8.2 (3.8–17.9)	<0.00	2 (4.9)	1.7 (0.4–6.6)	0.35	7 (17.1)	5.0 (2.4–10.4)	0.00
TTH	100 (3.6)	1.7 (1.1–2.7)	0.01	103 (3.7)	1.3 (0.9–1.8)	0.26	141 (5.1)	1.5 (1.1–2.1)	0.02
Episodic TTH	26 (3.3)	1.6 (0.9–2.7)	0.12	23 (2.9)	1.0 (0.6–1.6)	0.95	40 (5.1)	1.5 (1.0–2.2)	0.09
Probable TTH	74 (3.7)	1.8 (1.2–2.8)	0.01	80 (4.0)	1.4 (0.9–2.0)	0.13	101 (5.1)	1.5 (1.1–2.1)	0.03
Chronic TTH	0	0	1.00	0	0	1.00	0	0	1.00

2.1%, RR 8.2; 95% CI 3.8–17.9), TTH overall (3.6% vs. 2.1%, RR 1.7; 95% CI 1.1–2.7), and probable TTH (3.7% vs. 2.1%, RR 1.8; 95% CI 1.2–2.8). For hyperactivity and impulsivity symptoms, the prevalence was significantly higher in children with migraine overall, episodic migraine, and probable migraine compared to children with no headache ($p < 0.04$). Compared to children with no headache, the prevalence of inattention symptoms was significantly higher in children with migraine overall, episodic migraine, probable migraine, chronic migraine, TTH overall, and probable TTH ($p < 0.03$) [36] (Table 8.3).

According to the multivariate analysis, in children with any migraine subtype (migraine overall, episodic migraine, probable migraine, and chronic migraine), ADHD diagnosis was most significantly influenced by frequency of headache attacks ($p < 0.04$), headache severity ($p < 0.001$), nausea during attacks ($p < 0.000$), phonophobia ($p < 0.024$), conduct problems ($p < 0.008$), an abnormal SDQ total score ($p < 0.000$), and a below-average school achievement ($p < 0.000$) [36].

8.7 Treatment

Pharmacological treatment. Among the drugs with proved efficacy and safety in the treatment of primary headaches, no one is approved to the treatment of ADHD; on the other hand, no RCT exist evaluating the gold standard drugs for ADHD in the treatment of primary headaches in children and adolescents.

A single randomized, double-blinded, controlled, multiple-crossover study has shown a preventive effect of dextroamphetamine in some adult patients with migraine compared to caffeine [41].

In fact, headache is one of the most frequent adverse events of the psychostimulants happening from 19 to 27% of the trials with mixed amphetamine salts, from 14 to 25% with methylphenidate, and from 7 to 30% with atomoxetine, a selective norepinephrine reuptake inhibitor.

If treating ADHD occurs improvement or remission of primary headache, and vice versa, is another issue for which we have no answer.

Limited evidence coming from personal experience treating children with both conditions in the last 30 years leads us to expect a robust control of migraine after prescribing methylphenidate for children and adolescents.

Nonpharmacological treatment. Cognitive behavior therapies delivered face to face [42] and even remotely delivered [43] have been documented as effective interventions helping children and adolescents with primary headaches and other chronic and recurrent pain. Among the evidence-based behavioral and cognitive strategies are biofeedback, relaxation training, stress management, guided imagery, and cognitive coping skills.

The efficacy of psychosocial treatments in children and adolescents with ADHD has been evaluated in a recent extensive literature review. The authors concluded that organization training, behavioral parent training, behavioral classroom management, and behavioral peer interventions are well-established treatments. On the other hand, combined training programs were considered probably efficacious treatment; neurofeedback as possibly efficacious, and cognitive training as an experimental treatment [44]. In other review limited to adolescents, the authors concluded that psychosocial treatments focused in behavior contingency management, motivational enhancement, and academic, organizational, and social skills training techniques are associated with inconsistent effects on ADHD symptoms, however with a significant benefit for academic and organizational skills [45].

8.8 Conclusion

Our studies suggest that migraine and ADHD are comorbid. In the first study, we showed comorbidity of migraine and symptoms of ADHD but not ADHD per se. In the second, we found the full comorbidity to exist.

Being comorbid, both diseases may add to the impact on quality of life, mental health, school performance, and other important outcomes in the lives of children and adolescents.

Accordingly, we offer the following suggestions to practitioners:

1. When attending children with headaches, clinicians should also look to symptoms such as inattention, hyperactivity, impulsivity and executive dysfunctions, and vice versa.

2. It is not enough to diagnose the disease, but providers should also quantify the impact of these disorders and of the comorbid conditions, on aspects of daily life. Several tools are available for this aim.
3. By identifying children with ADHD and comorbid headaches, providers will be more capable to offer a complete and holistical therapeutic approach, maximizing the chance for improvement and the outcomes of therapy.

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Chapter 9
Comorbidity of Migraine with Asthma and Other Atopic Disorders

Aynur Özge and Kentaro Kuwabara

9.1 Introduction

Migraine, a disorder in which neurovascular headaches recur, is characterized by episodes of severe throbbing, pulsatile, commonly unilateral headaches, associated with nausea, vomiting, photophobia, phonophobia, and aversion to physical activity, with or without premonitory symptoms [1]. Migraine is one of the most common reasons for children and adolescents to be referred to headache centers. Puberty is an important milestone in the clinical picture of migraine [2]. Potential reasons for the emergence of chronic migraine in children and adolescents, in addition to an increasing frequency of attacks and inappropriate management of attacks (i.e., attacks not managed in a timely fashion), are the comorbidities involved, such as atopic disorders [2].

The term "atopic disorders" defines a clinical situation in which chronic inflammation occurs with a genetically mediated predisposition for an excessive immunoglobulin E (IgE) reaction after exposure to allergic triggers. The target tissues are the nasal mucosa in allergic rhinosinusitis, the bronchial wall in asthma, the membrane covering the sclera in allergic conjunctivitis, and the dermis in allergic dermatitis (eczema) [3]. Atopic disorders and migraine are common health problems worldwide, even in children and adolescents. Allergic rhinitis, asthma, conjunctivitis, food allergies, and dermatitis-like atopic disorders are among the most common chronic diseases in adults in the United States, and allergic rhinitis is the most common

A. Özge (✉)
Professor of Neurology, Department of Neurology, Algology and Clinical Neurophysiology, Mersin University School of Medicine, Çiftlikköy Kampusü, Yenişehir, Mersin 33430, Turkey
e-mail: aynurozge@gmail.com

K. Kuwabara
Department of Pediatrics, Hiroshima City Hiroshima Citizens Hospital 7-33, Motomachi, Naka-ku, Hiroshima 730-8518, Japan

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chronic disease in children. Atopic disorders are also a huge health problem in Europe. According to the European Academy of Allergy and Clinical Immunology, 150 million Europeans, or one in five, have allergies. In the pediatric population in Europe, allergy is estimated to occur in one in three children. Many supporting reports showing problems with atopic disorders come from other countries [4].

Migraine headache and atopic disorders including asthma are both common functional syndromes of childhood in which nature of the relationship is still debated [3]. Epidemiological data showed that 39.5% of boys and 46.2% of girls (aged 7–22 years) with migraine headache reported allergy symptoms [5]. In another study, 25.4% of men and 37.4% of women with migraine headache reported a history of atopy [6]. Atopic diseases particularly asthma was detected in 20 % of childhood migraine patients [7]. Two reviews of gender and age differences in asthma prevalence and incidence during childhood and adolescence reported a male preponderance before the age ten but is more common in girls thereafter [8, 9]. A comprehensive retrospective case-control study of children (5–15 years old) with and without migraine showed that the prevalences of atopic dermatitis (odds ratio [OR] = 7.1; $p < 0.01$), rhinoconjunctivitis (OR = 7.3; $p < 0.01$), and allergic asthma (OR = 4.69; $p < 0.01$) were significantly higher and the conditions were more severe in children with migraine. Dermatitis and rhinitis are more commonly diagnosed in migraine patients with aura than in those without aura [10].

9.1.1 Reasons for the Relationship between Migraine and Atopic Disorders

Migraine and atopic disorders may share common pathophysiological features. The similarities between these two distinct disorders include: a strong genetic basis; alternations in vasoactive mediators and common triggers such as foods, exercise or emotional stress. Comorbidity of migraine and atopic disease suggest immune system dysfunction and a potential role of neuro-inflammation in migraineurs [11].

Migraine is a common disorder in children and adolescents, and is characterized by severe brief headache attacks accompanied by autonomic and neurological symptoms. Sterile neurogenic inflammation, defects in arachidonic acid or serotonin metabolism, cyclical changes in concentrations of ovarian steroids, food allergies, and atopic disorders have been postulated as underlying the peripheral mechanisms of migraine [12].

The past 30 years of basic and clinical research in the field of headaches has greatly improved our understanding of migraine pathophysiology as a functional neurological syndrome different from simple headache. Most likely, migraine headache depends on: (a) activation of the trigeminovascular pathway by pain signals that originate in peripheral intracranial nociceptors, and (b) dysfunction of central nervous system (CNS) structures involved in the modulation of neuronal excitability and pain. The potential effect of age, gender, and comorbid medical problems on strategies for the treatment of headache attacks is an interesting topic for researchers. Actually, the

main purpose of research in the field is to create a rationale for the personalized management of primary headache disorders [13].

Multiple threads of research have informed the concept that migraine is generated from a hyper-excitable brain, and bronchial asthma has been described as "pulmonary migraine" or "acephalic migraine" in a manner. Both migraine and asthma show a paroxysmal and recurrent pattern of appearance and a hypersensitive response fits well after the attack. On the other hand, the results of some studies suggest a link between migraine (vascular reactivity) and asthma (bronchial reactivity) that is independent of any allergic mechanism [3]. It is also known that migraine is strongly associated with non-atopic asthma, a factor which might also account for the increased risk of chronic obstructive pulmonary disease in migraine patients [14]. So, determination of forced expiratory flow, one of the variables in the pulmonary function test (PFT) that is considered to be a marker of small airway resistance, is important for subjects at risk, especially those with a positive family history of migraine or atopic disorders [3].

Many studies have reported alterations in vasoactive mediators in patients with migraine and bronchial asthma. Platelet aggregation is mediated by platelet activating factor, which also causes bronchoconstriction, similar to migraine. Substance P is involved in migraine pathogenesis and is also localized in the unmyelinated sensory fibres (C-fibres) of airways; it may also be involved in the asthma inflammatory response, potentially stimulates the secretion of airway mucus, and increases airway microvascular permeability and exudation of plasma into the lumen [11].

Migraine and atopic diseases are regarded as multifactorial, with both familial and environmental influences affecting their expression [11]. A cross-sectional population-based survey of 12- to 22-year-olds (9565 individuals) has demonstrated that low back pain is positively associated with both asthma and headache/migraine [15]. An analysis of 19 United States population-based studies of childhood atopic dermatitis (or eczema) and headaches found that eczema associated with atopy, fatigue, and sleep disturbance was associated with even higher odds ratios of headaches than eczema alone in childhood [16]. In a study of the association of asthma with extra-respiratory symptoms in school children, the term "asthma-associated extra-respiratory symptoms" (AA-ERS) was used to refer to the presence of one or more of three extra-respiratory symptoms (urticaria, itching, or recurrent abdominal pain). The adjusted risk of lifetime asthma increased linearly with the number of reported AA-ERS. However, other extra-respiratory symptoms, including headache, were not significantly associated with asthma [17].

9.1.2 Importance of Atopic Disorders in Migraine Sufferers

The patients with migraine, 77 (41.4%) reported at least one atopic disorder. There is no defining feature migraine with atopic disorders compared to migraine without atopic disorders. However, PFT screening showed generally decreased pulmonary capacity in patients with migraine, as well as a significant correlation between a

positive history of atopic disorders and increased levels of both eosinophils and IgE even in headache-free periods [3].

A multicenter study showed significantly higher ratios of interleukin (IL)-1β , IL-2 and IL-6 to tumour necrosis factor (TNF)-α in a migraine group compared to an episodic tension-type headache group (16.6% vs. 10.5%, 20.0% vs. 5.3%, 13.8% vs. 2.6% and 15.9% vs. 5.3%, respectively), and to healthy controls [18].

A genetic association and polymorphism study showed significant differences in the genotypic distribution of the TNF-α –308 G/A and IL-1β +3953 C/T polymorphisms for migraineurs compared to controls. These results indicate a possible contribution of TNF-α and IL-1β gene polymorphisms to migraine headache in patients with migraine without aura (MwoA) [19].

There are also strong data that support the relationship between migraine and bronchial hyperreactivity, enabling us to postulate inflammation as an underlying mechanism in migraine [20].

A recent comprehensive tertiary headache centerbased study showed that atopic disorders are more commonly reported in patients with migraine with aura (MwA) (21.6 %) than those with MwoA and tension type headache (TTH). The most commonly reported types of atopic disorder are seasonal rhinitis, conjunctivitis and asthma. There is also a close relationship between atopic disorders and generalized anxiety disorders in patients, and between atopic disorders a family history of migraine (particularly mothers). The peak age for an association between migraine and atopic disorders is 11–14 years according to clinical data. Headache phenotype in children commonly changes around puberty (i.e. in 71.3% of cases). The most common predictors of clinical phenotype are the unilateral location and throbbing quality of the headache attacks [12].

Atopic dermatitis is one of the most common skin disorders of allergic etiology in the western world, although the prevalence of the disease varies considerably between different countries. Comorbidity of migraine and atopic disorders is frequent, with a frequency of 15.8% in girls and 7.1% in boys. The risk of associated mental distress in girls with such comorbidity shows a twofold increase compared with the risk in the general population (95% CI: 1.7–2.5), with a 2.8-fold increase (95% CI: 1.9–4.0) shown in boys with the comorbidity [21].

9.1.3 Importance of Migraine in Atopic Disorders Sufferers

The relationship between migraine and atopic disorders has been a focus of historical interest. Since 1985, there is some evidence of a close association between these disorders. Recent studies have confirmed this association. The practical applications of a known disease association are invaluable, not only in research but for accurate diagnosis, particularly for a condition such as migraine, which, without accepted markers, is notoriously difficult to diagnose in young children [3, 11].

Headache attacks in children with asthma have been reported different frequencies. Worldwide, the most common reported primary headache disorder is migraine

[17]. Migraine comorbidity has been reported in at least one-third of children with allergic rhinosinusitis [4]. Apart from being coincidental, there are data showing disturbed clinical courses of asthma in patients with migraine [22].

Atopic dermatitis (or eczema) is a chronic inflammatory disorder associated with different functional syndromes, including migraine. Maternal but not paternal migraine-like headaches were associated with the child having eczema (maternal: OR 1.87 [95% CI, 1.46–2.40]; paternal: OR 1.47 [95% CI, 0.92–2.37]). There were significant interactions between a history of eczema and maternal/paternal headaches. A pooled analysis of 19 US population-based studies of the association between childhood eczema and headaches reported that children with eczema, compared with those without eczema, had a significantly higher prevalence of headaches (10.7% vs. 5.4%) and significantly higher ORs for headaches (1.52 [95% CI, 1.45–1.59]). Mild (OR 1.79 [95% CI, 1.07–2.98]) and severe (OR 2.72 [95% CI, 1.33–5.57]) eczema were associated with significantly higher odds of having headaches. In particular, eczema was associated with other atopic disorders, fatigue, excessive daytime sleepiness, and insomnia [16].

The prevalence of migraine in children with atopic disease was 12.2% in those with rhinitis, 7.8% in those with eczema, and 7.6% in those with asthma, compared with a prevalence of migraine of 4.9% for all children in the study. Atopic illnesses were more common in migraineurs (overall figures for non- migraineurs in parentheses): asthma, 30.2% (19.6%); eczema, 32.1% (20.2%); and rhinitis, 18.9% (7.6%). Of the child migraineurs, 20.8% had both asthma and eczema and 7.5% had asthma, eczema, and rhinitis. Significantly more children with rhinitis were born to mothers with a history of migraine. The strength of the association between maternal migraine and childhood rhinitis showed a ratio of 1.63(Yules Q, 0.26). Patients with perennial allergic rhinitis had a higher level of comorbidities than those with seasonal allergic rhinitis [11].

9.1.4 Effect of Comorbidities on Clinical Course of Migraine

There are supportive data showing the association of allergy with migraine headaches. Lower “degrees of atopy” were associated with less frequent and less disabling migraine headaches in younger subjects [23]. Frequent or severe headaches, including migraine in the past 12 months, were reported in 17.1% of children with atopic disorders. Asthma, hay fever, and frequent ear infections were more common in children with headache, with at least one of these factors occurring in 41.6% of children with headache versus 25.0% of children free of headache [24].

There are some controversial reports about the effect of diet on the clinical courses of migraine and atopic disorders. Many studies based on strict diet restrictions are far from practical message for daily routines. In an important clinical study investigating the effects of IgG antibodies against food antigens on the course of migraine attacks, there was a statistically significant reduction in the number of headache days and number of migraine attacks, compared with baseline, during the elimination diet period [25].

Sinus headache is a common presentation of migraine in all age groups, especially in children and adolescents. Migraines and sinusitis are common problems for about 10%–20% of Americans and 41% of Europeans [26].

Migraine and headache due to allergic rhino-sinusitis are easily confused because the symptoms of the conditions often overlap; both may co-occur with sinus headache, nasal congestion and lacrimation, and may worsen with atmospheric changes and exposure to allergens. No precise clinical definition exists for sinus headache upto now, which has always presented a diagnostic dilemma. Contrary to popular belief, headache is not a typical symptom of rhinosinusitis. Some studies have shown that up to 90% of sinus headaches are in fact migraine in contrast to common belief. Interestingly, up to one-third of individuals with upper respiratory allergies also have migraine. Nevertheless, patients with self-diagnosed sinus headache, who self-treat or who are treated with rhinosinusitis medications by primary care physicians and/or otolaryngologists, are ignoring the potential neurogenic causes of the symptoms, when in fact most of these patients fulfil the diagnostic criteria for chronic migraine [4].

Nasal congestion, rhinorrhea, pressure/pain behind the eyes, a feeling of fullness in the head, and lacrimation are known as cranial autonomic symptoms; these symptoms have been focused on in the past few years in relation to migraine, and they are commonly confused with trigeminal autonomic cephalalgias, which are also potentially associated with migraines. Of note, there is an important report supporting the idea that cranial autonomic symptoms are an independent diagnostic component of migraine in children and adolescents [27, 28].

The degree of allergic sensitization determines not only the severity but also the frequency of headache attacks in those whom allergic rhinitis is a risk factor, as evidenced by higher levels of IgE, especially in younger age groups and females [29].

9.1.5 Effect of Comorbidities on Management of Migraine

It has been found that 46% of all patients with migraine reported at least one unilateral symptom of nasal congestion, rhinorrhea, ocular redness, or lacrimation (due to the trigeminal-autonomic reflex), and 82% of patients with self-reported sinus headaches had a significant response to triptans [30–32].

Atopic comorbidities have a large impact on the diagnosis and treatment of migraine. Information about atopic comorbidities is important and may lead to a more accurate diagnosis in adults and children, because there is no accepted biomarker to diagnose migraine. A history of atopy (particularly rhinosinusitis) in a child with paroxysmal headache attacks associated with nausea and /or vomiting, photo-or phono-phobia supports the diagnosis of migraine [11].

The demonstration of an association of childhood atopic disease with maternal migraine is interesting. It has been shown that maternal migraine is associated with childhood rhinitis, while another study showed an association of maternal migraine

with childhood asthma. The association between individual atopic disorders is well established, and it may well be possible that in different populations the relationship between migraine in the mother and the expression of asthma, eczema, or rhinitis in her child will depend on the "genetic pool mix". Support for possible connections between migraine and atopy, in the form of genetic linkage, comes from the observation that both migraine and asthma have common specific HLA associations. Childhood migraine occurs more frequently when the mother is also a sufferer [11].

Atopic dermatitis (or eczema) is the most common chronic inflammatory skin disorder of childhood, affecting approximately 10%–20% of children in the United States. Eczema is associated with increased headaches in childhood, particularly in patients with severe disease accompanied by other atopic conditions, fatigue, and sleep disturbance. It might be that fatigue and sleep disturbance are merely a proxy measure of eczema severity. However, the results of Silverberg's association study indicate that sleep disturbance per se is associated with headaches and might be the driver of headaches; from this result, it appears that treatment of eczema might contribute to a decreased risk of migraine [16].

Of note, it has been reported that montelukast (an antagonist of the cysteinyl leukotriene receptor), which is used in the treatment of asthma, showed an important beneficial effect in the prophylaxis of migraine, and this result suggested the presence of some pathophysiological links between migraine and asthma. Inflammation-induced trigeminal hyperalgesia could explain why migraineurs report the highest headache intensity after infection and why certain precipitants generate migraine in some conditions but not others. In asthma patients, β-stimulants are usually used for therapy, but for this reason, β-blockers should not be recommended as prophylactic medications in migraine patients with bronchial asthma [3].

Key Features

- Migraine and atopic disorders are highly prevalent conditions associated with a socioeconomic burden and decrease quality of life, particularly when both disorders coexist in the same children or adolescents.
- The presence of atopic diseases in migraine is far from a coincidence and particularly rhino sinusitis, asthma, atopic dermatitis and seasonal changes are more prevalent in children and adolescents with migraine headache.
- Allergic rhino sinusitis in childhood and adolescence always need to be differentiated from migraine even highly exist associated with migraine. Cranial autonomic symptoms are important clues for comorbid migraine and other diagnostic criteria should be strictly revised for each rhino sinusitis attack.
- Migraine and atopic disorders may share common pathophysiological features with some genetical basis; periodicity, alterations in vasoactive mediators and common triggers such as foods, exercise or emotional stress.
- Atopic diseases need to be questioned in all patients and relatives, and ICHD-3 has to include questioning atopic disorders in childhood migraine.

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Chapter 10
Comorbidity with Brain Tumors

Pier Antonio Battistella and Marcelo R. Masruha

10.1 Introduction

Brain tumors are the most common solid tumors in children [1]. They occur almost as often as acute lymphoblastic leukemia and are now the commonest cause of cancer deaths in childhood [2, 3]. The World Health Organization (WHO) classification of central nervous system (CNS) tumors is shown in the Table 10.1, and Fig. 10.1 [4] demonstrates the location of the common pediatric brain tumors and their frequency of occurrence (about half occur above the tentorium and half in the posterior fossa) [2].

Headaches are common in patients with brain tumors, occurring in up 50% of adults and 60% of children [5]. However, clinical studies have found that headache, as a single symptom of a brain tumor, is rare, occurring in only 2% of patients [6, 7].

Before we address the headache in the context of brain tumors, and more specifically the possibility of comorbidity with primary headaches, we will rapidly describe the characteristics of the most common pediatric brain tumors.

P.A. Battistella, M.D. (✉)
Department of Woman's and Child's Health, Child and Adolescent Headache Center, University of Padova, Padova, Italy
e-mail: pierantonio.battistella@unipd.it

M.R. Masruha
Division of Child Neurology, Universidade Federal de São Paulo, São Paulo, Brazil
e-mail: marcelomasruha@gmail.com

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Table 10.1 The 2007 WHO classification and grading of CNS tumors [4]

1. Tumors of neuroepithelial tissue

a. Astrocytic tumors
- Pilocytic astrocytoma (I)
- Pilomyxoid astrocytoma (II)
- Subependymal giant cell astrocytoma (I)
- Pleomorphic xanthoastrocytoma (II)
- Diffuse astrocytoma
  - Fibrillary astrocytoma (II)
  - Gemistocytic astrocytoma (II)
  - Protoplasmic astrocytoma (II)
- Anaplastic astrocytoma (III)
- Glioblastoma
  - Giant cell glioblastoma (IV)
  - Gliosarcoma (IV)
- Gliomatosis cerebri (IV)

b. Oligodendroglial tumors
- Oligodendroglioma (II)
- Anaplastic oligodendroglioma (III)

c. Oligoastrocytic tumors
- Oligoastrocytoma (I)
- Anaplastic oligoastrocytoma (IV)

d. Ependymal tumors
- Subependymoma (I)
- Myxopapillary ependymoma (I)
- Ependymoma
  - Cellular (II)
  - Papillary (II)
  - Clear cell (II)
  - Tanycytic (II)
- Anaplastic ependymoma (III)

e. Choroid plexus tumors
- Choroid plexus papilloma (I)
- Atypical choroid plexus papilloma (II)
- Choroid plexus carcinoma (III)

f. Other neuroepithelial tumors
- Angiocentric glioma (I)
- Chordoid glioma of the third ventricle (II)
- Astroblastoma (IV)

g. Neuronal and mixed neuronal-glial tumors
- Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos) (I)
- Desmoplastic infantile astrocytoma/ganglioglioma (I)
- Dysembryoplastic neuroepithelial tumor (I)
- Gangliocytoma (I)
- Ganglioglioma (I)
- Anaplastic ganglioglioma (III)
- Central neurocytoma (II)
- Extraventricular neurocytoma (II)
- Cerebellar liponeurocytoma (II)
- Papillary glioneuronal tumor (I)
- Rosette-forming glioneuronal tumor of the fourth ventricle (I)
- Paraganglioma (I)

h. Tumors of the pineal region
- Pineocytoma (I)
- Pineal parenchymal tumor of intermediate differentiation (II/III)
- Pineoblastoma (IV)
- Papillary tumor of the pineal region (II/III)

i. Embryonal tumors
- Medulloblastoma
  - Classic medulloblastoma (IV)
  - Desmoplastic/nodular medulloblastoma (IV)
  - Medulloblastoma with extensive nodularity (IV)
  - Anaplastic medulloblastoma (IV)
  - Large cell medulloblastoma (IV)
- CNS primitive neuroectodermal tumor (PNET)
  - CNS neuroblastoma (IV)
  - CNS ganglioneuroblastoma (IV)
  - Medulloepithelioma (IV)
  - Ependymoblastoma (IV)
- Atypical teratoid/rhabdoid tumor (IV)

2. Tumors of cranial and paraspinal nerves

a. Schwannoma (neurilemoma, neurinoma)
- Cellular (I)
- Plexiform (I)
- Melanotic (I)

b. Neurofibroma
- Circunscript (I)
- Plexiform (I)

c. Perineurioma (I/II/III)

d. Malignant peripheral nerve sheat tumor (MPNST) (II/III/IV)
- MPNST epithelioid
- MPNST with mesenchymal differentiation
- MPNST melanotic
- MPNST with glandular differentiation

Table 10.1 (continued)

3. Tumors of the meninges	Rhabdomyoma	*4. Lymphomas and hematopoietic neoplasms*
a. Tumors of meningothelial cells	Rhabdomyosarcoma	Malignant lymphomas
Meningioma (I)	Chondroma	Plasmocytoma
Meningothelial	Chondrosarcoma	Granulocytic sarcoma
Fibrous (fibroblastic)	Osteoma	*5. Germ cell tumors*
Transitional (mixed)	Osteosarcoma	Germinoma
Psammomatous	Osteochondroma	Embryonal carcinoma
Angiomatous	Hemangioma	Yolk sac tumor
Microcystic	Epithelioid hemangioendothelioma	Choriocarcinoma
Secretory	Hemangiopericytoma (II)	Teratoma
Lymphoplasmacyte rich	Anaplastic hemangiopericytoma (III)	Mature
Metaplastic	Angiosarcoma	Immature
Chordoid	Kaposi sarcoma	Teratoma with malignant transformation
Clear cell	Ewing sarcoma – PNET	Mixed germ cell tumor
Atypical (II)	**c. Primary melanocytic lesions**	*6. Tumors of the sellar region*
Papillary	Diffuse melanocytosis	Craniopharyngioma
Rhabdoid	Melanocytoma	Adamantinomatous (I)
Anaplastic (malignant) (III)	Malignant melanoma	Papillary (I)
b. Mesenchymal tumors	Meningeal melanomatosis	Granular cell tumor (I)
Lipoma	**d. Other neoplasms related to the meninges**	Pituicytoma (I)
Angiolipoma	Hemangioblastoma (I)	Spindle cell oncocytoma of the adenohypophysis (I)
Hibernoma		*7. Metastatic tumors*
Liposarcoma		
Solitary fibrous tumor		
Fibrosarcoma		
Malignant fibrous histiocytoma		
Leiomyoma		
Leiomyosarcoma		

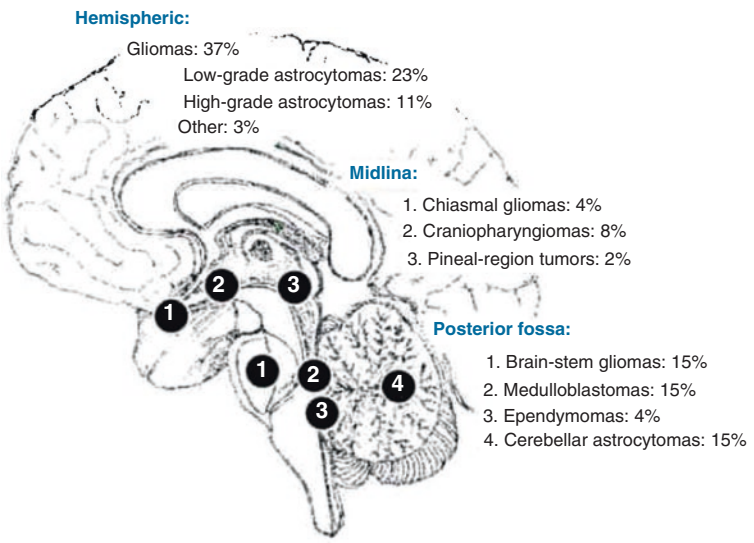

Fig. 10.1 Location and frequency of occurrence of common pediatric brain tumors [2]

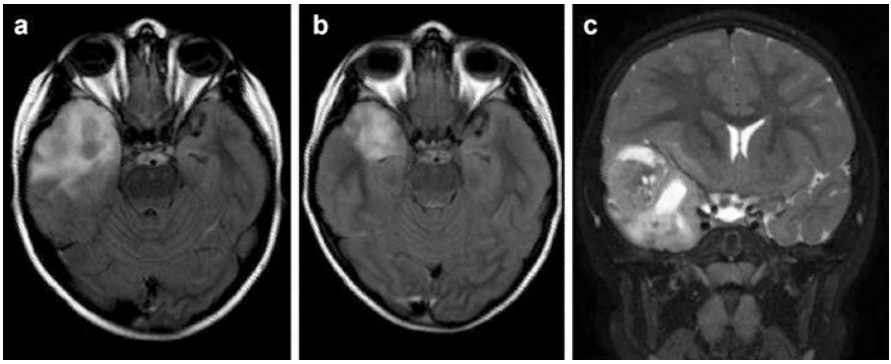

Fig. 10.2 Grade II astrocytoma in a 6-year-old boy. Brain MRI shows a hyperintense lesion in axial FLAIR images in the right temporal lobe (**a**) and (**b**) and hyperintensity in the coronal T2 image

10.2 Supratentorial Tumors

10.2.1 Astrocytomas

Supratentorial astrocytomas constitute about 35% of pediatric brain tumors and represent the most commonly diagnosed type of tumor of the cerebral hemispheres. It affects all age groups, girls as frequently as boys. The symptoms depend primarily on the location of the tumor. The diagnostic evaluation for astrocytoma is often limited to an MRI of the brain or spine (Fig. 10.2). The prognosis of supratentorial astrocytomas is slightly inferior to the infratentorial astrocytomas [3].

10.2.2 Ependymomas

Intracranial ependymomas are the third most common primary brain tumor in children, following astrocytomas and medulloblastomas, and are usually located in the posterior fossa, with a radial glial cell of origin [8]. In children, approximately 90% of ependymomas are intracranial, in contrast approximately 75% of ependymomas in adults arise within the spinal canal [9]. The WHO classification includes three grades of ependymoma (Table 10.1) [4].

These tumors represent 5–10% of all brain tumors in the pediatric age group, and the majority occurs in children less than 5 years of age. The incidence of ependymomas is approximately equal in males and females. Supratentorial ependymomas are rare. In general, patients with supratentorial ependymomas have a better survival rate than patients with posterior fossa ependymomas, because gross total resection is more commonly achieved [10]. Ependymomas are generally slow-growing

tumors of children and are usually well demarcated with frequent areas of calcification, hemorrhage, and cysts [11]. Headache and seizures are the most common presenting symptoms and papilledema the most common sign [9].

10.2.3 Craniopharyngiomas

Craniopharyngiomas are a rare suprasellar solid or solid-cystic slow-growing childhood tumor with an estimated incidence of 5% of all brain tumors in children, and it frequently involves intracranial pain-sensitive structures (Fig. 10.3). Craniopharyngiomas are epithelial tumors that usually arise in the pituitary stalk in the suprasellar region, adjacent to the optic chiasm [12].

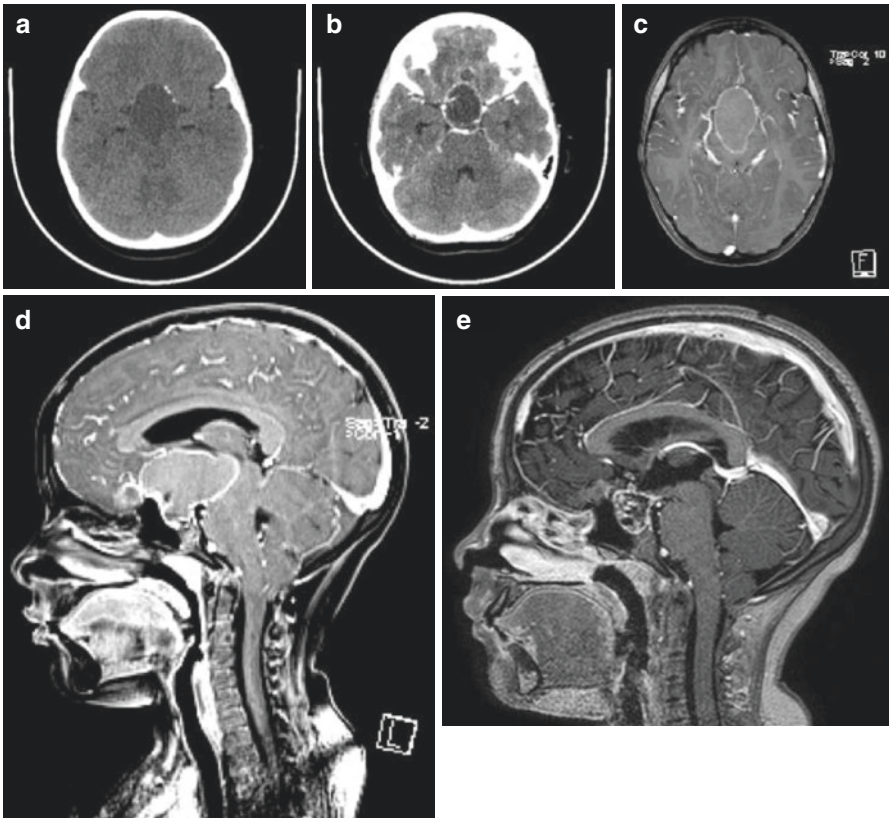

Fig. 10.3 Craniopharyngioma in an 8-year-old girl. Brain CT shows a hypodense solid-cystic lesion with calcifications in the sellar region (**a**) and, after contrast injection, annular enhancement (**b**). Brain MRI shows an isointense solid-cystic lesion with annular enhancement in T1 sagittal image (**d**), with reduction of its dimensions after alfa interferon local injection

The incidence of headache in patients with craniopharyngioma is consistent with the rate in children with brain tumors in general (around 60%) and most commonly described as moderate to severe daily headache, mimicked migraine without aura followed by tension-type headache. This may be due to direct involvement of pain-sensitive structures in craniopharyngioma, obstructive hydrocephalus from tumor compression of the third ventricle, meningeal irritation by escaped cyst contents, or because the encroaching tumor triggers the trigeminal-vascular system. Presence of torsion of the circle of Willis by tumor and larger total tumor volume also indicated an association with headache [5].

10.3 Infratentorial Tumors

10.3.1 Cerebellar Astrocytoma

Cerebellar astrocytomas account for 30% of all posterior fossa tumors in children, with the most common histologic subtype being juvenile pilocytic astrocytoma (JPA) [13]. Peak age is 5–13 years; approximately half arise in the midline and half from the cerebellar hemispheres. They are circumscribed, discrete, slow-growing lesions, often associated with cysts within and around the tumor [4]. On T1-weighted magnetic resonance imaging (MRI), the solid component tends to be iso- to hypointense in comparison with gray matter; heterogeneity is due to microcystic and necrotic areas. It is hyperintense on T2-weighted images. The solid and mural components enhance prominently. Pilocytic astrocytomas maintain their WHO grade I status for years; they only rarely show malignant transformation. Median duration of symptoms before diagnosis is 5–9 months. The clinical presentation usually shows increased ICP (headache, nausea/vomiting, head size) and cerebellar deficits (ataxia, dysmetria, nystagmus). Usual signs even are convergent strabismus and papilledema secondary to hydrocephalus. The treatment goal in patients with JPA is total resection; this goal is achieved in 60–80% of operative cases with a 10-year survival rate of more than 94% [14, 15].

Case 1: Clinical Case of Sudden Headache A 7-year-old boy, 2 days after a minor trauma, started to complain attacks of headache “as a pinch/stab” at the nuchal region, lasting seconds, twice a day, without other associated symptoms. The mother suffered from migraine without aura. His past personal history was unremarkable. After 2 days he had an isolated episode of vomiting without headache, and then he complained headache only during coughing or exercise, sometimes associated with dizziness and mild unsteady gait. He had a stabbing and bilateral pain at the occipital region; the headache was moderate in intensity, had sudden onset, and lasted a few seconds. Apart from the headache attacks, the child was asymptomatic. He presented to our hospital after 2 months for a single episode of paroxysmal torticollis lasting about 2 h; at admission neurological examination and fundus oculi were normal. Considering the atypical headache pattern, the episode of

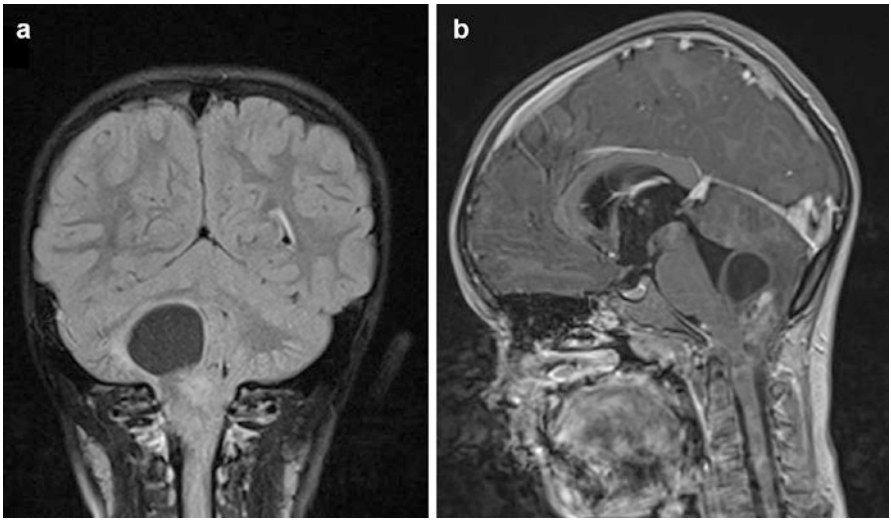

Fig. 10.4 Sagittal contrast-enhanced T1-weighted (**a**) and axial T2-weighted (**b**) images showing cystic cerebellar mass (*asterisk*) in the right cerebellar hemisphere, with a large dishomogeneous enhancing nodule (*white arrows*) in the left cerebellar hemisphere

vomiting without headache and the paroxysmal torticollis, he underwent a brain magnetic resonance imaging (MRI) that showed a cerebellar expansive lesion (Fig. 10.4) and a triventricular hydrocephalus. The spinal MRI was negative. The cerebellar lesion was surgically removed with complete exeresis; the histopathological examination was consistent with a pilocytic astrocytoma (grade 1, World Health Organization). At a 2-year follow-up the neurological examination was normal, and the child was completely asymptomatic.

10.3.2 Medulloblastoma

Medulloblastomas are primitive neuroectodermal tumors (PNETs) and represent the most common malignant brain tumor in children, i.e., 35–40% of all posterior fossa tumors in children. Medulloblastomas occur more often in boys than in girls and between the ages of 4 and 10 years [16]. These tumors typically arise in the middle of the cerebellum, interfering with the flow of CSF and causing hydrocephalus. A child may have headaches, vomit, or ataxia. Sometimes pain at the back of the head occurs. Medulloblastomas can spread to other parts of the brain through the CSF. MRI-T2-weighted imaging shows heterogeneous signal: the solid components appear hypointense relative to gray matter because of the highly cellular nature of the tumor, and the cystic components, which are seen in 59% of cases, appear hyperintense [17]. Calcifications can be found in up to 20% of cases, and hemorrhage is quite rare as well [18]. Approximately 92% of medulloblastomas can

enhance; therefore, at the time of diagnosis, an MRI examination of the entire spine is needed in order to determine if a leptomeningeal dissemination occurred [19]. This last kind of tumor is identified as enhancing nodules on the surface of the brain and spinal cord, often referred to as "sugar coating." Treatment includes surgical excision with adjuvant chemotherapy and craniospinal irradiation when the child is older than 3 years old.

10.3.3 Ependymoma

Ependymomas represent from 8% to 10% of pediatric tumors and may occur at any time during childhood: over 50% of cases arise in children under 5 years of age [20]. Ependymoma is the third most common posterior fossa tumor in children. Incidence peaks in patients are 0–4 years old. Seventy percent of ependymomas develop in the posterior fossa. These tumors are not always distinguishable, on scans, from medulloblastomas. Infratentorial ependymomas arise from the floor or roof of the fourth ventricle and grow into the ventricular lumen. They cause similar symptoms, and hydrocephalus is often involved.

Patients most commonly present with headache, nausea, and vomiting and have a prolonged time to presentation, reflecting the slow growth of the tumor. On conventional MRI it shows high signal intensity relative to uninvolved gray matter on T2-weighted and FLAIR pulse sequences [21]. Areas of low signal intensity relative to gray matter on T2-weighted images and FLAIR images may represent calcifications or hemorrhage. Calcification is a common feature seen in 50% of ependymoma cases, and contrast enhancement is heterogeneous. The usual treatment adopted for the treatment of this kind of tumor is the surgical removal of the same, followed by radiation therapy on the site of the resection. The most important prognostic factor is the extent of surgical resection, so the goal of treatment is a total resection [22]. However, complete resection of posterior fossa ependymomas is often difficult because of adherence and infiltration of vital structures. Thus, radiation is considered the standard adjuvant treatment of ependymomas in older children. Radiotherapy may also be combined with chemotherapy when postoperative residual disease is present. Leptomeningeal dissemination at presentation is less common than in medulloblastoma.

10.3.4 Brainstem Glioma

Approximately 10–15% of childhood brain tumors are brainstem gliomas [23] which most commonly affect children between the ages of 5 and 10 years [24]. Because of their location, brainstem gliomas may cause sudden dramatic symptoms, such as double vision, clumsiness, difficulty swallowing, and weakness. Hydrocephalus occurs late. The classic triad of presentation—long tract signs, cranial nerve deficits, and ataxia—is seen simultaneously in 35% of patients [25].

Brainstem gliomas are not designated as a specific pathologic category in the WHO classification of CNS tumors [4] and are classified by location rather than histology. These are often referred (80%) to as diffuse pontine gliomas. The diffuse intrinsic tumor type is the most common, with an approximate frequency of 75–85% [26]. In these cases, surgery is not usually possible. Radiation therapy, with or without chemotherapy, instead, represents the preferred option. A small percentage of slow-growing tumors that cause slowly progressive symptoms can be treated surgically or with chemotherapy.

On MRI, diffuse pontine gliomas characteristically expand the pons and are usually hypointense relative to gray matter on T1-weighted images and hyperintense relative to gray matter on T2-weighted and FLAIR images. Most diffuse brainstem gliomas do not enhance; however if they do enhance, enhancement is very little and heterogeneous [18]: the cervicomedullary tumor type commonly enhances, and the dorsal exophytic tumor type commonly enhances homogeneously [26]. The diffuse intrinsic type has the worst prognosis of all brainstem gliomas, with median survival rarely exceeding 9 months [27]. Surgery is not a viable option in the diffuse intrinsic tumors but represents the mainstay of treatment of dorsally exophytic tumors and cervicomedullary tumors [28].

Case 2: Clinical Case of Headache and Progressive Clinical Deterioration 5-year-old girl. Onset of symptoms at 3.5 years: from about 1 month appearance of fatigue, instability in the walking with some fall to the ground, drooling with suspected dysphagia, episodes of mixed speech, and occasional right ptosis. Her past personal history was unremarkable. For progressive clinical deterioration, the family accesses a second-level Italian hospital, while on vacation in Italy. In light of the persistent symptoms, brain MRI with contrast-medium and spectroscopy was performed with finding of expansive lesion and then characterized as infiltrating pontomesencephalic glioma associated with obstructive triventricular hydrocephalus (Fig. 10.5). The little girl was sent immediately to a third-level hospital to perform ventricular-peritoneal shunt. Oncologists have given indication to perform specific cancer therapy that the parents have decided to take in their country. After 7 months from diagnosis, increased size of brainstem tumor was documented on MRI, and then she has been subjected to therapy with bevacizumab. Currently, she continues treatment and follow-up in her country of origin.

10.3.5 Atypical Teratoid-Rhabdoid Tumor (ATRT)

ATRT constitutes 1–2% of pediatric brain tumors and has a predilection for infants; it most commonly occurs in children younger than 3 years old [4]. Approximately 15% of children under 36 months with a malignant brain tumor have an ATRT [29]. Within the CNS, ATRT most commonly (38–65%) occurs infratentorial and off midline [30]. Due to its high growth, presentation is often rapid, with macrocephaly and progressive neurological deficit. Up to 20% of cases present with disseminated disease [31].

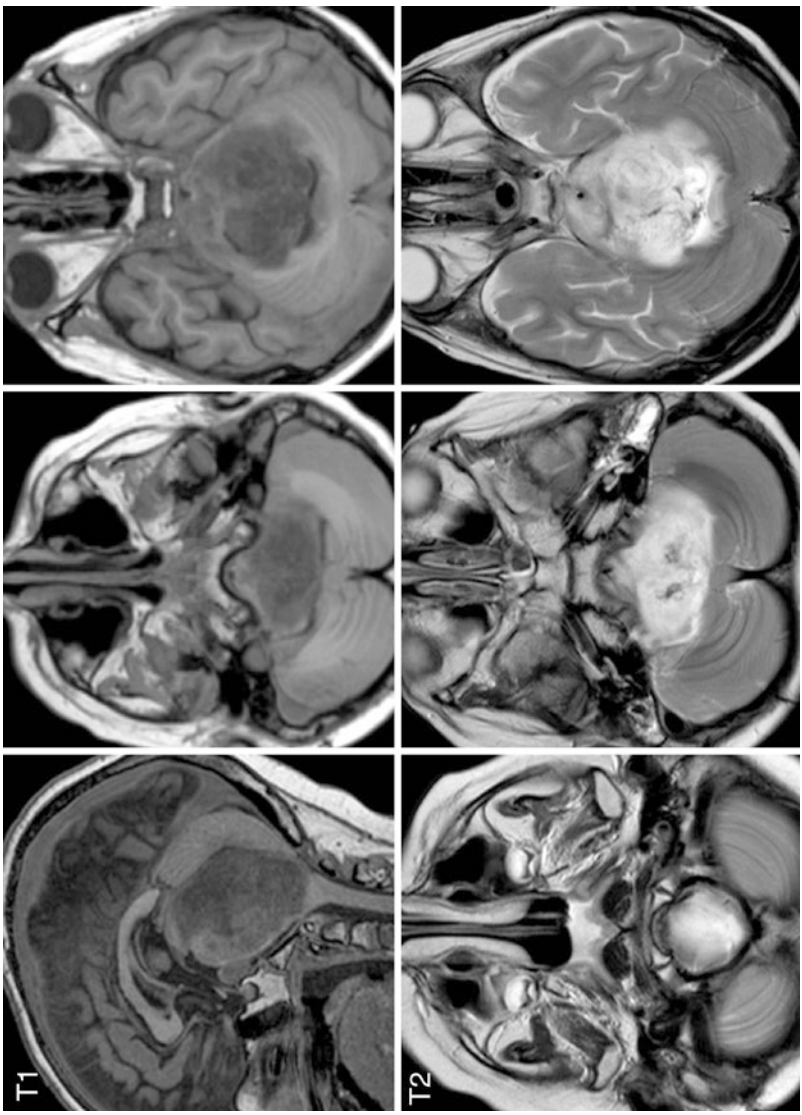

Fig. 10.5 Brain MRI (T1, T2, T1 after contrast and FLAIR sequences) of a 5-year-old girl showing a large infiltrating pontomesencephalic glioma, with contrast enhancement after gadolinium

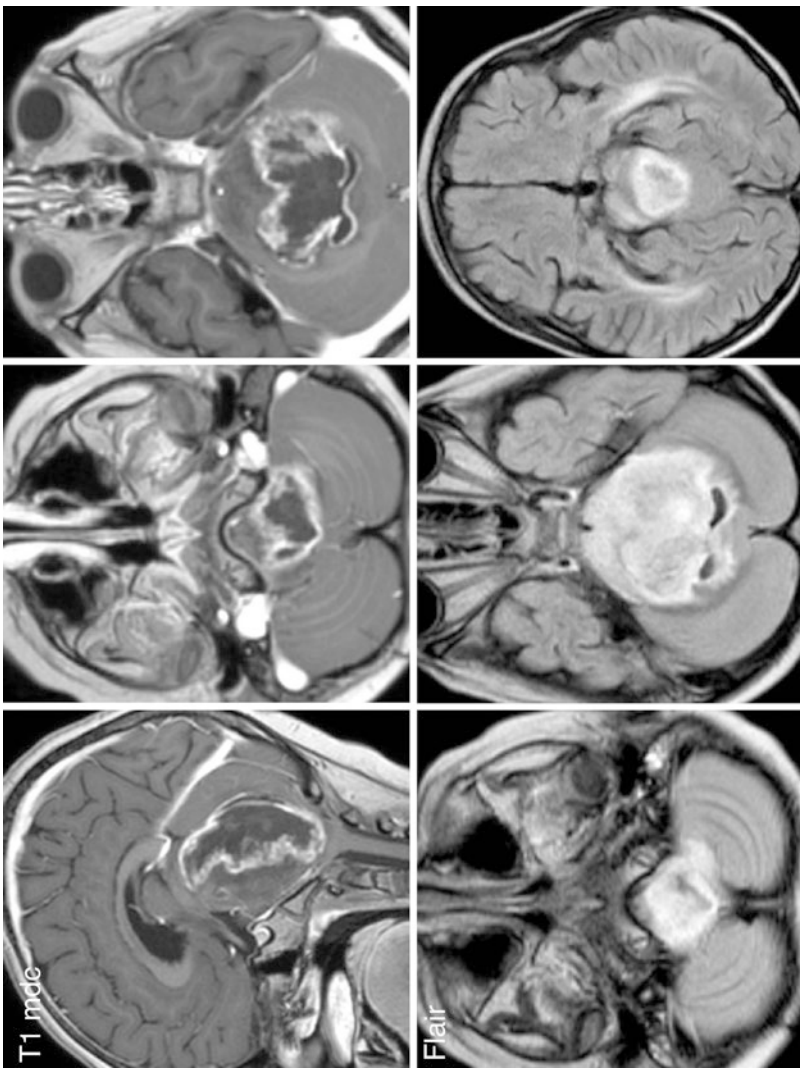

Fig. 10.5 (continued)

ATRT mimics medulloblastoma radiologically and histologically and has been misdiagnosed in the past. ATRT can now be differentiated from medulloblastomas using specific immunohistochemical markers and by detecting certain gene mutations or deletions [32]. Conventional MRI shows heterogeneous signal intensity on T1- and T2-weighted pulse sequences because the mass commonly contains cysts, hemorrhage, and calcifications [32]. Eccentrically located cysts may favor the diagnosis of ATRT over primitive neuroectodermal tumor and medulloblastoma [32]. The enhancement pattern of ATRT is most commonly heterogeneous while it is rarely homogeneous, reflecting the complex histopathology of this tumor [30]. Treatment of ATRT involves surgery and chemotherapy. Radiation is rarely an option because of the young age of the patient [33]. Distinguishing between an ATRT and a medulloblastoma is important because the prognosis associated with ATRT is worse than one associated with medulloblastoma. Median overall survival for a large cohort was 17.3 months [34].

10.3.6 Hemangioblastoma

Hemangioblastomas account for 1–3% of all intracranial neoplasms. In children younger than18 years old, these tumors are extremely uncommon, with an incidence of less than 1 per one million [35]. One of the most frequent manifestations of von Hippel-Lindau (VHL) syndrome is multiple CNS hemangioblastomas, with the most common site of presentation being in the cerebellum (44–72%) [36]. Approximately 25–40% of hemangioblastomas are associated with VHL syndrome.

Patients with cerebellar hemangioblastomas typically present with headache, vertigo, ataxia, and ninth cranial nerve palsy; in some cases, polycythemia has been noted given that up to 40% have been reported to secrete erythropoietin [37]. Hemangioblastomas are highly vascular tumors and may present as a mural nodule within a large cyst cavity (45%) or a purely solid tumor (45%) [37]. Typical hemangioblastomas are hypo- to isointense relative to gray matter on T1-weighted pulse sequences and hyperintense relative to gray matter on T2-weighted pulse sequences with enhancement of the mural nodule. The cyst wall usually does not enhance unless lined by neoplasm [37].

En bloc surgical resection is considered to be the standard of care in adults with cerebellar hemangioblastomas. Data about the appropriate management of children and adolescents with VHL presenting with multiple hemangioblastomas are limited. Recurrence rates range from 8% to 25% [37].

10.4 Headache and Brain Tumor

Despite the high prevalence of headache in children with brain tumors, little data exist regarding the characterization of headaches experienced by these patients. A headache attributed to intracranial neoplasia is defined in the International

Classification of Headache Disorders (ICHD-III) as a headache that improves after effective treatment, if its develops in close temporal relation with the diagnosis of the tumor, or if there is good evidence that the intracranial disorder can cause headache [38].

In a few patients with brain tumors, approximately 25%, the headache did not change quality (character and location) and quantity (severity and frequency) around the time of the tumor diagnosis or still the same after treatment. In these cases the pain was probably independent of the tumor, and a primary origin is assumed [5, 39, 40]. Therefore the term headache *associated* with brain tumors seems to fit better than "headache *attributed* to intracranial neoplasms."

Besides headache, symptoms of pediatric posterior fossa tumors include increased irritability, unsteadiness, ataxia, vomiting, and progressive obtundation, while supratentorial tumors in children are more commonly associated with seizures, motor weakness, visual deficits, speech difficulties, and intellectual disturbance. This mainly depends on the tumor topography, the age of the child, and the size of the tumor [1].

Very early signs of an infratentorial tumor can include drowsiness, headaches, imbalance, ataxia, nausea, and vomiting. Other symptoms of an infratentorial tumor occur when the tumor damages nearby structures of the brain, such as, for example, the cranial nerves. Symptoms associated with cranial nerve damage include dilated pupils, eye problems, facial muscle weakness, hearing loss, loss of feeling in part of the face, problems with taste, ataxia, and vision problems.

Infratentorial and intraventricular tumors are accompanied by headache more frequently than those located supratentorially, probably because of the disturbance of CSF circulation and midline dislocation with increased intracranial pressure [41, 42]. The site of headache may not reflect the tumor localization: infratentorial tumors, in fact, are usually accompanied by frontotemporal pain and only in 27% with nuchal and occipital sufferance [40].

The pathophysiology of headaches in brain tumor patients is not completely understood. Traction of pain-sensitive intracranial structures (include basal arteries, venous sinuses, and basal meninges), expanding tumor mass, and hydrocephalus are the most common cause of it [43]. In brain cancer, traction results from the expansion of tumoral tissue, edema, and/or hemorrhage. Headache seems more common in infratentorial tumors, especially in children because of the high incidence of fourth ventricle neoplasms, and this is probably related to the small space of posterior fossa and the obstruction of cerebrospinal fluid pathways [40, 44].

Generally, in the absence of increased intracranial pressure, in unilateral headache, the headache tends to be on the side of the tumor, showing an association between the location of the headache and the tumor. Infratentorial tumors were found to be significantly more often associated with occipital pain, while supratentorial tumors are more frequently associated with vertex and frontal pain [15, 39, 42, 45]. Unfortunately, frontal pain has poor localizing value. Published prevalence estimates pairing supratentorial tumors with frontal headaches indicate that this association happens in less than 50% of cases [45, 46].

The presence of headache is age dependent: 62% of all patients with brain tumors had chronic or frequent headache, while only 8% of those under 1 year suffered

from headache [41]. In a consistent series of children with brain tumors, less than 1% had headache as their only symptom, and less than 3% had no neurologic abnormality on examination [41].

The relative frequency of headache in children with brain tumors increased through age 5 and keeps increasing with age until young adults, and it is presenting as the most common presenting symptom in patients older than 4 years with CNS tumors [41, 47]. Children aged under 4 years usually cannot clearly describe symptoms such headache, nausea, photophobia, and phonophobia and therefore have a different presentation to older children [48, 49].

Clinical studies show that the "classic" brain tumor headache of severe intensity, worse in the morning, coughing, or with the Valsalva maneuver and associated with nausea and vomiting, was uncommon, affecting approximately 20% of cases [39, 46]. However morning headache associated with nausea and vomiting was observed in 72% of children with supratentorial tumors and 86% with infratentorial malignancies [3]. The most common headaches in children who have brain tumors were nonspecific, mild, and mimicked migraine, followed by tension-like headache, unlike adults in which the most common is described as similar to tension type [5, 6, 50].

Certain specific features of headache have been identified as "red flags," which may suggest the presence of a structural lesion, such as a brain tumor. These "red flags" may include a change in previous headache pattern, progressive course, headache worsening with coughing, sneezing or Valsalva maneuver or exertion, headache getting worse when bending over, nocturnal onset, and headache unresponsive to therapy; any new motor (weakness), sensory, or visual symptoms or signs; a change in memory, personality, or thinking; prolonged/repetitious vomiting; and meningismus [51]. In general terms, however, it must be said that these symptoms can occur also in benign headaches as well. Thus, clinicians may fail to recognize headaches due to brain tumors following ICHD-3 criteria [38], because the distinction between primary and secondary headache disorders may not be so clear-cut [52].

Uncommon headache syndromes caused by infratentorial brain tumors were described in children: trigeminal autonomic cephalalgias, i.e., SUNCT-like headache was caused by astrocytoma in posterior fossa [52, 53]; paroxysmal headache associated with nausea, vomiting, photophobia, and vertigo was caused by a brainstem glioma [54]. Cough or exertional headaches are brief, severe headaches precipitated by coughing or other Valsalva maneuvers. Usually, they have benign etiology, but rare cases in children are reported with symptomatic etiology [55].

The association of headache with strain or a cough shall therefore be regarded as an important clinical issue, which should always be investigated and that can be a sign of alarm for secondary headaches, especially when related to children. When headache has a recent onset, it presents suddenly, and it is triggered by strain; even with normal neurological examination, neuroimaging is mandatory in order to exclude secondary headaches, particularly in children. An early clinical diagnosis allowed in our case a good control of underlying disease [56].

Diagnosis is based on a thorough medical history and physical examination, followed by imaging tests. The best way to analyze the posterior fossa is MRI scan. CT scans are usually not helpful to evaluate that area of the brain.

The incidence of migraine headaches, defined as recurrent headaches that are often pulsating, unilateral, and associated with symptoms such as nausea and light and sound sensitivity, varies in the literature between 13 and 70% of all brain tumor headache in children, depending on the age, type of tumor, and location [3, 57]. The similarity to primary headaches is even higher for pituitary adenomas. Levy et al. [43] found in a case series of 84 patients with pituitary adenoma and headache that 76% had migraine, 27% had primary stabbing headache, 5% had short-lasting unilateral neuralgiform headache, 4% had cluster headache, and 1% had hemicrania continua. The fact that brain tumor headaches can present similarly to primary headaches in those with a predisposition to headaches suggests a shared pathophysiology between primary and tumor-related headaches and implies that the distinction between primary and secondary headache disorders may not be so clear-cut [58].

The most important risk factor for developing headache while suffering from a brain tumor is having a preexisting headache disorder, followed by a positive family history. This reinforces that a common pathophysiologic mechanism is involved [59, 60]. In fact, since the neuronal pathways that lead to headache pain are probably common between the primary and secondary forms of headache, we can hypothesize that in predisposed individuals the tumor may trigger headache attacks or, alternatively, may determine a lowering of threshold for headache [61].

Despite therapeutic advances, children with central nervous system tumors still have a rather poor prognosis: the 5-year survival being 65–70% [62], and the incidence of significant disabilities among survivors is high [63]. The median interval from onset of symptoms to diagnosis is 2 months or more [1, 64], and diagnostic delay may play a significant role in the subsequent development of disabilities [65].

In those cases that surgical removal or volume reduction of neoplasm did not resolve the headache, and so a primary origin is assumed, the approach should be the same as any primary headache without brain tumor. The headache, since there were no signs of elevated intracranial pressure, usually presents of moderate intensity and lasts less than 4 h when not using abortive treatment. Using nonsteroidal anti-inflammatory drugs for abortive treatment (like acetaminophen, triptans), there is resolution within 2 h of headache onset [66]. The intake of β-blockers or antiepileptic drugs significantly reduces the incidence of pain suggesting a prophylactic effect [39].

It is also described in the literature other neurological disorders that predispose CNS tumors and present migraine as comorbid. Pinho et al. [67] found on a transversal study of 50 patients with neurofibromatosis type 1 (NF1), aged 4–19 years, and 50 age-matched controls that migraine was significantly more frequent in the NF1 group than on the control group.

So, children who have headaches and a brain tumor are a heterogeneous population. One subgroup consists of children with no preexisting headache tendency whose brain tumor has resulted in headache. A second subgroup could be children whose inherited headache tendency is exacerbated by intracranial disturbances due to an expanding mass. There may also be a subgroup of children whose headaches are not related to their brain tumor. The magnitude of each of these subgroups is not completely estimated [41].

Diagnosis and treatment of pediatric CNS tumors need a multidisciplinary approach and require the utmost expertise and diligence of all parties involved. Imaging is essential for the correct treatment of these patients and has evolved greatly over the past decade. We are improving the preoperative diagnosis of the tumor type, the recurrence diagnosis, and the surgical management to avoid any injury to vital brain structures. Advanced neuroimaging, combined with refined surgical techniques and progress in chemoradiation treatments, is resulting in better outcomes for affected children.

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Chapter 11
Headache and Epilepsy

Nathan Watemberg and Vincenzo Guidetti

11.1 Historical Aspects

Both headaches and epilepsy received attention in the Bible, in ancient texts, and in scriptures and were addressed to by the forefathers of medicine. Hippocrates around 400 BC provided a detailed description of a man with an aura followed by an intense migraine headache. Epileptic attacks were already described in Babylonian scriptures about 1000 BC. Thereafter, the two entities received significant attention by physicians throughout the centuries. Eventually J.H. Jackson in 1888, before much of the physiology and biochemistry of the central nervous system were discovered, may have been the first to identify the overlap between epilepsy and headaches, as he reported "I have seen cases intermediate in type between migraine, epileptiform seizures and epilepsy proper." W. Gowers [1] added to this observation: "migraine is given a place in the borderland of epilepsy, the two maladies are sometimes mistaken, and more often their distinction is difficult" [2].

The two clinical phenomena share various clinical and pathophysiological aspects: both migraine attacks and epileptic seizures involve paroxysmal episodes of transient altered brain function, including sudden changes in behavior, consciousness, sensory symptoms involving the special senses, motor phenomena, and speech function [3]. Although throughout life epilepsy affects both genders similarly, migraine is more prominent among females, especially after puberty [4].

N. Watemberg, M.D. (✉)
Pediatric Neurology Unit, Meir Medical Center, Tel Aviv University Medical School, Kfar Saba, Israel
e-mail: nathan.watemberg@clalit.org.il

V. Guidetti, M.D.
Department of Pediatrics and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, Rome, Italy

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Headaches may precede a seizure, may be a manifestation of the epileptic event, or may represent a prominent postictal symptom. Indeed, epileptic seizures and migraine headaches may be mistaken one for the other [3]. Adolescents with any headaches aged 13–18 years reported higher rates of epilepsy, persistent nightmares, motion sickness, and abdominal complaints [5]. In a sample of 400 children with epilepsy, the prevalence of migraine was greater than that of non-epileptic children (25% vs. 3–23%). Migraine was more prevalent in adolescents, in patients with Rolandic epilepsy, and in youngsters with juvenile myoclonic epilepsy. Of note, a diagnosis of migraine was more likely to be made in children with well-established epilepsy [6].

Among a large sample of children with headache, the risk of epilepsy was 3.2 times higher in patients with migraine than among those with tension-type headache. Conversely, children with epilepsy were 4.5 times more likely to develop migraine than tension-type headache. Photic sensitivity on EEG and family history of epilepsy were associated with a higher incidence of headaches [7]. Nevertheless, a very recent study from Greece reported a much lower co-occurrence of migraine and epilepsy among children and adolescents: only 2.3% of 84 children had both conditions, although 11% of children with epilepsy reported non-migraine headaches [8]. Hence, an association between migraine as a specific type of headache and epilepsy in children and adolescents has not been firmly established. On the contrary, adults with epilepsy have a higher prevalence of migraine and other headache types, occurring independently of epileptic seizure activity [9]. Remission of epilepsy in epileptic patients who also suffer from migraine seems less likely than that seen in people with epilepsy without migraine [10], and comorbid psychiatric conditions including depression are more frequent when epilepsy and migraine co-occur [11].

Lennox introduced the term “migralepsy” to describe a condition of classical migraine with aura followed briefly by an epileptic seizure, creating the impression that migraine may trigger an epilepsy seizure. Conversely, in some epilepsy syndromes, particularly the occipital epilepsies, the seizure is followed by severe headaches [12, 13]. Although the existence of migralepsy as a distinct entity has been challenged by researchers, the 2013 International Classification for Headache Disorders-3 beta (ICHD-III beta) of the International Headache Society still recognized the existence of “a seizure fulfilling diagnostic criteria for one type of epileptic attack, occurring in a patient with migraine with aura during, or within 1 h after, an attack of migraine with aura, and not better accounted for by another diagnosis.”

11.2 Headache and Epilepsy: Overlapping Features

Both migraine and epilepsy are disorders that are common, paroxysmal, and chronic. Attacks of both migraine and epilepsy have been divided into four phases (premonition, aura, ictal, and postictal) [2]. Premonitory symptoms may be felt

minutes to hours, sometimes even days prior to a migraine attack: fatigue, nausea, neck pain, and photo- or phonophobia are quite common. Epilepsy patients often describe premonitory symptoms, albeit less frequently than their migraine counterparts. Both epileptic seizures and migraine attacks may begin with a brief aura, most commonly visual (Nye). In migraine, visual auras tend to begin gradually and to be black and white with a linear or zigzag pattern, whereas epileptic auras start abruptly and are colored and rounded [14]. However, depending on their site of origin, epileptic auras and, less frequently, migraine auras may consist of unilateral paresthesias and gustatory or olfactory symptoms [2].

A particular source of confusion and misinterpretation occurs in the presence of occipital lobe lesions, such as arteriovenous malformations (AVM), tumors, or gliosis. The occipital lobes are the structures most commonly responsible for the co-occurrence of migraine and epilepsy in the same patient, to the point that visual auras and acute headache (ictal headache) may be intermittently epileptic or migrainous in specific individuals. Ictal EEG during the headache episode may assist in establishing the nature of the event although, as discussed later, treatment options are frequently based on the same pharmacologic agents [15].

Regarding the ictal event, i.e., the attack itself, the headache of migraine is less likely to be mistaken for a seizure. In the same manner, the epileptic seizure is quite different from the subjective symptomatology of headache. However, in recent years it has become obvious that at times an acute headache with migrainous features may represent an epileptic event ("ictal epileptic headache" or "epileptic headache" [16]. Moreover, occasionally migraine attacks may be confused with complex partial seizures and vice versa, particularly in the case of acute confusional migraine, a rare migraine manifestation almost exclusively seen in adolescents [17].

Finally, both migraine and epilepsy attacks may have a postictal stage, usually more dramatic following a generalized tonic-clonic seizure characterized by a period of minutes to hours of confusion or lethargy. Nevertheless, after the acute headache in migraine, patients are often sleepy or very fatigued [2]. A particularly overlapping feature between both conditions is that of Todd's paresis (unilateral motor weakness after an epileptic seizure) and acute hemiparesis occurring at the beginning or during the migraine attack [18].

In clinical practice, a different approach by specialists is seen: experts in epilepsy usually define an electroclinical event by EEG findings. Conversely, headache specialists use a purely clinical diagnostic classification. This difference may have repercussions when attempting at finding common grounds between epilepsy and headache. Three types of headache in association with seizures are recognized by ICHD-III beta: migraine aura-triggered seizure ("migralepsy"), hemicrania epileptica, and postictal headache. Migralepsy, as previously mentioned, is a rare and controversial term for a seizure occurring during or within 1 h from the onset of a migraine aura; hemicranias epileptica, also rare, describes headache occurring during an ipsilateral partial seizure and remitting immediately or shortly after the seizure. Postictal headache, a much more common condition, refers to a headache appearing within 3 h after the epileptic attack and lasting up to 72 h [19]. This headache often has migraine-like features. Younger epilepsy patients and those with

longer epilepsy duration, refractory epilepsy, generalized tonic-clonic convulsions, and occipital epilepsy have a higher incidence of postictal headache [20].

While headaches are easily recognized as part of epilepsy syndromes, awareness about seizures occurring as part or during a migraine episode may help to avoid misinterpreting the seizure as an epileptic event [21].

11.3 Coexistence of Migraine and Epilepsy

11.3.1 Non-epileptic Conditions which May Raise a Suspicion of Epilepsy

Migraine with brainstem aura. In this condition, symptoms consistent with or suggestive of posterior circulation deficit with subsequent brainstem signs occur. The attacks involve dysarthria, tinnitus, vertigo, ataxia, and double vision. Neuroimaging studies are normal, although posterior epileptiform activity may be seen during the event. This syndrome is seen more frequently in children and adolescents [2].

Alternating hemiplegia of childhood. This complex condition is characterized by recurrent episodes of hemiplegia lasting from minutes to days and alternating between the sides. Abnormal ocular movements, seizures, and dystonia have also been described. Attacks begin in the first 1–2 years of life, and many cases appear to be sporadic, whereas others are clearly genetic and overlap with hemiplegic migraine. Given the abrupt onset of hemiplegia attacks, some cases could potentially be misdiagnosed as hemiplegic migraine. However, the almost universal presence of cognitive deficits and the onset of the disease in early childhood should help in ruling out migraine as the etiology of the attacks in these cases [22].

Confusional migraine. As aforementioned, occasionally adolescents, including those with migraine and those in whom classic migraine headaches have not yet appeared, present with abrupt confusion lasting minutes to hours, often (but not always) followed by headache. EEG shows unilateral or bilateral slowing, but no evidence of ongoing electrographic seizures. Of note, the confusion episodes do not recur but are rather followed by the development of classic migraine attacks [17].

Vestibular migraine. This migraine equivalent actually encompasses several subtypes, all resulting in vertigo and dizziness and frequently in ataxia as well. A particularly interesting case is that of the calcium channelopathy associated with mutations in the CACNA1A subunit. Here, specific mutations may result in familial hemiplegic migraine or in familial episodic ataxia, or in both syndromes occurring alike. Of note, epileptic seizures may also develop [23]. More recently, other mutations have been linked to early-onset paroxysmal events: mutations in the PRRT2 gene may also provoke paroxysmal dyskinesias, benign familial infantile seizures, hemiplegic migraine, and episodic ataxias [24]. Although movement disorders and epilepsy predominate as the clinical expressions of PRRT2 mutations, it seems likely that cases of adolescence-onset or of adult-onset migraine, particularly with

transient hemiplegia, will be recognized in the near future. On the other hand, in parietal lobe epilepsy without an obvious genetic component, sensory auras with vertigo and a feeling of "rotation" may occur prior to the epileptic seizure [2].

11.3.2 Epilepsy Syndromes with Headaches as a Common Clinical Feature

11.3.2.1 Benign Partial Epilepsy

All of the three predominant focal epilepsy syndromes of childhood: benign epilepsy with centro-temporal spikes (Rolandic epilepsy), Panayiotopoulos syndrome, and occipital epilepsy of the Gastaut type may involve either headaches or migraine-like features as part of their semiology. However, Gastaut-type occipital epilepsy is the syndrome most commonly associated with migraine-like features: these children depict normal cognition and tend to develop epilepsy toward the end of the first decade of life. Patients often have a personal or a family history of febrile seizures and a family history of migraine. Their EEG shows interictal occipital spike—or spike-and-wave discharges clearly exacerbated by eye closure. Visual phenomena (hallucinations) consisting of multicolor and circular shapes are the most frequent ictal epileptic manifestation, often occurring daily. As previously mentioned, non-epileptic visual symptoms associated with migraine develop more gradually and consist of linear or zigzag black-and-white patterns and are less frequent than the visual phenomena of occipital epilepsy. Transient ictal blindness and horizontal tonic eye deviation are also common ictal features of Gastaut-type occipital epilepsy. Secondary seizure generalization is frequent [25]. Interictal migraine headaches are seen in 16.3% of cases, and convulsive seizures may occur during the migraine attack in about one fifth of those who develop migraine [26].

Panayiotopoulos syndrome, formerly considered to be a form of benign childhood occipital epilepsy, is now recognized as a form of benign partial epilepsy with a migrating epileptic focus [27]. Autonomic seizures are predominant, and quite frequently the initial presentation of the syndrome involves ictal vomiting arising mostly from sleep and often (but not always) accompanied by hemiconvulsion or by secondary generalization [28]. The profuse vomiting and pallor of the epileptic attack may at times be misinterpreted as an expression of migraine, namely, of cyclic vomiting syndrome.

Rolandic epilepsy (benign epilepsy with centro-temporal spikes) is the most common epilepsy syndrome. Although most patients experience seizures during childhood, the low seizure threshold often extends into early adolescence. Seizures arise from the Rolandic area which involves both the prefrontal motor cortex and the primary somatosensory cortex. Hence, most seizures manifest as dysarthria and sialorrhea, unilateral facial twitching or paresthesia, hemibody clonic convulsion, or hemi-paresthesia. Although studies have suggested that migraine headaches are more prevalent in children with Rolandic epilepsy [3], others support a more general

association between all types of benign partial epilepsies (which include Rolandic epilepsy) rather than a specific correlation [29]. Nevertheless, there is strong evidence for familial aggregation of migraine in Rolandic epilepsy families [30] and even for a linkage to at least two chromosomal loci [31]. Very recent evidence suggests that Todd's paralysis, a relatively uncommon postictal feature in Rolandic epilepsy, is associated with a higher prevalence of migraine [32].

11.3.2.2 Juvenile Myoclonic Epilepsy

Among epilepsies affecting adolescents and young adults, patients with JME report a high prevalence of headaches: 47 of 75 patients reported chronic or recurrent headaches: migraine without aura in 20, tension-type headache in 16, and migraine with aura in 14 [33]. Among 400 children with epilepsy, migraine was also found to be significantly prevalent in JME [6].

11.4 Common Genetic Features of Migraine and Epilepsy

Although the etiology of migraine and of epilepsy is heterogeneous, a strong genetic component is suggested on clinical grounds. Particularly in epilepsy syndromes of childhood and adolescence, genetic mutations and channelopathies have been increasingly identified. Some of these genetic etiologies are also associated with certain, albeit rare, forms of migraine.

As mentioned above, rare monogenic forms of migraine such as familial hemiplegic migraine (FHM) are well recognized, and co-occurrence of epilepsy in some cases has been reported in mutations such as CACNA1A (neuronal P−/Q-type calcium channel), ATP1A2 (Na1-K1 transporter), and SCN1A (voltage-gated sodium channel) [25, 34, 35]. The most commonly shared genetic etiology of migraine and epilepsy pertains to ATP1A2 which causes FHM2, and about 20% of cases also depict febrile seizures and develop epilepsy, particularly in infancy and childhood [36]. On the other hand, SCN1A, encoding the voltage-gated Na + channel Na_vI.I. the most frequently identified genetic mutation in epilepsy with hundreds of identified mutations [37], has also been associated with the rarely occurring familial hemiplegic migraine 3 (FHM3). In most cases of epilepsy, SCN1A mutations seem to predict loss-of-function effect; so far the few mutations associated with migraine suggest a gain-of-function effect [38].

CACNA1A has been associated with both gain and loss of gene function, and besides FHM and epilepsy, it is associated with episodic ataxia type 2 and spinocerebellar ataxia type 6 [36].

Mitochondrial defects have been proposed by some authors as etiopathogenic factors in some cases of migraine. Although mutations found in classic mitochondrial disorders such as MELAS, MERRF, and Kearns-Sayres have not been detected in migraineurs, polymerase gamma—POLG—deserves special attention. In recent

years, epilepsy has been increasingly reported as a main clinical feature in some POLG-related cases, especially partial epilepsies, of which occipital seizures are most frequent. These patients often experience recurrent status epilepticus. Among associated symptoms, migraine and other headache types are reported by patients [39, 40]. A bimodal distribution of disease has been described: early childhood and adolescence [39].

11.5 Shared Pathophysiology of Migraine and Epilepsy

As previously mentioned, there is accumulating evidence for (at least some) common neocortical mechanisms underlying both conditions [41, 42]. Although neocortical hyperexcitability occurs initially in both migraine and epilepsy attacks, the subsequent neuronal changes are quite different: in migraine, neuronal hyperexcitability appears to be followed by spreading depression (CSD) [36, 43], whereas in epilepsy, hypersynchronous neuronal discharges and changes in membrane ion permeability occur [44]. Nevertheless, as our understanding of the processes that take place immediately after neuronal hyperexcitability increases and evidence accumulates linking seizures and headache within the same clinical event, it is likely that for many, if not most, attacks, common mechanisms will be found to predominate in both conditions [45]. In fact, neuronal synchronization and field oscillations appear to precede the onset of both CSD and neuronal hyperexcitability [46]. Interestingly, these synchronizations and oscillations do not occur through synaptic connections but rather through excitatory neurotransmitter, notably glutamate, and medications that block N-methyl-D-aspartate glutamate receptors such as ketamine and have potent antiepileptic effect and prevent the neuronal oscillations that precede CSD and even CSD itself [47]. Moreover, several antiepileptic drugs, irrespective of a specific mechanism of action, are effective in preventing both migraine and epileptic seizures [3], further supporting a common neuropathopysiologic mechanism. Finally, as previously stated, the increased incidence of postictal headaches in patients with occipital lobe epilepsy, the brain region where CSD begins, further emphasizes the shared mechanisms in the origin of epileptic seizures and migraine attacks [36].

11.6 Common Therapeutic Aspects

Prophylaxis of migraine with oral medications acting through various mechanisms of action is well established. Beta-blockers (propranolol), calcium channel blockers (flunarizine, verapamil), tricyclic antidepressants (amitriptyline), and antiepileptic medications (AEDs) are most commonly used. However, despite the fact that all these substances prevent CSD and are effective in migraine prevention, only some antiepileptic medications, notably topiramate and valproate, and occasionally

verapamil and flunarizine, are effective in preventing both migraine and epileptic attacks [48]. A purported explanation for the efficacy of calcium channel blockers is the inhibition of P-glycoprotein which allows higher concentrations of AEDs in the brain [49]. Hence, despite the accumulating evidence for common mechanisms in both conditions, particularly the role played by CSD, it is clear that processes yet uncovered are present, probably involving membrane channel subunits [2]. Indeed, both topiramate and valproate are broad-spectrum AEDs, each with multiple mechanisms of action. They are usually well tolerated, and the dosage needed for migraine is generally lower than that prescribed for epilepsy AEDs with single or limited mechanisms of action such as lamotrigine, carbamazepine, or levetiracetam which are usually not effective in the prophylaxis of migraine [3].

11.7 Conclusions

Migraine headaches and postictal headaches, particularly as part of specific epilepsy syndromes, are common among children and adolescents with epilepsy. Conversely, epileptic seizures occurring during migraine attacks are not rare. Both epilepsy and migraine share common mechanisms of action, and more common pathophysiologic phenomena are likely to be uncovered in the near future. Genetic defects, especially channelopathies, are probably responsible for most of the overlapping symptomatology of migraine and epilepsy and for the relative success of broad-spectrum antiepileptic drugs such as topiramate and valproate in preventing both seizures and migraine attacks. As our understanding of the mechanisms underlying migraine and epilepsy broadens, new and exciting therapeutic modalities will no doubt enhance therapeutic armamentarium.

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Chapter 12
Comorbidity with Psychiatric Disorders

Marco A. Arruda, Noemi Faedda, Giulia Natalucci, and Vincenzo Guidetti

12.1 Introduction

Headache is one of the most frequently reported somatic complaints by children and adolescents [1], and it affects about 54.4% of children and adolescence in the world [2]. Tension-type headache (TTH) (prevalence of 20–25%) is the most common cause of primary headache, followed by migraine (prevalence of 8%) [3]. TTH and migraine were identified as second and third most common diseases all over the world [4], and furthermore they are associated with a great number of comorbidities such as anxiety, mood disorder, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), etc. [5, 6]. Although some authors suggested that fundamental cause of migraine in children is largely genetic [7], Arruda et al. [8] showed in a large sample of Brazilian children that patients with migraine are at an increased risk of having emotional symptoms, conduct problems, hyperactivity, peer problems, and total difficulties in psychosocial adjustment. Children with ETTH, in turn, were significantly more likely to have emotional symptoms and total difficulties causing impact in their psychosocial adjustment compared with controls.

Furthermore it is widely recognized that headache patients with comorbidity made a greater use of health services, and they have a poor health perception than headache patients without comorbidity [6, 9, 10]. Indeed studies about health-related quality of life (HRQOL) in migraine patients found a poor HRQOL, further reduced when individual had another disorder in comorbidity, especially a mood disorder [11, 12].

M.A. Arruda, Ph.D., M.D.
Child and Adolescent Neurologist, Glia Institute, Ribeirao Preto, SP, Brazil

N. Faedda, Ph.D. • G. Natalucci • V. Guidetti, M.D. (✉)
Department of Paediatrics and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, Via dei Sabelli, 108, Rome, Italy
e-mail: Vincenzo.guidetti@uniroma1.it

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So it is very important to recognize the presence of these comorbidities, because if they are not acknowledged, they could have a negative impact on adherence to treatment and quality of life, and they could increase the risk of headache chronicity [6].

12.1.1 Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder in childhood [13]. The prevalence of ADHD in pediatric headache is still unclear. Genizi et al. [14] in a recent retrospective study on children and adolescents with primary headaches reported a high rates of prevalence of ADHD (28%) in their sample with general pediatric population. This association could be explain, on the one hand, by the fact that symptoms of headache and the core symptoms of ADHD (inattention and hyperactivity) both can be caused by stress in family or school; on the other hand, headaches by themselves may increase distractibility especially in children with a primary short attention span [14]. Arruda et al. [15] have found that migraine is not comorbid to ADHD overall, but are comorbid to hyperactive-impulsive behavior, and other studies showed an association between pediatric migraine and impaired attention span [16]. It was showed that alterations of neuronal network and cerebral regions underlie both conditions [17]. Some neurotransmitters such as dopamine and noradrenaline are involved in the pathophysiology of migraine and ADHD. Several drugs acting on dopamine receptors are effective in migraine treatment, and stimulant drugs regulated the altered patterns of activation in some dopamine-rich regions in patients with ADHD. Other studies explain the relationship between headache and ADHD, taking into account the fact that sleep disorders are implicated in both disorders. ADHD and headache involved the same brain structure that acts in control of the sleep-wake cycle as well as in the arousal generation during sleep and modulation of pain [17]. It is crucial to acknowledge the association between ADHD and headache, because it may cause impairment in social and academic functioning [5, 14]. Future research is needed to better explain this complex relationship and its impact on child development.

12.1.2 Obsessive-Compulsive Disorder

The obsessive-compulsive disorder (OCD) is characterized by obsessions out of the patient's control which cause anxiety and compulsions which are repetitive behaviors to prevent or reduce this anxiety [18, 19]. Several studies detected that OCD may have prognostic significance in the clinical course of chronic migraine (CM) patients [18, 20].

Vasconcelos et al. [21] reported a case of a 14-year-old patient with refractory chronic migraine and OCD, showing as OCD may contribute to the development or maintenance of treatment-resistant chronic headache.

Vulić-Prtorić et al. [22] found that children with headaches have significantly more obsessive and compulsive problems (11.6%) than healthy controls (5.1%). The authors suggest that the relationship between headache and OCD can be described through the different rituals children can use to avoid the appearance of physical symptoms (e.g., excessive washing and cleaning, afraid of contamination or diseases).

Curone et al. [18] found a prevalence of obsessive-compulsive traits in patients with chronic migraine and medication overuse, suggesting that the lack of control on impulsivity can increase the drug intake and thus enhance the risk for progression from episodic to chronic migraine.

Further studies are needed to plan a specific treatment strategy fort these patients and to know whether an appropriate management of headaches may help children and adolescents with OCD to reduce the tics or other problems caused by the syndrome.

12.1.3 Risk of Suicide

Suicide is one of the most common causes of death among adolescents [23, 24]. Horton has coined the term "suicide headache" because the severity of headache attacks can lead patients to consider suicide. Indeed several studies showed a great prevalence of suicide attempts, suicidal ideation, and intentional self-harm in adults with headache [25–29]. To stop the pain, sufferers may beat their heads, strike objects with their fists, or even bang their heads against a wall [30]. As of today, few studies investigated the risk of suicide in pediatric population with headache. Wang et al. [31] identified high comorbidity of suicidal risk in adolescents with chronic daily headache. In particular migraine with aura seemed to be the higher predictor for these associations. The same authors in 2009 confirmed previous finding, identifying a higher frequency of suicidal ideation in adolescents (13–15 ages) with migraine with aura or high headache frequency [32].

Luntamo et al. [33] found that childhood pain predicts severe suicidality among males, but not among females. Parent-reported child's abdominal pain at age 8 was associated with severe suicidality by age 24 among males. The association between 8-year-old boys' own report of headache and severe suicidality by age 24 reached borderline significance.

Future research, focusing on the relationship between headache and suicide risk, is needed during adolescence. The teens are at higher risk of suicidal ideation or suicide attempts, and the presence of a several pain condition, like headache, may cause further complications.

12.1.4 Learning Disability

Several studies showed the burden of pediatric headache on quality of life and its impact on school [1, 34]. Learning disabilities affect about 24.7% of children and adolescent with headache [14].

A previous study reported that children with migraine were absent from school activities, did not perform household tasks, and did not participate in leisure activities for 23.9 days, during the last 3 months, because of migraine [35]. The loss of school days due to headache affects school performance, and it is one of the major causes of learning disabilities.

Genizi et al. [14, 36] reported that learning disabilities were more common among children with migraine compared to children with TTH, in children with long duration of headache, and among children with more than ten episodes of headache per month.

Parisi et al. [37] investigated whether children affected by tension-type headache and migraine without aura, compared with a healthy control group, showed two different intellectual functioning and two separate "cognitive profile." They found a negative correlation between the total intelligence quotient, verbal intelligence quotient, performance intelligence quotient, and the frequency of attacks, as well as between the total intelligence quotient score and the age at headache onset.

Future research, addressing on the relationship between headache and learning disabilities, is needed. It would be interesting to evaluate the cognitive profile of children with headache during the first examination, to see if children with this disorder have a typical cognitive profile or if it is the frequency and the severity of the pain to cause a negative impact on school performance.

12.1.5 Depression

As well as headache, depression is a widespread problem in children, especially among teenagers. Internalizing disorders, just as depression and anxiety, are most frequently associated with primary headaches, and it has been noted that such symptoms are much more common in patients diagnosed with migraine, rather than in people without any pathology [38].

Many researches have studied depressive symptoms in children and adolescents with headache or the incidence of depression in headache population. For example, Blaauw and colleagues [39] noted that children with chronic daily headache had higher depression scores than the headache-free population. Moreover, children with chronic migraine were more anxious and more depressed than those with chronic tension-type headache, whereas there were no differences between children with episodic migraine and chronic headache. The strong association between chronic migraine and depressive symptoms in children and adolescents is well recognized in literature [40, 41]. It has also been seen that a higher intensity and

frequency of headache are associated with a higher number of depressive symptoms. The risk of a first migraine attack in people with diagnosis of major depression is three times higher than in people without a history of depression [42]. On the other hand, some studies suggest that psychiatric disorders, like depression, might not specifically relate to migraine, but to chronic illness in general [43, 44].

The comorbidity of depression and headache can have a significant impairment on children's life. In a recent research, Öztop and colleagues [45] found higher depression scores in children with migraine compared to controls and a positive correlation between depression scores and quality of life, while quality of life and pain severity and degree of disability were negatively correlated. Regarding missing school days and absenteeism, it has been noted that adolescents with both depression and headache miss more school days than adolescents without any disease [46]. Other researchers find out that the association between headache duration and depression may influence school functioning independent of headache diagnosis. Furthermore, adolescents with tension-type headache and protective parenting seem to be linked to higher school difficulties [47].

There are also evidences of shared genetic factors underlying depression and migraine [48], and this could be very useful for the management of both disease. Through medical history, the clinician should consider the possible presence of depressive symptoms in the boy's parents because they could be an important index for a genetic predisposition.

All these evidences are extremely relevant because this association not only erodes quality of life but also increases overall costs of medical care [49]. Awareness of this comorbidity by clinician and a better understanding of the underlying mechanisms may facilitate headache treatment, and it may be suggested a combined therapy with the aim to decrease depressive symptoms and improve patient quality of life.

12.1.6 PTSD and Headache

Experiences or the exposition to personal violence, sexual abuse, natural disaster, chronic disease, or other traumatic events can lead to post-traumatic stress disorder (PTSD) [50, 51]. PTSD has a high prevalence rate among children and adolescents, and it can change according to different traumatic events.

Many studies have evaluated somatic symptoms among children with PTSD, and headache is quite common. For example, Zhang and colleagues [52] found that somatic symptoms were frequent in children and adolescents after the Lushan earthquake in China. About 41.7% of children and adolescents suffered from headache 6 months after the earthquake.

Generally, childhood adversities may contribute to greater risk of the development of headache and, in particular, chronic daily headache in young adolescents. Juang et al. [53] evaluate the relationship between childhood adverse events within the family and chronic daily headache. They enrolled students in three public

schools in Taiwan and noted that events like physical abuse and parental divorce were more frequent in the CDH group compared to control group. So they hypothesize that childhood adversities may contribute to greater risk of the development of CDH in young adolescents.

Regarding the relationship between migraine and PTSD, Smitherman and Kolivas [54] showed that PTSD in young adults was a robust predictor of migraine, whereas trauma exposure alone was not. The sole exposition to trauma is not enough to predict migraine, but a major severity of PTSD symptomatology can be associated to higher frequency, severity, and disability migraine.

On the other hand, and Juang and Yang [55] hypothesized that vulnerability to PTSD after trauma is related to migraine attacks, migraine chronicity, and especially migraine aura.

Many theories suggest the implication of serotonergic, autonomic nervous system, and HPA axis dysfunction underlying both PTSD and migraine. Also in anxiety disorders, these systems are involved, explaining the high comorbidity rates between anxiety and both migraine and PTSD [55]. The hypothalamic-pituitary-adrenal axis (HPA axis) controls multiple biological, affective, behavioral, and cognitive responses to stress, and its dysregulation may be one mechanism through which stress impacts health [56]. According to these evidences, Kuhlman and colleagues [57] studied the relationship between trauma and HPA axis activation, and they found different axis activations according to various types of trauma (exposure to non-intentional trauma, physical abuse, and emotional abuse).

12.1.7 Anxiety and Headache in Children

Anxiety and depressive disorders are among the most common forms of psychopathology affecting children and adolescents. Anxiety disorders prevalence rates are approximating 15–20% in the general population [58]. Children with headache often complain internalizing symptoms, and the most frequent are anxiety symptoms [5]. According to Machnes-Maayan and colleagues [59], anxiety is present in 68.8% in children with tension-type headache and in 56.3% in children with migraine, compared to 9.1% in children without any pathology.

Some studies support the hypothesis that frequency of headache attacks can influence anxiety symptoms. For example, Tarantino and colleagues [60] found higher scores in the migraineurs with a low attack frequency in separation anxiety subscale, compared to children with high frequency attack. Separation anxiety disorder is characterized by an excessive worry about separation from another person who represents safety for the affected child, typically a parent. This disorder often present in comorbidity somatic complaints, and the most frequent are headache, nausea, and abdominal pain [61]. Moreover, Fielding et al. [62] noted that children with anxiety disorders had a higher incidence of headache symptoms consistent with migraine and tensions type compared to children without anxiety disorders. They also found an association between separation anxiety disorder and a higher incidence of headache.

A specific anxiety disorder associated with chronic headache is school phobia [63]. Children with school phobia do not want to go to school, refuse everything that is linked to it, and have inappropriate behavior. They also refer frequent headache attacks, especially migraine attack. School phobia, and phobic disorder in general, seems to be more associated with migraine, followed by generalized anxiety disorder and obsessive-compulsive disorder [64].

Also social phobia can coexist with headache. This specific phobia is characterized by extreme anxiety and fear of embarrassment during social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others [65]. It seems that chronic migraine is strongly associated with high social anxiety score, whereas there are no differences between episodic migraine and population without migraine [66].

Anxiety and internalizing symptoms can be linked to fear of pain that could contribute to the maintenance and exacerbation of chronic pain [67]. Higher anxiety sensitivity can lead to a higher fear of pain and consequently to an increased likelihood of headache chronicity.

The association between headache and anxiety is not well known yet, but several theorists highlight the commonality of mechanisms that underlie anxiety and chronic pain, such as serotonergic dysfunction, hormonal influences, dysregulation of the hypothalamic-pituitary-adrenal axis, and/or psychological factors like interoceptive conditioning, fear of pain, anxiety sensitivity, and avoidance behavior [64, 68].

12.2 Conclusion

Treatment of comorbidity disorders in addition to headache therapy can improve headache management and may decrease the need for prophylactic therapy in children and adolescents [45].

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Chapter 13
Comorbidity with Sleep Disorders

Oliviero Bruni, Raffaele Ferri, Marco Angriman, and Marcin Zarowski

13.1 Introduction

The reciprocal relationship between headache and sleep has been documented in medical literature for over a century, and clinical texts allude to the importance of sleep as a headache precipitant. The precise nature and magnitude of the headache/sleep association and underlying mechanisms remains poorly understood [1].

Both sleep disturbances and headache disorders are widespread health problems during childhood: migraine and tension headaches alone occur in approximately 12% of the pediatric population, and 25% of children have experienced at least one type of sleep problem [2, 3].

Sleep represents a well-documented behavioral state related to the occurrence of some headache syndromes. Sleep disorders are observed among all headache subgroups, and headaches that occur during or after sleep are suggestive of sleep disorders.

In the adults, the presence of a specific sleep disorder has been identified in 55% of subjects with onset of headache during the night [4], and the treatment of the

O. Bruni, M.D. (✉)
Department of Developmental and Social Psychology, Sapienza University,
Via dei Marsi 78, Rome 00185, Italy
e-mail: oliviero.bruni@uniroma1.it

R. Ferri
Oasi Research Institute IRCCS, Troina, Italy

M. Angriman
Department of Pediatrics, Child Neurology and Neurorehabilitation Unit, Central Hospital of Bolzano, Bolzano, Italy

M. Zarowski
Department of Developmental Neurology, Poznan University of Medical Sciences,
Poznań, Poland

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underlying sleep disorders improved the headache. More recently [5] a direct correlation between the increase in sleep disturbance and headache severity has been found.

Sleep disorders are the most frequent comorbid disorders in children with migraine, followed by anxiety disorders and depression; further, 66% of migraine children with sleep disorders had enduring headache [6]. In young children not able to report correctly the symptoms, owing to immature language and cognitive abilities, migraine descriptors can be missed, or sleep disturbances may not be recognized as causative factors for migraine [7]. For these reasons some manifestations related to sleep can be missed or misdiagnosed. Similarly, childhood periodic syndromes that are difficult to diagnose are thought to represent early-life expression of migraine genes that later in life are expressed as migraine headache and include benign paroxysmal torticollis, benign paroxysmal vertigo, abdominal migraine, and cyclic vomiting syndrome. Recent research suggests infant colic may also fit into this category [8].

On the other hand, headache may cause various degrees of sleep disruption and seems to be associated with several sleep disturbances either in adults or in children.

From the headache perspective, a sleep disturbance (too much, too little, inappropriate timing, or inappropriate sleep behavior) can be a trigger for headache, but sleep commonly also terminated the attack; on the contrary, headache might be a symptom of sleep disturbance and side effect of sleep- or wake-modulating treatments [9, 10]. Furthermore, both conditions highly increase the risk for each other.

The mutual interactions between sleep and headache are mediated by:

(a) Time of occurrence (headache occurs during sleep, after sleep, and in relationship with sleep stages).
(b) Quantitative associations (excess, lack, bad quality, or short duration of sleep may trigger headache).
(c) Reciprocal link with pain: noxious stimuli and painful disorders interfere with sleep, and sleep disturbances affect pain perception.

Sleep deprivation and sleep schedule changes are common headache triggers for both migraine and tension-type headache, and even in children, one of the commonest self-perceived triggers of head pain was the lack of sleep [11], and on the other hand, sleep seems efficacious to relieve head pain or terminate the headache attack [12, 13]. Frequency of falling asleep during attacks is significantly more common in patients <8 years of age than in older children, and in these children, there is higher resolution of attacks with sleep [14].

An hypothesis on the intrinsic mechanism for which sleep determined the head pain relief is that sleep could trigger an autonomic reset [15].

Another important point in favor of this strict relationship comes from the fact that treating headache improves sleep (5-HT, serotoninergic drugs), and, conversely, that treating sleep improves headache (CPAP treatment, sleep hygiene, dopaminergic agents for restless legs syndrome, stimulant for narcolepsy, fibromyalgia treatment) [16].

13.2 The Specific Links Between Headache and Sleep in Infants and Children

Several studies in headache children reported that the major sleep complaints are linked to reduced sleep duration, bedtime settling, longer sleep latency, night awakenings, and nocturnal symptoms like nightmares, parasomnias, or restless sleep and daytime sleepiness [17–19].

Subjects with migraine reported a higher prevalence of sleep disturbances in parents, sleep disturbances in infancy, and colic, as well as an elevated level of familiarity for migraine, showing that a genetic link might be present between migraine and disturbed sleep and indicating that the common neurobiological substrate might act from the beginning of life and/or that a comorbidity exists between these two disorders [20].

Furthermore, sleep problems during infancy can be a predictive factor for the development or persistence of headache. Sleep disorders in the first months of life were found to be present in 78% of children with enduring headache vs. 25% of children showing headache remission [21].

The strict correlation between sleep and headache has been also supported by a research showing that sleep disruption at age 3 predicted headaches at 6 years [22].

Surveys in large pediatric populations have confirmed the strong association between headache and different sleep disorders such as parasomnias, insomnia, sleep breathing disorders, and daytime sleepiness [20]. Frequency and duration of migraine attacks predicted specific sleep disturbances such as sleep anxiety, parasomnias, and bedtime resistance [23].

In further support of this association, it has been demonstrated that the lack of sleep (69.6%) was the second disorder most commonly reported by children, preceded only by stress (75.5% of patients), followed by climate changes (68.6%), and video games (64.7%). Accordingly, in a large epidemiologic study on childhood migraine, our group reported that "a bad sleep" was found to be the primary predisposing or causative factor for headache attacks followed by emotional distress [24].

An early precursor of migraine could be represented by infantile colic, which represents one of the earliest manifestations of pain and crying in healthy infants. This association has been corroborated by sporadic reports showing an increased prevalence of infantile colic in migraine children and by a longitudinal study of hyperreactive infants, that is, infants exhibiting irritability, infantile colic, and crying bouts during their first months of life [25, 26].

A positive history of colic was reported in 38.4% of subjects with migraine, significantly higher than in controls (26.9%) and in subjects with TTH (25.2%) [20].

This was confirmed by another study showing an increased positive history of colic in children with migraine (52% vs. 20% in controls) [25]. In another recent study, 208 consecutive children with migraine aged 6–18 years presenting to the emergency department were more likely to have experienced infantile colic than those without migraine (72.6% vs. 26.5%; $p < 0.001$), either migraine without aura (73.9% vs. 26.5%; $p < 0.001$) or migraine with aura (69.7% vs. 26.5%; $p < 0.001$).

This association was not found for children with tension-type headache (TTH) (35% vs. 26.5%), confirming the specificity of the association [27]. This association was not found for children with TTH (35% vs. 26.5%), confirming the specificity of the association. In one report, an infant with colic experienced improvement after starting antimigraine (cyproheptadine) therapy, reinforcing the relationships between the two conditions [26].

13.3 Sleep Disorders and Headache in Infants and Children

Literature data showed that the most common sleep disturbances found in children with headache are represented by insufficient sleep, difficulties falling asleep, anxiety related to sleep, restless sleep, night waking, nightmares, daytime sleepiness, and parasomnias [28].

One of the first study on a large group of pediatric patients with headache showed that both migraine and tension headache were associated with different sleep disorders, but the migraine group tended to have "a more disturbed sleep" with increased prevalence of nocturnal symptoms, such as sleep breathing disorders, restless sleep, and parasomnias and of daytime sleepiness [20]. This questionnaire-based study involved 283 headache sufferers aged 5.0–14.3 years: 164 with migraine (M) headache (141 without aura and 23 with aura) and 119 with tension-type (T) headache (84 episodic TTH and 35 chronic TTH), compared with an age-matched healthy control (C) group. Significant differences between headache and controls were found: children with migraine and TTH presented shorter sleep duration and longer sleep latency, a higher prevalence of difficulty falling asleep, and sleep disruption, with more than two awakenings per night. Some parasomnias were more prevalent like sleep talking, bruxism, and reports of frightening dreams, whereas no differences were observed for sleepwalking, bed-wetting, or sleep terrors. Sleep breathing problems were more frequent in subjects with migraine, while restless sleep and daytime sleepiness occurred more frequently in subjects with migraine and tension headache vs. controls.

No significant differences were found between the migraine and headache groups.

Other researchers confirmed that children with migraine have a large range of sleep disturbances, such as bedtime resistance, insufficient and interrupted sleep, sleep-disordered breathing, disorders of arousal, sweating during sleep, difficulty waking up in the morning, and daytime sleepiness [7, 29, 30].

An old report in 48 children with headache confirmed the association of primary headache with night wakings (41.7%), difficulty falling asleep (20.8%), pavor nocturnus and nightmares (14.6%), enuresis (8.3%), and somnambulism (6.3%) [31].

Another study reported a high rate of sleep disturbances in children, sleeping too little (42%), bruxism (29%), cosleeping with parents (25%), and snoring (23%) and also showed that the frequency of migraine predicted parasomnias, whereas duration of migraine predicted sleep anxiety and bedtime resistance [23].

A more recent report confirmed the presence of excessive daytime sleepiness, narcolepsy, and insomnia in children with headaches while failed to corroborate the higher prevalence of symptoms of sleep apnea, restlessness, and parasomnias, reported in the previous studies [32].

A study showed that migraine without aura was a sensitive risk factor for disorders of initiating and maintaining sleep and chronic tension-type headache for sleep breathing disorders and that headache disorder as a whole was a cumulative risk factor for disorders of excessive somnolence [33].

13.3.1 Non-Rapid Eye Movement Sleep Parasomnias

Several reports have described the association between headache and parasomnias in children. The first studies showed a correlation between sleepwalking and migraine: Barabas et al. [34] in four groups of patients (60 with migraine, 42 with non-migraine headache, 60 with epilepsy, and 60 with learning disabilities/neurologic impairment) found history of at least two episodes of somnambulism in 30% of migraineurs vs. 4.8% of those with non-migraine headaches, 5% of those with learning disabilities/neurologic impairment, and 6.6% of epileptics. Pradalier et al. [35] found an incidence of sleepwalking in 21.9% of migraine subjects vs. 6.6% of controls. Giroud et al. [36] found history of somnambulism in 29.4% of migraine subjects vs. 5.4% of non-migraine headache subjects.

However, the association between migraine and parasomnias is not limited to sleepwalking but includes also pavor nocturnus and enuresis: Dexter [37] found an incidence of 71% of pavor nocturnus (vs. 11% of controls), of 55% of somnambulism (vs. 16% of controls), and of 41% of enuresis (vs. 16% of controls).

These findings are in agreement with some studies [20, 23], while another research failed to confirm this increased prevalence of parasomnias [32].

A recent study evaluated the predictive value of sleep terror history in childhood for the development of migraine in adolescence, based on the higher prevalence of a history of sleep terrors (40%) in adolescents with chronic migraine vs. those with episodic migraine (26%) and healthy controls (8%) [38].

It has been hypothesized that somnambulism and migraine can appear at different ages, the former in the late infancy, the latter in childhood, representing a different age-related expression of a disorder of serotonin metabolism. Furthermore, there is some evidence that sleepwalking and headache can be precipitated by sleep-disordered breathing [39].

The hypercapnic acidosis, secondary to sleep-disordered breathing, could stimulate the serotonergic neurons, resulting in increased excitability of motoneurons leading to the appearance of somnambulism. Further, the need for concomitant age-related increased excitability of 5-hydroxytryptamine (5-HT) neurons and acidosis explains why abnormal breathing during sleep only rarely induces sleepwalking in adults [40].

13.3.2 Sleep-Disordered Breathing

Few data are available on the relationship between sleep apnea and headache or migraine in children.

Guilleminault et al. first reported that 18 of 50 OSA patients suffered from frontal or diffuse morning headache, afterward several other reports supported this important relationship [41]. A varied range of symptoms and signs are associated with OSAS in pediatric population. In children and adolescents with OSAS, the most common clinical manifestation reported is snoring but also obesity, excessive daytime sleepiness, heavy habitual snoring, and neuropsychological disturbances [42].

In adults the prevalence of headache in (OSAS) patients is very high: Neau et al. [42] showed that 33% of OSAS patients had headaches, of whom 58.5% had morning headaches. However, it seems that early-morning headache is a not specific symptom of sleep apnea [43]; in fact, patients with abnormal sleep complained of early-morning headache even more frequently than patients with OSAS confirming the hypothesis that migraine attacks could be secondary to sleep disruption rather than to sleep apnea.

Hypercarbia, hypoxemia, altered cerebral blood flow, increased intracranial pressure, alterations in sympathetic nerve activity, rises in blood pressure secondary to multiple arousals, and brainstem dysfunction have been reported as etiologic or worsening factors for headache in patients with OSAS [42]. However, it has been hypothesized that migraine attacks could be secondary to sleep disruption rather than to sleep apnea by itself.

A polysomnographic study in children with headache indicated that sleep-disordered breathing was more frequent among children with migraine (56.6%) and nonspecific headache (54%) vs. chronic migraine (27%). These findings revealed a strong clinical association between migraine and sleep-disordered breathing, whereas chronic migraine was associated with more disrupted sleep and tension-type headache with bruxism [44].

Future studies may characterize the headache in OSAS patients to address the question if sleep apnea is the primary event leading to headache or if sleep disruption is the main pathogenetic factor for morning headache.

13.3.3 Restless Legs Syndrome

Restless legs syndrome (RLS) is characterized by an urge to move the legs, accompanied by unpleasant leg sensations, occurring at night, worsened by rest, and improved by movements. There is accumulating evidence that RLS is another condition that is frequently reported by patients with migraine, adults or children. RLS prevalence in migraine has been reported to range from 8.7 to 39.0%, with no apparent differences in gender and aura status, whereas migraine prevalence in RLS ranges from 15.1 to 62.6% [45].

Chen et al. [46] found that RLS was more common in migraine patients (11.4%) than in TTH (4.6%) and chronic headache (2.0%). Another study confirmed the higher occurrence of RLS in migraine adults but also suggested that RLS (the condition itself or the disruption of sleep patterns often found in patients affected by RLS) might affect migraine clinical presentation, being associated with chronic and highly disabling migraine [47].

A common pathophysiological origin for migraine and RLS has been proposed [48] with a link involving a disturbance of iron and a dysfunction within the dopaminergic system. This notion is supported by the rapid improvement of RLS symptoms after treatment with dopaminergic agents [49].

Dopamine is involved in migraine pathophysiology. In particular, dopaminergic premonitory symptoms like yawning, irritability, and mood changes, as well as nausea and vomiting, occurring during both the premonitory and headache phases, may be caused by dopamine and are present in 47.6% of patients with RLS and migraine but only in 13.1% in those without RLS [50].

Moreover, the risk of having RLS is increased in patients with migraine [45] and is 45 times higher in the presence of dopaminergic premonitory symptoms [51].

Only 1 pediatric study on children and adolescents aged 5–18 years focused on the correlation between RLS and headaches: 24 patients with migraine (21.6%), 4 (5%) headache-free controls, and 9 (8.3%) healthy children met the diagnostic criteria for definite RLS. This study showed an approximately fourfold higher frequency of RLS in pediatric patients with migraine compared with headache-free controls [52].

Based on the dopaminergic hypothesis, another recent study investigated daytime dysfunction in 25 children with RLS and the effects of treatment primarily with iron supplements on RLS symptoms. Following treatment, participants' daytime function had improved to levels similar to those of controls. Sixteen out of twenty-three cases were successfully treated primarily with iron supplement [53].

13.3.4 Periodic Limb Movements (PLMS)

There is only one published study on the prevalence of PLMS and migraine and their relationship with disability and pain intensity in a pediatric group of patients. Polysomnographic evaluation showed periodic limb movement index (PLMI) 45/h in 26.47% of children with migraine; these subjects with PLMI 45/h presented higher frequency, intensity, duration, and life impairment of migraine and lower efficacy of prophylactic and acute pharmacologic treatment, with respect to children with migraine without aura and normal PLMI. These findings suggest that PLMS might influence the clinical presentation of migraine, increasing its severity, frequency, and all disabling aspects and also affecting treatment efficacy [54].

13.3.5 Sleep Bruxism (SB)

SB, a sleep-related movement disorder characterized by teeth grinding and clenching, is frequently associated with orofacial pain and headaches. Children with SB may report approximately three times as many headaches than non-SB subjects with an odds ratio of 4.3; on the other hand, children with migraine showed a high prevalence (29%) of SB [55].

13.3.6 Narcolepsy

Patients with narcolepsy often reported suffering from headache independently from the drug administration.

Patients with narcolepsy fulfilled the criteria for tension headache significantly more often than by controls (60.3% vs. 40.7%) [56], and migraine prevalence showed a twofold to fourfold increase in patients with narcolepsy. The onset of narcolepsy symptoms is preceded by 12.3 years the onset of migraine symptoms. The increased prevalence of migraine was independent of the pharmacologic treatment of narcolepsy and of severity of narcolepsy symptoms [57].

No studies are available on the prevalence of migraine in children and adolescents with narcolepsy, and headache has often been reported as a side effect of treatment in these children [58].

The relationship between narcolepsy and migraine might be mediated by the orexinergic neurons of the posterior hypothalamus that are involved both in inhibition of analgesia and in narcolepsy [59].

13.4 Treatment for Migraine and Sleep in Children

Taking into account the connection between sleep and migraine could guide the correct treatment of migraine [15].

Sleep deprivation may enhance the response to pain stimuli and can trigger the migraine attacks [60, 61], but it seems that sleep continuity disturbance, rather than simple sleep restriction, impairs endogenous pain-inhibitory function and increases spontaneous pain [62].

Some drugs could improve migraine by reducing the sleep deprivation and improving the sleep continuity with a secondary effect on the pain threshold.

13.4.1 Non-pharmacologic Treatment

The use of non-pharmacologic preventive measures in children with migraine includes lifestyle adjustments (dietary changes, sleep hygiene), reassurance, stress management, biofeedback, relaxation techniques, and other behavioral therapies [63–65].

A recent study applied a non-pharmacologic treatment for migraine in 32 preschool children, and 60 older school-age children instructed to follow (a) sleep hygiene, (b) proper diet (refraining from food additives, with elimination of smoked lunch meats, smoked cheese, yellow cheese, chocolate and foods containing chocolate, pizza, and foods containing monosodium glutamate), and (c) no direct sun exposure. Mean age of the patients with no response to treatment was 10.6 ± 3.2 years, partial response 9.11 ± 4.6 years, and complete response 8.11 ± 3.9 years. The percentage of patients with complete to partial response was significantly higher in the younger group demonstrating that children younger than 6 years were more sensitive than older children to non-pharmacologic treatment [64].

In a pioneering study, the sleep hygiene rules have been applied to 70 children and adolescents with migraine. Patients showed a reduction in the mean duration and frequency of migraine attacks, while the severity of the attacks did not change.

In this study, based on the presence of at least two criteria for defining poor sleep hygiene, 70 migraineurs (42.7%) have been selected in a group of 164 migraine patients and randomly assigned to group A or B. The A group had been instructed to follow instructions to improve sleep hygiene; the B group did not have instructions on improvement of sleep hygiene.

After 6 months of follow-up, the sleep hygiene group reported lower mean headache duration than the control group, suggesting that better sleep quality led to altered migraine patterns. The frequency of migraine attacks showed also an improvement: at the first observation, the prevalence of A group subjects with more than one attack per week was 35%; at 3 months the number decreased to 15% and at 6 months it was 11%. In the B group, the percentage did not change significantly (at first observation, 42%; at 3 months, 37%; and at 6 months, 33%). Severity of migraine attacks was not affected by the sleep hygiene treatment [24].

Although this study represents an indirect measure of the effects that sleep disturbances can have on migraine, it supports the direction of the relationship (i.e., sleep disturbance can exacerbate migraine).

It has been reported that sleep has the power to stop the pain phase of headache attacks. Preschool-age children, especially under 6 years of age, have longer sleep duration, and they often sleep more easily during the day [66].

It is therefore possible that their shorter attacks depend on easier initiation of active mechanisms such as sleep stopping the pain phase.

13.4.1.1 Treatment of Sleep-Disordered Breathing to Improve Migraine

No data are available on the treatment of sleep apnea and migraine in children, but there are some studies showing that morning headache was totally resolved in 90% of patients treated with nasal CPAP [67].

A recent study provides new insights into the effectiveness of the mandibular advancement appliance (MAA) for treating headache associated with sleep bruxism. Sixteen adolescents reporting SB, headache, or snoring underwent four ambulatory PSGs for baseline and while wearing MAA during sleep for 1 week. Sleep bruxism index decreased up to 60%, and headache intensity showed a decreasing

trend with MAA [68]. However, interactions between sleep bruxism, breathing during sleep, and headache as well as the long-term effectiveness and safety of the MAA in adolescents need further investigation [55].

13.4.2 Pharmacotherapy

Based on the similarities in pathophysiology, it is not surprising that the drugs used for prophylaxis or treatment of migraine can improve sleep and vice versa.

In contrast to the large number of adult trials, relatively few trials have evaluated prophylactic treatment of pediatric headaches [69]. Different drugs have been used for headache/migraine prophylaxis like topiramate, trazodone, clonidine, flunarizine, pizotifen, propranolol, and valproate. Apart from these drugs, there are some compounds that act either on pain threshold or by modifying/improving sleep. These drugs, commonly used also in children, are mostly represented by antihistaminics, melatonin, and serotoninergic drugs.

13.4.2.1 Antihistaminics

Alterations in the histaminergic system have been proposed both in neurological and psychiatric diseases hypothesizing also a role as a potent modulator of meningeal nociceptors' activity in migraine. Activation of inhibitory H3 receptors has been suggested for migraine prophylaxis, and both H3R and H4R ligands may theoretically have prophylactic properties. Despite being promising drug targets for several diseases, the lack of specificity and undesired side effects discouraged the potential exploratory studies [70].

Cyproheptadine, an antagonist at the 5-HT2, histamine H1, and muscarinic cholinergic receptors, is widely used in the prophylactic treatment of migraine in children. The total dose ranges from 12 to 36 mg per day (given two to three times per day or at bedtime). Common adverse events are sedation and weight gain; dry mouth, nausea, lightheadedness, ankle edema, aching legs, and diarrhea are less common. Cyproheptadine may inhibit growth in children and reverse the effects of SSRIs. A single class II study showed cyproheptadine (4 mg per day) was as effective as propranolol (80 mg per day) in reducing migraine frequency and severity [71].

We can assume, however, that the antihistaminics could act in migraine indirectly through the improvement of sleep, and this effect could decrease the pain in migraine children.

13.4.2.2 Melatonin

There is evidence that melatonin, besides having a role in the biological regulation of circadian rhythms, sleep, mood, and aging, is also involved in various headache syndromes, including migraine and tension headache.

Melatonin may play a role in headache pathophysiology via several mechanisms. The antinociceptive effects of melatonin have been demonstrated in animal models, both in inflammatory and neuropathic pain [72, 73].

Beside the other several actions on different receptors, melatonin also reduces the upregulation of a variety of pro-inflammatory cytokines, interleukins, and TNF-alfa and affects the activity of nitric oxide synthase. It also decreases dopamine and glutamate release and potentiates the receptor-mediated response of GABA and the opioid immune response and modulate serotonin release [74, 75].

All these evidences supported the use of melatonin in patients with headache or migraine, and circadian rhythm disorders related also to the demonstration of a decrease of melatonin levels in these individuals [76, 77]. Furthermore, a decreased nocturnal melatonin secretion has been reported in patients with both migraine [78] and cluster headache [10]. The efficacy of melatonin in these cases could be related to regularization of the sleep-wake pattern through its chronobiological and "sleep hygiene" effect [79].

Despite several studies demonstrating a decrease of melatonin levels in adults with migraine, a recent report showed no significant difference in urinary 6-sulfatoxymelatonin between the migraine children and control group, indicating that nocturnal production of melatonin is not reduced in children with migraine [80].

A recent research showed that melatonin treatment decreased headache in 78.6% of 328 patients with circadian rhythm sleep disorders and headache while induced (slight) headache in 13.8% of 676 patients with circadian rhythm sleep disorders without headache [81].

In an open-label trial in children with primary headache, melatonin 3 mg twice daily reduced the number (by more than 50%), intensity, and duration of headache attacks in 14 of 21 children, showing a better efficacy in migraine vs. tension headache form [82].

A study of melatonin in a single dose of 0.3 mg/kg for 3 months indicated that melatonin might be considered as an effective and safe drug in the prophylaxis of migraine in children. Monthly frequency of attacks reduced from 15.63 ± 7.64 to 7.07 ± 4.42, severity scores from 6.20 ± 1.67 to 3.55 ± 2.11, and duration of headache, from 2.26 ± 1.34 to 1.11 ± 0.55 h. Pediatric Migraine Disability Assessment score decreased from 31.72 ± 8.82 to 17.78 ± 10.64 [83].

However, all these studies were nonrandomized and conducted in small samples; therefore there is still no definitive consensus about the therapeutic use of melatonin for headache in children.

13.4.2.3 Serotonergic Drugs

A congenital alteration of neurotransmitter pathways (serotonergic and dopaminergic) might predispose individuals to sleep disorders and to headache, a result of this neurotransmitter imbalance [84] that might act since the early period of life determining sleep disorders during infancy (i.e., colic, insomnia) followed by the development of migraine later in life [14].

Serotonin (5-HT) decrease may lower the threshold of pain perception but also might act through a derangement of sleep structure and predispose to headache [85], but 5-HT also plays significant roles in modulation of sleep [86]. It has been further demonstrated that a reduction in brain synthesis of 5 HT intensifies photophobia and other migrainous symptoms [87].

A recent study investigated the plasma tryptophan, 5-hydroxytryptophan (5-HTP), 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA) levels in migraine adults patients with (MWA) or without aura (MWoA) and in controls. The plasma 5-HT level was significantly lower in MWA patients than in the controls, whereas no significant difference was observed between the levels in MWoA patients and controls. On the other hand, the plasma 5-HTP and 5-HIAA levels were not significantly different between the MWA patients, the MWoA patients, and the controls. These data suggest that an enzymatic dysfunction in the metabolic pathway from 5-HTP to 5-HT may be present in MWA patients [88].

A double-blind crossover study of 27 migraine children aged 6–12 years treated with L-5HTP (5 mg/kg body weight) vs. placebo showed that both L-5HTP and placebo led to a significant reduction of the migraine index and frequency of migraine attacks with no differences on final efficacy [89].

On the other hand, another report on 48 elementary and junior high school students with primary headache associated with sleep disorders showed that treatment with L-5-HTP in these patients determined the improvement of both conditions, headache and sleep disorders, in particular frequent awakenings and some parasomnias [31].

Tricyclic antidepressants are used for migraine prevention; however, only one tricyclic antidepressant (amitriptyline) has proven efficacy in migraine.

The mechanism by which antidepressants work to prevent migraine headache is uncertain, but they are useful in treating many chronic pain states, including headache, independent of the presence of depression, and the response occurs sooner and at lower dosages than that expected for an antidepressant effect. The antidepressants that are clinically effective in headache prevention either inhibit norepinephrine and 5-hydroxytryptamine (5-HT) reuptake or are antagonists at the 5-hydroxytryptamine 2 (5-HT2) receptors.

A randomized, double-blind, placebo-controlled trial of amitriptyline (1 mg per kg of body weight per day), topiramate (2 mg per kg per day), and placebo in children and adolescents 8–17 years of age with migraine showed no significant between-group differences in the primary outcome (50% reduction of attacks), which occurred in 52% of the patients in the amitriptyline group, 55% of those in the topiramate group, and 61% of those in the placebo group. There were also no significant between-group differences in headache-related disability, headache days, or the percentage of patients who completed the 24-week treatment period. Amitriptyline adverse events were fatigue (30%) and dry mouth (25%), and three patients had serious adverse events of altered mood [90].

13.5 Conclusion

A better understanding of the pathophysiology and the high comorbidity between the migraine or headache and disturbed sleep could be helpful both in diagnoses and management of the headache syndromes.

In the last few years, several studies have converged in demonstrating that the link between sleep and migraine is more complex and not limited to the association with parasomnias or sleep apnea but also with RLS, PLMS, and narcolepsy. Sleep disturbances, therefore, are now viewed as comorbid, predisposing, predictive, or even prognostic factors for headache development or endurance.

Almost all of the pharmacological studies in children with migraine have not included the evaluation of any sleep parameters, but we believe that screening for sleep disorders with the use of proper tests including PSG and referral to a sleep clinic when appropriate could be very helpful. Patient education and lifestyle modification including sleep hygiene might play a significant role in overall success of the treatment. It is important for the clinicians to perform the clinical evaluation of childhood headache with a careful analysis of sleep habits and patterns and the evaluation of the presence of sleep disturbances to adequately treat these conditions.

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Chapter 14
Headache in Autism Spectrum Disorders

Roberto Canitano and Carmen M. Schröder

14.1 Headache in Autism Spectrum Disorders: Gastrointestinal Disorder or Migraine?

14.1.1 Gastrointestinal Disorders in ASD

Gastrointestinal (GI) disorders are among the most common medical conditions associated with autism spectrum disorders (ASD). These conditions include chronic constipation or diarrhea and irritable and inflammatory bowel symptoms. The pain and discomfort caused by GI symptoms can worsen behavior and even trigger regression in children with ASD, and this may be overlooked in nonverbal with difficulties in expressing this condition. Constipation is particularly common among children with ASD, overall it is the most common GI diagnosis in ASD, and it is most likely to occur in younger children, with significant social and communication difficulties. Further as to the opposite point of view, it found a significant increase in communication disturbances in children with both ASD and GI disorder, compared to children with ASD only.

The most frequently reported GI symptoms were alterations in bowel habits, chronic abdominal pain, reflux, and vomiting. It is notable that untreated GI symptoms may increase behavioral problems in children with ASD [1]. Interestingly

R. Canitano, M.D. (✉)
Division of Child and Adolescent Neuropsychiatry, University Hospital of Siena, Viale Bracci, 53100 Siena, Italy
e-mail: r.canitano@ao-siena.toscana.it; canitano@unisi.it

C.M. Schröder, M.D., Ph.D.
Faculty of Medicine, Strasbourg University, Strasbourg, France

Department of Child and Adolescent Psychiatry, Strasbourg University Hospital, Strasbourg, France
e-mail: schroderc@unistra.fr

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in those patients experiencing GI symptoms, increased intestinal permeability has been reported [2]. Several studies reported also dysbiosis or various altered composition of intestinal microbiota in ASD children that complicated the clinical presentation and treatment. GI disturbances in ASD might be linked to gut dysbiosis of a gut-brain axis disruption [3, 4]. Strategies which can restore normal gut microbiota and reduce the gut production and absorption of toxins, such as probiotics addition/supplementation in a diet, may represent a non-pharmacological option in the treatment of GI disturbances in ASD and have the potential to impact core social and language symptoms as recently described in controlled studies [5]. Furthermore permeability to food antigens derived from wheat and cow's milk has been reported in both ASD and SCZ [6, 7, 24, 25].

A dysfunctional gut-brain axis associated with neuroinflammation involving the intestinal barrier and blood-brain barrier integrity/function in ASD has been postulated and recently demonstrated [8].

In a psychophysiological study of ASD, 42.5% of participants met criteria for functional constipation, a disorder of the lower gastrointestinal tract. Heart rate variability, a measure of parasympathetic modulation of cardiac activity, was found to be positively associated with lower gastrointestinal tract symptomatology at baseline. This relationship was particularly strong for participants with co-occurring diagnoses of anxiety disorder and for those with a history of regressive ASD or loss of previously acquired skills. Autonomic dysfunction and gastrointestinal problems are closely related in children with ASD although it is not possible to assess causality. Future research should examine the impact of treatment of gastrointestinal problems on autonomic function and anxiety, as well as the impact of anxiety treatment on gastrointestinal problems [9].

14.1.2 Minicolumn Abnormalities in ASD

Recent studies indicate the presence of minicolumnar disturbances in autism. In this regard it is considered a putative minicolumnopathy as applied to the gastrointestinal symptoms (GI) commonly reported in ASD. Following this paradigm a minicolumnopathy provides for both a hyperexcitable cortex with E/I imbalance and for GI disturbances and a serotonergic abnormal tone that manifests early in childhood as abdominal migraines and migraine equivalent [10]. "The minicolumn is a radially oriented assembly of neurons and cellular elements considered to be an elemental modular microcircuit of the neocortex. The minicolumn core contains pyramidal cell arrays surrounded by a peripheral neuropil space that contains GABAergic inhibitory that protects the minicolumn core from the excitation from other surrounding minicolumns". The peripheral neuropil space has been shown to be reduced in postmortem brain tissue from ASD individuals with this reduction most prominent over the prefrontal cortex [10]. The neuropil space is reduced within the region that contains the inhibition circuits of minicolumns. A reduction of GABAergic inhibitory activity has been proposed to result in hyperexcitability of minicolumn circuits and implicated in the symptoms of ASD, including the high incidence of seizures and auditory

hypersensitivity. It has been hypothesized that in ASD, the presence of the smaller minicolumns of normal-sized thalamocortical terminal fields would require an increase of inhibitory tone to balance the overall E/I balance of the cortex [11].

14.1.3 Serotonin in ASD

Regarding serotonin, peripheral blood biomarkers demonstrate abnormalities similar to those reported in the brain, e.g., platelet serotonin is increased in approximately one third of autistic patients. Furthermore the increased level of serotonin is found in ASD patients and also in first-degree relatives. In ASD it is likely that altered metabolic processing would be implicated in the abnormal elevated levels of serotonin [12].

Repetitive behaviors are thought to be strongly related to serotonergic (5-HT) dysfunction in ASD. It has been observed that sumatriptan, an antimigraine medication that is a serotoninergic 5-HT1d receptor agonist, improved symptoms of ASD and migraine in patients who suffered from both disorders, and the severity of repetitive behaviors paralleled the sensitivity of the 5-HT1d receptor, as documented by sumatriptan-elicited GH response [13]. Although sumatriptan is a 5-HT1d receptor agonist, it may also bind to other subtypes of 5HT receptors with additional actions that might be involved in repetitive behaviors. Controlled double-blind studies of serotonin reuptake inhibitors (SSRI) have been found to impact ASD repetitive and restricted behaviors with variable results. In a systematic meta-analysis of SSRI studies in ASD, different inconsistencies were noted in the studies examined. Varying inclusion criteria were used with regard to diagnostic criteria and cognitive levels of participant; furthermore different outcome measures were reported making it hard to compare one another result. Although more than one study reported data for Clinical Global Impression (CGI) and obsessive-compulsive behavior (OCB) scales of evaluation, different components of these outcomes were used in each study again limiting the conclusions to draw [23] and leaving uncertainties. In a meta-analysis conducted to evaluate the efficacy of selective serotonin reuptake inhibitors (SSRI) on the treatment of repetitive behaviors in ASD, a small but significant effect of SSRI was observed; however an accurate analysis of the studies ascertained that the effect would be mainly attributable to selective publication of trial results, e.g., publication bias flawed the overall results reported. These negative findings have been discouraging the use of SSRI for repetitive behaviors in ASD [14] irrespective to the additional coexistence of migraine.

14.1.4 Migraine in ASD

Headache and related conditions may affect children with ASD as an additional problem and as a comorbidity to keep in mind when evaluating pain of uncertain origin. Further it may increase disruptive behaviors and worsen the overall adaptive level of children affected.

The mechanism of E/I imbalance with cortical hyperexcitability in children with migraine also is poorly known and may be related to increased levels of glutamate and increasing excitability, associated to reduced brain levels of Mg^{2+}. Serotonergic agonists during acute episodes and serotonergic antagonists and anticonvulsants as migraine prophylaxis have been largely and successfully employed. In addition anticonvulsants have been found to be effective in children with abdominal migraine and epileptiform discharges, and epileptiform activity has been observed during attacks [15, 27].

Migraine and related disorders in children and adolescents are mainly diagnosed by clinical history with a thorough evaluation of primary and associated symptoms. Diagnostic criteria are referring to the International Headache Society last revised in 2013 (ICH-3) [29]. Headache is the most prominent feature of migraine, but the underlying pathophysiological mechanisms often cause other systemic manifestations that may appear without headache. Migraine equivalent and variant are the terms used in these cases [16, 30]. Symptoms include vertigo, abdominal pain, vomiting, and diarrhea. These paroxysmal attacks are usually associated to phonophobia/photophobia and other autonomic dysfunction symptoms such as pallor and flushing. Children and adolescent with a mean age of onset of 7–10 years suffer from these attacks. Resting in darkness with low or absent sensory stimulation is usually searched for by children affected along with avoidance of routine day life activities; overall a condition of suffering and need for rest and sleep is the hallmark of the condition [26].

Approximately one third of patients with ASD suffer from seizures with two peaks of onset, in early infancy and in adolescence. An even higher percentage present with epileptiform EEG in the absence of seizures, ranging from 40 to 60% [17]. Relevant to these findings, it has been hypothesized that early serotonergic disturbances alter the development of cortical thalamocortical innervation contributing to the paroxysmal disorders in ASD, e.g., seizures and migraine attacks mechanisms are closely related in ASD [22]. Though the electroencephalographic abnormalities are frequently found in children and adolescents with ASD, up to 60% of cases, the proportion appearing in migraine and its equivalent is undefined as yet.

Abdominal migraine is a subtype of migraine that deserves attention because it has similarities with gastrointestinal symptoms observed in children with ASD. Foods frequently trigger for abdominal migraine and include milk, chocolate, cheese, wheat products, and others. As many children affected have intolerance to many kinds of food, it has been proposed that migraine is a food allergy supported by an oligoantigenic diet that was found to be beneficial in the majority of children [16].

As mentioned above a putative minicolumnopathy would be implicated in GI symptoms commonly reported in ASD. The hypothesis is that a minicolumnopathy provides for both an E/I imbalance with hyperexcitability and a serotonergic abnormality appearing early in life as abdominal migraine. Consistent with this hypothesis, recent studies report an increased prevalence of migraine in children with ASD [18].

14.1.5 Anxiety and Hyperreactivity in ASD and Migraine

It has been detailed that children with ASD and migraine showed greater sensory hyperreactivity and anxiety symptomatology than those without migraine. In addition ASD and migraine are both comorbid with anxiety, and a significant subgroup of individuals with ASD present with anxiety disorders in turn anxiety is associated with sensory hyperreactivity [19, 20]. High rates of anxiety and mood disorders as well as internalizing and sensory hyperreactivity are also frequently associated with migraine disorders. As a result ASD comorbid with migraine and sensory hyperreactivity may well be considered as a subtype of ASD, and this points to searching strategies for subtyping and exploring a common pathogenesis of both disorders [18]. The association of anxiety and GI symptoms with ASD has been documented repeatedly; in another study 24% of the sample of children with ASD experienced at least one type of chronic GI problem, e.g., constipation, abdominal pain, diarrhea, and/or nausea lasting 3 or more months. Children with each type of GI problem had significantly higher rates of both anxiety and sensory overresponsivity. Anxiety, sensory hyperreactivity, and GI problems are possibly interrelated phenomenon for children with ASD [28] and may be related to abdominal migraine and or migraine equivalent [21]; common underlying mechanisms are probably at play and in need of further research to elucidate the unfolding disturbances.

14.2 Conclusions

At present it is plausible to consider the GI complaints in ASD children as migraine equivalents because the comorbidity of headache and ASD has been demonstrated. Difficulties in firmly establishing a relationship arise from the fact that diagnostic criteria for migraine rely exclusively on history, and on the other hand, young patients with ASD often show difficulties in language and communication which makes it difficult for them to communicate symptoms and explain the kind of disturbances they are experiencing. Additional evidence is awaited from complimentary and instrumental evaluations such as transcranial magnetic stimulation (TMS) that may shed light on the mechanisms and the relationship between the two disorders.

Supplementary S1: Autism Spectrum Disorder - 5th ed.; DSM–5; American Psychiatric Association, 2013

Diagnostic Criteria

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted repetitive patterns of behavior.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior.

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Supplementary S2: Abdominal Migraine Modified by Winner P. [16]

Description

An idiopathic disorder seen mainly in children as recurrent attacks of moderate to severe midline abdominal pain, associated with vasomotor symptoms, nausea and vomiting, lasting 2–72 h, and with normality between episodes. Headache does not occur during these episodes.

Diagnostic Criteria

A. At least five attacks of abdominal pain, fulfilling criteria B–D.
B. Pain has at least two of the following three characteristics:
    1. Midline location, periumbilical, or poorly localized
    2. Dull or "just sore" quality
    3. Moderate or severe intensity
C. During attacks, at least two of the following:
    1. Anorexia
    2. Nausea
    3. Vomiting
    4. Pallor
D. Attacks last 2–72 h when untreated or unsuccessfully treated.
E. Complete freedom from symptoms between attacks.
F. Not attributed to another disorder.

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Chapter 15
Headache: Comorbidity with Vascular Disorders

Ishaq Abu-Arafeh and Kenneth Mack

15.1 General Overview

Headache is a common problem in children and primary headaches such as tension-type headache and migraine are the most common causes. In a small number of children, headache is caused by serious underlying causes including cerebrovascular diseases (CVD). The diagnosis of primary headaches is largely made on clinical features, and clinical examination and investigations are only required if an underlying cause is suspected; the presentation is atypical or the headaches are unclassifiable. CVD often present with other specific symptoms and signs besides the headache, and as such these clinical features serve as red flags to highlight the need for further investigations and brain imaging.

Headaches caused and associated with CVD are rare in children. The incidence of CVD in children is estimated between 5 and 8/100,000 children/year [1]. The most common causes of CVD in children are congenital vascular malformations, genetically determined disorders of coagulation or metabolism and the complications of medical intervention and treatment of childhood neoplasia such as acute lymphoblastic leukaemia.

The common clinical presentations of CVD in children are related to arterial ischemia, venous thrombosis, intracranial haemorrhage (subarachnoid, subdural and intracerebral), arteriovenous malformation and vasculopathy. The advancement in imaging technology of the brain and the availability of different imaging modalities CT, spiral CT, MRI, MRA, MRV and functional MRI improved the detection of these conditions and helped raising the awareness and increasing the opportunities for their diagnoses.

I. Abu-Arafeh, M.D., F.R.C.P.C.H (✉)
Paediatric Neurosciences Unit, Royal Hospital for Children, Glasgow, UK
e-mail: iabuarafeh@aol.co.uk

K. Mack, M.D., Ph.D.
Mayo Clinic, Rochester, MN, USA

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Table 15.1 Criteria for the diagnosis of headache attributed to CVD-ICHD-3 beta [2]

A. Headache fulfilling criterion C
B. A cranial or cervical vascular disorder known to be able to cause headache is demonstrated
C. Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in temporal relation to onset of cranial or cervical vascular disorder
2. Either or both of the following:
(a) Headache has significantly worsened in parallel with worsening of the cranial or cervical vascular disorder
(b) Headache has significantly improved in parallel with improvement of the cranial or cervical vascular disorder
3. Headache has characteristics typical for the cranial or cervical vascular disorder
4. Other evidence exists of causation
D. Not better accounted for by another ICHD-3 diagnosis

The clinical manifestations of CVD depend on the site of the lesion and the age of the child. Headache, among other symptoms, is a common feature of intracranial vascular diseases, and on some occasions, headache is the chief complaint and the main reason for children and their parents to seek medical attention. The criteria for the diagnosis of headache attributed to cerebrovascular disorders are presented in Table 15.1.

Headache attributed to CVD may present as a new symptom in a child who has never complained of headache or possibly as an exacerbation or worsening of a pre-existing headache disorder. The International Classification of Headache Disorders (ICHD-3 beta) describes this group of headache disorders as "occurring for the first time in close temporal relation to a cranial or cervical vascular disorder" [2]. The headache phenotype can be nonspecific but can also be that of a primary headache.

In this chapter, CVD related to children will be discussed with emphasis on the following disorders:

- Cerebral venous thrombosis (CVT)
- Arteriovenous malformations (AVM)
- Arterial aneurysm
- Moyamoya
- Haemangioma
- CADASIL
- MELAS
- Posterior Reversible Encephalopathy Syndromes

15.2 Cerebral Venous Thrombosis

Cerebral venous thrombosis (CVT) has an estimated incidence of 1.32/100,000/years in high-income countries and higher incidence in middle- and low-income countries [3]. The incidence in children is probably slightly higher.

Children with prothrombotic conditions, antiphospholipid syndrome, on contraceptive pill, conditions associated with intravascular hypovolemia, infection, trauma and malignancy are at increased risk of CVT. Children undergoing treatment for acute lymphoblastic leukaemia (ALL) seem to be under a specially increased risk of CVT. In a study of 3126 children, receiving treatment for ALL in several centres in the UK, 1.4% had CVT mostly during induction phase of treatment [4].

CVT in children is almost always symptomatic. Headache is a common feature, often presenting as a subacute or a chronic symptom. CVT may also present with papilloedema and intracranial hypertension. Younger children with CVT may present with seizures and rarely as encephalopathy.

A multicentre study of 42 children with CVT showed a median age of 5.75 years, and boys (24) are slightly more affected than girls. The median duration of symptoms before diagnosis was 5 days. Seizures, focal neurological deficits and features of raised intracranial pressure are also common presenting features. The presentation was acute in 83% and subacute in 17%. Headache was the most common symptom reported in 68% of patients followed by fever, lethargy, drowsiness, seizures, cranial nerve palsies, vomiting and hemiparesis [5]. There was no detailed description of the headache phenotype or the outcome of the headache on the resolution of CVT.

ICHD-3 beta defines headache due to CVT (Table 15.2) as a headache with no specific characteristics in quality of pain, location of maximum pain, severity or the associated symptoms. The headache attributed to CVT may be indistinguishable from other types of headache such as those of raised intracranial pressure, intracranial hypotension, migraine, thunderclap headache and subarachnoid haemorrhage. In the presence of other neurological deficits or lethargy, it is prudent for these patients to be investigated with appropriate neuroimaging. If CVT is confirmed, further investigations should include screening for thrombophilia, metabolic disturbances, neoplastic diseases and medications that are known to increase the risk of CVT.

Treatment should be aimed at the cause of CVT, anticoagulation, prevention of dehydration and relief of symptoms. The prognosis is variable and is affected by the underlying condition. Low Glasgow Coma Scale at presentation is usually associated with poor outcome and death.

Table 15.2 Criteria for the diagnosis of headache attributed to CVT-ICHD-3 beta [2]

A. Any new headache, fulfilling criterion C
B. Cerebral venous thrombosis (CVT) has been diagnosed
C. Evidence of causation demonstrated by both of the following:
1. Headache has developed in close temporal relation to other symptoms and/or clinical signs of CVT or has led to the discovery of CVT
2. Either or both of the following:
(a) Headache has significantly worsened in parallel with clinical or radiological signs of extension of the CVT
(b) Headache has significantly improved or resolved after improvement of the CVT
D. Not better accounted for by another ICHD-3 diagnosis

Table 15.3 Diagnostic criteria of headache attributed to arteriovenous malformation (AVM)-ICHD-3 beta [2]

A. Any headache fulfilling criterion C
B. An arteriovenous malformation (AVM) has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in close temporal relation to other symptoms and/or clinical signs of AVM or has led to the discovery of an AVM
2. Either or both of the following:
(a) Headache has significantly worsened in parallel with worsening of the AVM
(b) Headache has significantly improved in parallel with improvement of the AVM
3. Headache is localised to the site of the AVM
D. Not better accounted for by another ICHD-3 diagnosis, and intracranial haemorrhage has been excluded by appropriate investigations

15.3 Arteriovenous Malformations

AVM are congenital lesions of abnormal connections between arteries and veins bypassing the normal capillary system. In children, AVM affect boys and girls equally and may present with intracranial bleeding in about half the patients. One in five children with AVM may present with headache, but others may be asymptomatic or present with seizures [6].

AVM are usually small in size and often located in the supratentorial cavity. A few AVM are in the cerebellum. The criteria for the diagnosis of headache attributed to AVM are presented in Table 15.3.

Headache phenotypes can be non-specific, but it can also be that of migraine with or without aura, cluster headache and paroxysmal hemicrania. The maximum location of pain and the aura symptoms tend to be, but not exclusively, on the same side of the AVM.

15.4 Arterial Malformations (Aneurysm)

Cerebral arterial aneurysms are rare in children and familial aneurysms are more likely to present in adults than in children. However, if a child with a primary headache has a family member who suffered a haemorrhagic stroke due to a ruptured aneurysm, it is not unusual for his parents to seek reassurances and ask for investigations to exclude the presence of an arterial aneurysm in their child. In these situations and because of parental anxiety, children with primary headaches may undergo unnecessary neuroimaging.

The majority of children with cerebral arterial aneurysms present unexpectedly with intracerebral bleed. A systematic review of intracranial aneurysms in children showed that 55% present with rupture aneurysm, 30% with neurological symptoms secondary to mass effect and 15% with non-specific symptoms,

Table 15.4 Criteria for the diagnosis of headache attributed to cerebral arterial aneurysm-ICHD-3 beta [2]

A. Any new headache fulfilling criterion C
B. An unruptured saccular aneurysm has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in close temporal relation to other symptoms and/or clinical signs of unruptured saccular aneurysm or has led to its diagnosis
2. Either or both of the following:
(a) Headache has significantly worsened in parallel with other symptoms or clinical or radiological signs of growth of the saccular aneurysm
(b) Headache has resolved after treatment of the saccular aneurysm
3. Either or both of the following:
(a) Headache has sudden or thunderclap onset
(b) Headache is associated with a painful third nerve palsy
D. Not better accounted for by another ICHD-3 diagnosis, and intracranial haemorrhage and reversible cerebral vasoconstriction syndrome have been excluded by appropriate investigations

predominantly headache without evidence of subarachnoid haemorrhage [7]. The same study showed the mean age at diagnosis of the aneurysm was 7.6 years and 59% were male.

The headache in children attributed to cerebral arterial aneurysm should fulfil the ICHD-3 beta diagnostic criteria as in Table 15.4.

15.5 Moyamoya Disease

Moyamoya is a rare progressive vasculopathy of the branches of the internal carotid arteries, and it causes arterial occlusion and a secondary collateral circulation. The anterior cerebral circulation is commonly affected. Moyamoya disease refers to an idiopathic vasculopathy, and moyamoya syndrome refers to cerebral vasculopathy in association with other conditions such as Down syndrome, neurofibromatosis type 1 or sickle cell disease.

Moyamoya is a leading cause of strokes in children after the age of 1 year. Ischemic strokes are usually the presenting features of moyamoya in children between 6 and 9 years of age. The disease can be suspected and diagnosed in asymptomatic infants upon the incidental finding of morning glory appearance of the retina on ophthalmological examination. The diagnosis is made on MRI and MR angiography.

Headache can be a common complaint in patients with moyamoya vasculopathy. In a study of 55 adult patients, headache was reported in 37 patients (67%). The headache phenotype was migraine with aura in 10, migraine-like headache in 7, tension-type-like headache in 10 and mixed headaches in 10 patients. Headache intensity and frequency were improved after surgical revascularisation, and 9 patients developed new-onset headache postoperatively [8].

In a study of 204 children under the age of 17 years with moyamoya, the occurrence of headache before and after indirect bypass surgery over a period of 12 years between 1988 and 2000 was investigated. Preoperative headache was documented in 44 (22%) patients. Headache resolved after surgery in 16 of the 44 patients (37%), but new headache was observed in 6.3% (10 of 160) of those without preoperative headache. It has been suggested that the decreased cerebral blood flow, progressive recruitment and redistribution of blood flow should be considered as possible causes of headaches in patients with moyamoya disease [9].

The symptomatic treatment of headache in moyamoya disease is an integral part of the management plan that will also include prevention of dehydration, reducing the risk of thrombosis, and the surgical revascularisation procedures for the underlying vasculopathy.

15.6 Cavernous Haemangioma

A cavernous haemangioma (CH) is a benign vascular lesion manifested with dilated blood vessels and thinning of the vessels' walls. CH can arise in any part of the body including the central nervous system. Some of the intracranial CH are congenital and others may develop over the course of childhood. Sporadic CH occurs as a solitary lesion and familial CH are often multiple.

The incidence of CH in children and young people is estimated to be around 0.6%. A review of all brain MRI scans that were carried out in one centre in the USA, over a 12-year period, showed that 92 out of 14,936 children and young people under the age of 25 years had at least one CH (total 164). The incidence was also shown to increase from 0.53% in children 1–5 years of age to 0.88% in those between 13 and 17 years old [10]. Boys are slightly more likely to be affected than girls.

In many patients CH are asymptomatic and may remain undetected until they present with intracranial bleeding or a haemorrhagic stroke. The risk for bleeding is not well defined and varies greatly between studies. In some patients CH may present with epilepsy or headache.

Headache is a common indication for brain imaging. Up to one in five of the brain scans carried out in the above-mentioned US study was for the investigation of children with headache. It is not known if CH found on a brain MRI scan represents an incidental finding or if it is responsible for the headache syndrome. Only if headache improves or resolves upon resection of the CH, the cause and effect relationship can be established.

In a review of ten studies of CH in children, headache was reported as a presenting feature in up to 50% of patients, but it is not clear if headache was the only symptom or in association with an intracranial bleed [11].

Management of CH depends on the burden of symptoms and the risk of bleeding. Non-surgical treatment and follow-up may be appropriate for some patients, and resection of the haemangioma may be appropriate if it was causing pressure or mass effect. In children presenting with seizures, resection may be indicated if medical treatment of epilepsy is unsuccessful.

15.7 Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited disorder of the cerebral arteries manifested with recurrent ischemic strokes and headache, mostly as migraine with aura. The underlying molecular abnormalities are related to accumulation of granular osmiophilic material (GOM) on the surface of degenerating vascular smooth muscles and fibrotic thickening and stenosis of the arterioles [12]. Mutation of NOTCH 3 gene is responsible for the disease.

The recurrent nature of the ischemic strokes and the evolving motor disability and cognitive function impairment are characteristics of CADASIL. It can also be associated with seizures and multiple sclerosis-like presentations. Migraine with aura and migraine with atypical aura are common manifestations of the disease and were reported in over 50% of adult patients [13].

The diagnosis of CADASIL is usually made after the onset of ischemic strokes in mid-adult life, but the onset of symptoms may start during late childhood and adolescence. Migraine with aura has been reported to have an onset in childhood in up to 10% of patients especially women [13].

Childhood onset of ischemic strokes and subcortical infarctions in CADASIL has also been recognised in several case reports including children 3 and 8 years of age [14, 15].

The criteria for the diagnosis of headache disorders associated with CADASIL are given in Table 15.5. Headaches have not been well studied in children with CADASIL due to the small number of patients and the usually late diagnosis. However, headaches are better defined in adult patients, and a large study of 378 CADASIL patients in France reported at least 54% of individuals had a history of migraine. The majority of patients were women (62%) and most patients (84%) had migraine with aura. Migraine with aura presented at an earlier age in women than in men. In 60% of patients the aura symptoms were atypical and in about 20% the aura was not followed by headache.

Table 15.5 Criteria for the diagnosis of CADASIL-ICHD-3 beta [2]

A. Recurrent attacks of migraine with typical, hemiplegic or prolonged aura, fulfilling criterion C
B. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) has been demonstrated by genetic testing for NOTCH-3 mutations and/or skin biopsy evidence
C. Either or both of the following:
1. Migraine with aura was the earliest clinical manifestation of CADASIL
2. Attacks of migraine with aura improve or cease when other manifestations of CADASIL (e.g. ischaemic stroke, mood disturbances and/or cognitive dysfunction) appear and worsen
D. Not better accounted for by another ICHD-3 diagnosis

On assessing teenage children with migraine with aura, it is important to keep in mind CVD such as CADASIL, if the aura is atypical, prolonged, complex or consistently not followed by headache [16].

15.8 MELAS

Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a disorder that presents with a variety of symptoms, including migrainous headaches. Many patients will have migraine headaches as one of their initial symptoms [17]. Other symptoms may include muscle weakness and hypotonia, myoclonic seizures, cognitive decline, diabetes and metabolic stroke. Lactic acidosis may be present during acute symptomatic episodes. There are reports that administration of L-arginine, a nitric oxide precursor, may decrease the frequency and severity of the stroke-like episodes [18].

15.9 Posterior Reversible Encephalopathy Syndromes

Childhood posterior reversible encephalopathy syndrome (*PRES*) is characterised by headaches, seizures, visual disturbances and altered mental status [19]. Risk factors include immunosuppression in the setting of renal disease, hypertension and cancer treatment. Radiographically, an increase in FLAIR and T2 signals is seen in the cortex and white matter of the occipital and parietal lobes, although other areas may be affected [20]. MR angiography demonstrates vasoconstriction that outlasts the headache resolution [21].

The symptoms and the radiological findings in PRES overlap with and can be similar to reversible cerebral vasoconstriction syndrome (RCVS) which is characterised by recurrent thunderclap headache with evidence of subarachnoid haemorrhage.

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Chapter 16
Pediatric and Adolescent Headache and Obesity

Tal Eidlitz-Markus and Irene Toldo

16.1 Introduction

Childhood obesity and headaches are critical health problems that often have a marked impact on personality and social interactions that, if not addressed, can carry over into adulthood [1, 2]. The purpose of this chapter is to summarize current knowledge regarding these issues and the potential relationships between them.

There is a relative void in studies investigating treatment options that address the underlying conditions of both obesity and headache in children.

16.1.1 Definition and Epidemiology of Obesity

In contrast to adults, the classification of obesity by body mass index (BMI) in children is not an absolute value (obesity in adults is classified as a BMI $\geq$ 30). In pediatric populations, obesity, as estimated by BMI, is classified by a range of age- and sex-specific BMI cutoff points. Specifically, the cutoff for being overweight is defined as a BMI $\geq$ 85th%, and obesity is defined as a BMI $\geq$ 95th% [3].

T. Eidlitz-Markus (✉)
Pediatric Headache Clinic, Day Hospitalization Department,
Schneider Children's Medical Center of Israel, Petach Tikva, Israel

Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
e-mail: eidlitz@post.tau.ac.il

I. Toldo
Juvenile Headache Centre, Department of Woman's and Child's Health,
University Hospital of Padua, Padua, Italy
e-mail: irene.toldo@unipd.it

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Globally, during 1980–2013, the prevalence of overweight or obese children and adolescents in developed countries has increased substantially, affecting 23.8% of boys and 22.6% of girls in 2013. Prevalence has also increased in developing countries, reaching 8.1–12.9% in boys and 8.4–13.4% in girls [4].

16.1.2 Epidemiology of Primary Headaches

The most common types of primary headaches in the general pediatric population are migraine- and tension-type headache (TTH) [5–7].

In a widespread meta-analysis, the overall calculated prevalence of headache over a minimum period of 3 months (at any point in time) in a total population of 80,876 children was 58.4% [7], and the overall prevalence of migraine in children and adolescents was 7.7% [5]. The reported prevalence of TTH was 18–37% [5, 6].

16.2 Headache and Obesity

16.2.1 Headache in General and Obesity

Recent studies gave contradictory results regarding potential associations between obesity and headache in the pediatric population [8–17] that may be attributed to differences in the study populations as well as methodology. The weight of data lends credence to a positive association between headache and obesity among children and adolescents. However, more multinational epidemiologic studies are needed to verify associations.

Several studies tested for a possible association between pediatric headaches and obesity [9–17]. In particular, two studies reported an association between obesity and migraine [9, 11], while three other studies found no association [10, 16, 17]. To the best of our knowledge, the first study [9] that specifically examined the relationship between pediatric obesity status and headache was a cross-sectional study of 273 children, aged 9–17 years old, presenting at pediatric obesity clinic and general pediatric clinics in Israel; 14.2% (n = 39) fulfilled criteria for obesity. Only obese girls (not boys) experienced a fourfold increase in headaches compared with girls with a normal BMI. The study was limited due to the small number of obese children [9].

In 2010, Robberstad et al. [11] reported on 5847 Norwegian students aged 13–18 years with recurrent headache. They found an association between recurrent headache and overweight, reporting a 60% greater risk of migraine in overweight or obese adolescents compared to normal-weight adolescents (OR 1.6; 95% CI, 1.4–2.2; $p < 0.0001$).

Hershey et al.'s [10] retrospective longitudinal multicenter study of 913 children (aged 3–18 years) found a modest positive correlation between headache frequency and BMI percentile ($P = 0.003$); however, prevalence of overweight patients in their

study was not significantly different from the general pediatric population (17.5% versus 17.1%, respectively).

Eidlitz Markus et al. [16] reported no association between primary headaches (TTH and migraine) and obesity. Furthermore, no statistical difference was found between obesity rate in their study population (25.3%) and the 26% rate described in the 2010 Organization for Economic Co-operation and Development (OECD) report.

16.3 Tension Type Headache and Obesity

The data evaluating the association between TTH and obesity in pediatric population is limited and conflicting. Three studies [14–16] reported no association between TTH and obesity, while two other studies reported a significant association between them [11–13]. One study [9] reported a possible trend for the association between obesity and episodic TTH but not with chronic TTH. However small number of overweight TTH patients (8–10.1%) obese patients of 79 patients with TTH is a study's limitation that precludes conclusive results [10].

In Lu et al.'s study [15] obesity was not found to be a predictor for chronic TTH. In contrast to the above studies, Robberstad et al. [11] noted the risk of TTH was 40% greater in adolescents whose BMI was above the overweight cutoff for age and sex (OR 1.4; 95% CI, 1.1–1.6; $P < 0.0001$) compared to adolescents whose BMI was below the overweight cutoff. Pakalnis and Kring [12] also reported a significant higher prevalence of chronic or probable chronic TTH without medication overuse in obese adolescents compared to the reported general population obesity 26% (95% CI, 16.5–37.6) and 16.3%, respectively.

16.3.1 Chronic Daily Headache and Obesity

Recent studies tested for possible associations between obesity and chronic daily headache (CDH) in pediatric populations [12, 14, 15]. In two retrospective studies, a positive association was reported between obesity and CDH [14, 15]; in the third clinical study, no association was found with measured BMI scores [12].

The contradictions may be explained by differences in data collection methodology as self-reported BMI [12] and in population characteristics, especially age discrepancies, given the lower prevalence of obesity in younger compared to older children.

16.3.2 Migraine and Obesity

For adults, research supports associations between obesity and migraine [18, 19].

In the pediatric population, several studies evaluating possible associations between obesity and migraine [9, 11, 13–15] found a positive association; two

studies showed no association [12, 16]. Robberstad et al. [11] conducted a cross-sectional analysis of 5847 students in Norway; the risk of migraine was 60% greater for overweight or obese adolescents (OR 1.6; 95% CI, 1.4–2.2; $P < 0.0001$) compared with students of normal weight [12]. Kinik et al.'s study, conducted in a neurology clinic, showed an association between obesity and increasing frequency of headache and episodic migraine in 124 children with migraine [13].

Ravid et al. [14] tested for association between obesity and migraine and headache in general. Migraine (episodic and chronic migraine (CM) combined) was more prevalent in obese (62.5%, 15/24) and overweight (60.4%, 29/48) patients than in people with normal weight (33.9%, 37/109; $P = 0.01$). When comparing genders, overweight girls had a 3–5 times greater odds of migraine compared to girls of normal weight. However, migraine was not significantly more frequent in overweight or obese boys compared to boys of normal weight [14]. Similarly, Lu et al. [15] reported 2.5 times more at risk for CM in obese students [15].

In contrast, no correlation between migraine frequency and obesity was found in Pakalnis and Kring's 2012 retrospective clinic-based study [12]. Additionally, no significant difference was found between overweight and obese participants having episodic migraine or probable CM without medication overuse, compared to the historically reported prevalence of CM in the general population of over normal weight children and adolescents (32.9 and 31.9%, respectively) [12]. Again, the age discrepancy between the clinical and historical general populations and the small number of patients might explain these findings. Similarly, no correlation was found between migraine frequency and obesity grade in the Eidlitz Markus et al.'s study [16].

16.3.3 Secondary Headaches and Obesity

Obesity has been demonstrated to be a risk factor for secondary headache conditions such as idiopathic intracranial hypertension (IIH) both in adults [18] and in adolescents [20]. Moreover Stiebel-Kalish et al. [21] found that the risk for IIH recurrence was fivefold higher in children with a BMI $\geq$ 85th percentile (57%) than in healthy weight children (11%; log-rank test $P = 0.04$).

16.4 Pathogenesis of Migraine and Obesity

Recent data support that obesity is comorbid with migraine, both episodic and chronic, in adults [18] and also in children [22]. While this observed association is not new, it is only recently that studies have focused on mechanisms explaining how obesity-related bioactive substances might be involved in migraine pathophysiology [23].

The association between obesity and migraine is likely to be multifactorial and involve both central and peripheral mechanisms [23]. Multiple bioactive substances (e.g., serotonin, dopamine, calcitonin gene-related protein, histamine, leptin) have long been recognized as playing important roles in energy homeostasis [22, 23].

16.4.1 Hypothalamus Appetite Regulation and Migraine

There may be overlap in the role of the hypothalamus in regulating feeding and other activities. The lateral hypothalamus (LH) nucleus contains two groups of neurons: orexin neurons that stimulate feeding and melanin-concentrating hormone neurons, which inhibit food intake. These neurons subsequently project to the brainstem nuclei where the descending hypothalamic inputs are integrated with peripheral inputs from the gastrointestinal system [24].

The hypothalamus has also been implicated in migraine: it was found to be activated in migraine attacks and influence food cravings as well as mood and sleep disturbances [25]. This pathological modulation of the hypothalamus in migraine may result in hyperphagia and weight gain. Additionally, data supports the hypothesis that several hypothalamic peptides, proteins, and neurotransmitters (serotonin, orexin, and adipokines (e.g., ADP)) involved in feeding may contribute to migraine pathophysiology [25, 26].

16.4.2 Serotonin

Low brain serotoninergic activity has been co-implicated with interictal levels of plasma serotonin, found to be low in adult migraineurs [27]. Conversely, there is a 60% increase in 5-hydroxytryptophan (5-HT) plasma levels and a 30% reduction in platelet serotonin levels during acute migraine attacks [28]. Thus, low serotonin states in migraineurs interictally may promote an increased drive for feeding, whereas high levels interictally may promote hypophagia and increased 5-HT plasma levels, along with a 30% reduction in platelet serotonin levels [28].

16.4.3 Calcitonin Gene-Related Peptide

CGRP is a neuropeptide that is released into the cranial circulation after stimulation of the trigeminal ganglion during acute migraine attack [29] and is also a potent vasodilator of cerebral and dural vessels. CGRP levels are higher in obese individuals [30].

16.4.4 Orexin

The orexines are hypothalamic peptides reported to be involved in a variety of functions, including feeding, sleep, hormone secretion, and also in modulating nociceptive processing [31]. Orexin A is able to inhibit neurogenic dural vasodilatation,

resulting in reduced release of CGRP from trigeminal neurons. Low levels of orexin in obese persons may be associated with increased susceptibility to neurogenic inflammation causing migraine attacks [32].

16.4.5 Adiponectin

Adiponectin (ADP) is an adipocytokine, secreted primarily by adipose tissue participating in energy homeostasis as well as during immunity and inflammation. ADP exists in three patents: low (LMW), medium, and high molecular weight. The LMW ADP ratio level was associated with migraine severity and was predictive of acute treatment response. Both pretreatment migraine pain severity and treatment response were associated with changes in adipokine levels [26].

16.4.6 Inflammatory Mediators

Expansion of adipose tissue during weight gain leads to the induction of several pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and IL-1 [33], all of which can contribute to local and systemic inflammation. Likewise, increased levels of serum TNF-α and IL-6 have been documented at the onset of migraine attacks [33, 34].

16.4.7 Leptin

Like ADP, leptin is primarily produced by adipocytes but also by several other tissues, including brain [35]. As with ADP, leptin has been implicated in inflammation and pain modulation, and there is evidence that leptin may be involved in mechanisms for cortical spreading depression [36] in migraine pathogenesis. However, studies evaluating leptin levels in migraineurs have been inconclusive; data suggests both low [37] and elevated [36] leptin levels in migraineurs as well as the non-affected population [38].

16.5 Treatment Considerations

In the following section, we will discuss the evidence and precautions associated with treatment options directed at weight loss and their efficacy in improving headache.

16.5.1 Exercise and Lifestyle

At the most basic level, physical exercise is a key weight loss strategy, and preventive measures are often recommended to overweight and obese patients. However, activity has also been reported by migraineurs to be a headache trigger [39]. This concern often leads to a debate as to whether exercise is an appropriate treatment option.

Although a good training program has been demonstrated to reduce the frequency of migraine in adults, no direct studies have been reported in pediatric population [40]. In adolescents, Robberstad et al. [11] reported that recurrent headaches in both girls and boys were associated with inactivity. Furthermore, the authors suggested an association between migraine and inactivity and between tension headache and inactivity (OR 1.2; 95% CI, 1.0–1.4; $P = 0.02$) [11].

In 2010, Milde-Busch et al. [41] examined associations between multiple lifestyle factors, including diet and activity level, and headaches in adolescents. In a cross-sectional analysis, 1260 German 10th and 11th graders (14–20-year-olds) completed a questionnaire that assessed multiple dietary and lifestyle factors as well as headaches. Most participants ($n = 1047$, 83.1%) had primary headaches [41]. The authors noted that the most frequently reported types of headaches—migraine or TTH (except "miscellaneous headaches")—were more prevalent in those with low physical activity compared with adolescents with high levels of physical activity.

A regular physical activity is recommended in recent guidelines for the management of pediatric migraine [42].

16.5.2 Diet

In a 2013 Italian multicenter trial of obese adolescent migraineurs, Verrotti et al. [43] studied the effects of weight loss on headache outcomes over a 12-month period. Study patients (14–18-year-olds) presented to a pediatric neurologic center and then participated in weight loss therapy consisting of an interdisciplinary intervention program including dietary education, physical exercise, and behavioral therapy. All participants had an initial BMI ≥97%; BMI reduction was significantly associated with reduction of headache frequency and intensity for the 12-month period. However it may have been the interdisciplinary intervention program rather than the weight reduction itself that led to improvement in headache symptoms. Furthermore, it was difficult to distinguish between the triggering role of being overweight and a select nutrient, as the overweight children's diet was most likely rich in chocolate, citrus fruits, cheese, hot dogs, monosodium glutamate, aspartame, fatty foods, and ice cream that can trigger migraine attack in children [44–46]. Similar findings have been reported by Hershey et al. [11] showing a positive correlation between a change in BMI and reduction in headache frequency during a 6-month follow-up period.

In Kossoff et al.'s 2010 study, the modified Atkins diet was tested on eight adolescents with chronic daily headache (CDH). Only three participants completed the 3-month study, and despite demonstrated weight loss (1.4–8.2 kg each), they did not have any reduction of headache frequency [47].

16.5.3 Bariatric Surgery

Bond et al. [48] reported a parallel weight reduction with headache frequency trend 3 months after bariatric surgery in adult obese episodic migraineurs, similarly to other studies [48, 49]. The success of bariatric surgery and its long-term effects is still unknown and under researched in the pediatric and adolescent population [50, 51].

To date, no studies have been published offering bariatric surgery treatment for pediatric obese migraine patients, and further research is needed.

16.5.4 Medications

Weight gain is among the most common side effects for many prophylactic medications used to treat migraines and one of the leading reasons for a patient to refuse or stop a prophylactic medication [52].

Of the FDA-approved migraine medications, only topiramate has been shown to result in weight loss, suggesting that its use may be beneficial in alleviating migraine symptoms while aiding individuals in weight loss efforts. However, when patients discontinued treatment, they gained weight [53].

16.5.5 Other Treatments

Cervoni et al. [54] suggested behavioral weight loss interventions complement existing behavioral treatments for migraine and obese patients. Further studies relating behavioral therapy for reducing weight in obese pediatric patients are needed.

In summary many open questions remain regarding the modifiable nature of the obesity–headache relationship and its implications in clinical practice, and further studies addressing these issues are needed.

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Chapter 17
Comorbidity with Learning Disabilities

Jacob Genizi and Marco A. Arruda

17.1 Introduction

Scientific evidences supporting the impact of migraine and other recurrent and chronic headache on child emotional regulation and behavioral control are more robust and widely recognized than those indicating a possible impairment in cognitive functioning. However, in this chapter we review the evidences from clinical and population studies supporting the impact of headache, mainly migraine, on school achievement as well as the possible comorbidity between migraine headache and learning disorders in general. In our revision, we have not found any study focusing on specific learning disorders like dyslexia and dyscalculia in children with migraine. The clinical implications of the findings are discussed, and a proposal for clinical approach is presented.

17.2 Learning Disabilities

Learning disabilities (LD) are a group of disorders which are characterized by failure of a student to competently acquire, retrieve, and use information. The definition of LD varies. The main feature is academic achievement that is lower than expected based on the child's intelligence [1–3]. LD presents as a failure to obtain reading,

J. Genizi (✉)
Bruce and Ruth Rappaport Faculty of Medicine, Pediatric Neurology Unit, Bnai Zion Medical Center, Haifa, Israel
e-mail: genizij@gmail.com

M.A. Arruda
Child and Adolescent Neurologist, Glia Institute, Ribeirao Preto, Brazil
e-mail: arruda@institutoglia.com.br

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writing, or math skills at grade- and age-appropriate levels. In 2013, the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM5] was published by the American Psychiatric Association [4]. In this edition, specific learning disorder is the term for mathematics, reading, and written expression disorders. This sole diagnosis includes all deficits that impact academic achievement. The diagnosis requires persistent difficulties in reading, writing, arithmetic, or mathematical reasoning skills during formal years of schooling. [DSM5] Symptoms may include inaccurate or slow and effortful reading, poor written expression that lacks clarity, difficulties remembering number facts, or inaccurate mathematical reasoning. Current academic skills must be well below the average range of scores in culturally and linguistically appropriate tests of reading, writing, or mathematics. The individual's difficulties must not be better explained by developmental, neurological, and sensory (vision or hearing) or motor disorders and must significantly interfere with academic achievement, occupational performance, or activities of daily living.

The exact mechanism by which specific learning disorder develops has not been completely elucidated, and numerous theories have been advanced. LD have a multifactorial etiology and are originated from abnormalities in brain function or even structure [5–7].

Imaging studies has demonstrated alternations in the right temporoparietal-occipital region in patients with dyslexia, as well as asymmetries in the angular gyrus and corpus callosum. The angular gyrus is located in the parietal lobe, specifically Brodmann's area 39, and is engaged in mathematics, cognition, and language. This may explain the association between dyscalculia and dyslexia.

Studies demonstrated that a reading disorder is found in clusters among families. This reflects an autosomal dominant pattern of transmission. Genetic research has found a high familial incidence of dyslexia among both monozygotic and dizygotic twins. However, only eight isolated genetic defects have been identified among dyslexic patients. New evidence shows that the environment can modify expression of reading disorder phenotype. The explanation might be that the genes could be manipulated by enrichment experience to express the nonpathologic aspect of the dyslexia phenotype [8].

17.3 Headache and Learning Disabilities

Some clinical studies assessed the impact of headache on school performance in children. D'Andrea et al. [9] investigated intelligence, digit span, and visual–motor integration among 20 elementary school children with migraine and found them to be normal, as opposed to performance in short- and long-delayed memory tasks that were significantly impaired. Haverkamp compared the cognitive performance of children with migraine to their healthy siblings and found no significant difference in sequential and simultaneous information processing [10]. Riva et al. [11] found among children and adolescents with migraine dysfunction in the information processing rate. The simple reaction time to visual stimuli was slow compared to the normal population; however, they did not have a headache-free control group. Villa

et al. [12] did match 30 children with migraine and 30 healthy children. Children with migraine in that study exhibited impairment in all the variables except the reaction time in the visual attention test tasks. Parisi et al. [13] conducted a cross-sectional controlled study and compared children with TTH and a control group and found significant lower grades in the intelligence quotient scale and in the verbal comprehension subtest score. The same difference was revealed between children with migraine and the control group. The difference was significant in the verbal intelligence scale quotient score as well as in the verbal skills. Parisi hypothesizes that the cognitive impairment in headache is exacerbated by age at onset and the frequency of attacks. Higher rates of learning disabilities (24.7%) were found by Genizi et al.'s study group, compared with the reported rates in the general population (Genizi 2013) [14]. Learning disabilities were more prevalent in children with migraine compared to children with tension-type headache, in children with long duration of headache, and among children with more than ten episodes of headache per month.

Some studies looked at school achievement in children suffering from headache rather than at learning disabilities itself. Powers et al. [15] in a survey study conducted on 572 consecutive outpatient clinic headache children (11.4 ± 3.6 years) found that impairments in school and emotional functioning among children with migraine was similar to that found for other chronic illness conditions such as cancer. In a complementary study, they demonstrated that among children with migraine, older children had more profound school impairment [16].

Only few population-based study evaluated the connection between headache mainly migraine and school performance. In a longitudinal study conducted on children with migraine, Waldie et al. [17] reported impaired verbal skills in children with migraine compared with the control group. He claimed that verbal performance was not influenced by migraine attacks but was due to a prenatal shared risk factor. He suggested that the origins of both migraine headache and cognitive impairment are probably found in an early developmental phase. Arruda and Bigal [18] in a very large population study (5671 children were interviewed by their teachers) found that children with migraine (either episodic or chronic) were significantly more likely to have school performance below average compared to children with no headache. The risk was not significantly increased in children with TTH, relative to children with no headache.

17.4 Pathophysiology

17.4.1 What Is the Connection Between Headache and High Cognitive Function?

A possible explanation might be the theory of fear of failure that was found in children with chronic headaches and as a result an overachievement approach to school work. Greater motivation to achieve has been reported in adolescents with headaches, with a positive interaction between desire for successes and achievements [19]. Another explanation can be more anatomic. In children with headache, the

involvement of cognitive function might be functionally related to cortical areas, such as the frontal and prefrontal areas, as a consequence of poor sleep [20], or structurally related to subcortical areas, as a consequence of iron accumulation in deep brain nuclei [21]. Cortical and subcortical diffuse neuronal networks are responsible for higher cognitive functions [22]. According to the "diffuse hypothesis," and the recent theory of migraine (the cortical spreading depression) [23, 24], Parisi et al. [13] postulated that since migraine attacks are associated with repeated activation of neuronal networks, this recurrent activation may result in a cognitive involvement.

17.5 Clinical Implications

The implications of the relations between headache, especially migraine, and school performance are vital to the clinical evaluation of children and adolescents with headache. Taking a thorough history relating to learning and school performance is essential when evaluating a child or an adolescent with primary headaches and should be given no less attention than talking about his diet. Early diagnosis and treatment of learning disabilities may improve school performance and thus the child's well-being. Consequently, there might be a positive effect on the reduction of headache episode. It is to be evaluated whether a better control of headaches improves school performance.

17.6 Conclusion

The higher risk of learning difficulties and poor school achievement in children with chronic and recurrent headaches has immediate clinical implications in the diagnostic approach and in the therapeutic decision making process. In front of a child with chronic or recurrent headaches, we should expand the investigation to aspects not only related to school performance but also to school functioning as a whole, getting more information from parents and the teachers. We urgently need population and clinical studies specifically investigating the possible comorbidity between chronic headache, dyslexia, dyscalculia, and other specific learning disabilities in children.

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Chapter 18
Comorbidity with Fibromyalgia

César Fernández-de-las-Peñas and Massimiliano Valeriani

18.1 Fibromyalgia Syndrome in Childhood and Adolescence

Fibromyalgia syndrome (FMS) is a chronic and disabling musculoskeletal pain condition featured by widespread pain, fatigue, and cognitive and physical problems, as well as sleep disturbances [1]. The mean worldwide prevalence of FMS in adult populations has been estimated to be 2.7% [2]. In fact, an estimation from the United States of America showed that FMS is the third most common rheumatic disorder only after low back pain and osteoarthritis in adult women [3]. Although the exact etiology of FMS is conflicting, it is accepted that central sensitization mechanisms are relevant for this pain condition [4] and that this sensitization of the central nervous system is moderately associated with a decrease in gray matter volume in specific brain regions, such as the anterior cingulated cortex and prefrontal cortex [5]. Recent data on skin biopsy have shown that in some FMS patients, there is a reduction of the cutaneous small unmyelinated fibers, thus suggesting that, at least in some cases, FMS pain can have a neuropathic etiology [6, 7].

While a majority of research on FMS has focused on adults, increasing evidence has provided insights into the presence and impact of widespread pain in children and adolescents. Commonly referred as juvenile fibromyalgia (JFM), childhood,

C. Fernández-de-las-Peñas, P.T., M.Sc., Ph.D., Dr. Scient
Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain

Cátedra de Investigación y Docencia en Fisioterapia: Terapia Manual y Punción Seca, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain

M. Valeriani, M.D., Ph.D. (✉)
Headache Center, Neurology Unit, Ospedale Pediatrico Bambino Gesù, Piazza Sant'Onofrio 4, 00165 Rome, Italy

Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark
e-mail: m.valeriani@tiscali.it

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particularly adolescent girls, presents with persistent widespread pain and other cardinal symptoms similarly observed in adults. Its prevalence ranges from 1.2 to 6.2% in the general childhood and adolescent population [8]. Childhood and adolescents suffering from JFM exhibit lower functional capacity [9], poorer emotional support, and fewer positive social interaction than healthy children [10]. Although JFM has their specific diagnostic criteria [11], 51% of children with JFM will also meet diagnostic criteria for adult FMS with years [12]. In fact, up to 80% of the adolescents with JFM continue to experience widespread pain symptoms when they are adults [13]. Nevertheless, the diagnosis of JFM in childhood and adolescents is not as investigated as FMS in adults [14].

Although JFM and FMS could be considered two entities of the same spectrum, they have several similarities but also differences. For instance, the psychological [15] and the clinical [16] spectrum of JFM is similar to that of FMS but with better outcome. As in adults with FMS, it has been hypothesized that JFM also involves abnormal pain processing in the central nervous system resulting in hypersensitivity to painful and non-painful stimuli [17]. Some authors defend that differences between adults with FMS and childhood with JFM can be observed with regard to comorbidities, e.g., joint hypermobility was proposed as being more common in adolescents and children than in adults. This hypothesis is based on the premise that hypermobility syndrome in children has emerged as a risk factor for the development of FMS [18]. However, since the frequency of joint hypermobility in adults with FMS is 64.2%, we do not know if this syndrome is a risk factor or a comorbid condition of FMS [19]. In fact, there is no clear evidence of an association between joint hypermobility and widespread chronic pain [20].

Finally, compared to adults with FMS, pharmacological treatments for JFM are promising, but no particular drug is still accepted [21]. However, similarly to adults with FMS, cognitive-behavioral therapy and exercises have shown promising positive results in JFM [22–24]. It would be therefore relevant to consider the presence of JFM in childhood or adolescents who develop other pain condition, e.g., headache, for proper management or early identification of potential risk factors. The presence of JFM could promote the development of comorbid conditions or, on the other hand, other pain conditions can be a risk factor for development of JFM. In the following section of the chapter, we will discuss comorbidity between FMS/JFM and headaches.

18.2 Comorbidity of Headache and Fibromyalgia

Headache is a common condition observed in childhood and adolescents. As in adults, pediatric headache can be primary or symptomatic. While in the last cases, headache represents a symptom of a different disease, such as benign upper respiratory tract infections or life-threatening intracranial lesions, primary headaches have a genetic background [25]. Migraine represents the far most frequent primary headache in children and adolescents, showing a prevalence around 10% [26]. Primary

headaches can occur in isolation or in conjunction with comorbid diseases. Headache comorbidities look at the issue of two (or more) conditions that are comorbid with the headache condition or of other conditions for which the own headache is itself a significant comorbidity. It is difficult to determine which is first, the "chicken" or the "egg," mostly when migraine occurs in as much as 20–30% of different conditions, such as epilepsy, asthma, stroke, psoriasis, rheumatoid arthritis, and, as the topic of the current chapter, FMS [27].

There is evidence for both situations, migraine as a potential risk factor for JFM and migraine as a comorbid and perpetuation factor of JFM. A previous study found that the greatest risk of developing persistent pain in adolescents was daytime fatigue, frequent headache, or participating in vigorous activity [28]. A recent study showed that the strongest nongenetic predictor for having a cluster of symptoms consistent with FMS being adult was the presence of frequent headache (OR 8.6, 95% CI 3.8–19.2) [29]. In these studies, the presence of a pain condition such as frequent headache was able to stimulate the central nervous system to higher levels of sensitization and future developing of widespread pain and FMS.

On the other side, other authors observed that 56% of patients with a previous diagnosis of FMS also met the criteria for migraine [30]. In fact, Tietjen et al. [31] described three groups of patients with migraine and grouped into the same subgroup those individuals with migraine and depression, anxiety, FMS, and sexual abuse. This was supported by several studies observing that FMS was present in 40–55% of adults with headache, particularly those with chronic tension-type headache or chronic migraine [30, 32, 33]. There is just one study, whose objective was to evaluate the relation of childhood maltreatment with the prevalence of different pain conditions comorbid with migraine, reporting that 10% of children with migraine attending to a pediatric headache center exhibited comorbid JFM [34]. No other epidemiological study investigating the comorbidity between JFM and headache in childhood or adolescents is available.

The observations in adults have raised the question as to whether the association of FMS with headache may involve higher degree of central sensitization with respect to one condition only. It is observed that subjects suffering from FMS with concurrent headache, particularly migraine, often present an exacerbation of their typical FMS symptomatology in concomitance with or immediately subsequent to a headache attack, suggesting that headache represents a triggering factor for FMS. Tietjen et al. [35] observed that the presence of cutaneous allodynia, a manifestation of sensitization of the central nervous system, was more common in adults with FMS than in subjects without FMS. A study has confirmed that comorbidity between FMS and migraine involves higher levels of widespread hypersensitivity to pain compared to one condition only [36]. In fact, higher frequency of migraine attacks enhanced pain hyperalgesia and spontaneous FMS pain suggesting that migraine may be considered as a triggering factor for FMS pain in a subgroup of patients [36]. It is possible that a similar phenomenon occurs in children or adolescents with comorbid JFM and headache, although there is no current evidence on this topic. It is interesting that the reduced habituation of the brain evoked potentials to repetitive stimuli of any modality, that is commonly considered as a

neurophysiological marker of migraine [37], can be also found in individuals with FMS [38]. This suggests that an abnormal brain excitability is probably a common background shared by both pain diseases.

There are several other factors that may potentially play a role in comorbidity between JFM and headaches. For instance, depression and anxiety are clearly associated with either chronic headache [39] or JFM [40], although quality of life is more affected in JFM. Other psychological aspect related to an increased risk of comorbid FMS and migraine is the presence of lower dynamism with a high score in denial coping style [41]. Therefore, early identification and proper management of anxiety or depressive symptoms and implantation of proper active copying strategies should be considered by clinicians for avoiding sensitization of the central nervous system. In fact, early identification of the risk factors and preventive strategies should be incorporated for avoiding future comorbid FMS and migraine since there is evidence supporting that comorbidity of FMS is a strong predictor of suicidal ideation (OR 2.61) and attempts (OR 1.99) in individuals suffering from migraine [42].

Other factor associated with comorbidity of JFM and headache can be familiar relationships. For instance, mothers of adolescents with JFM report twice as many pain conditions and significantly greater depressive symptoms than mothers of comparison peers. In addition, childhood with JFM also exhibits poorer overall family functioning and more conflicted family relationships [43]. In the same direction, Tietjen et al. [34] reported an association between childhood maltreatment and the presence of multiple and severe pain conditions. Therefore, clinicians should identify potential familiar conflicts when treating childhood and/or adolescents with only JFM, only headache, or both.

In conclusion, although there is almost inexistent literature investigating comorbid JFM and headache in childhood and adolescents, this relationship in adults can help us in better understanding of potential repercussion of this comorbid situation. Moreover, the increasing evidence that primary headache and FMS are often associated in adults and that the comorbid occurrence of both painful conditions worsens the quality of life of these individuals by a further measure than the mere summations of their respective symptoms should hopefully lead researchers to investigate this important issue even in pediatric age.

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Chapter 19
Headache and Compliance in Children

Aynur Ozge and Giulia Natalucci

19.1 Introduction

Compliance defines as the act of obeying an order, rule, or request. It also means the extent of patient conformity to provider recommendations with respect to medication timing, dosage, and frequency. *Adherence* defines as the fact of someone behaving exactly according to rules, beliefs, etc. It also means that the extent to which a patient's behavior matches the agreed-upon medication treatment regimen. *Concordance* defines shared decision-making between the patient and physician in the structuring of a treatment regimen. Finally, *persistence* defines the renewal rate of prescriptions, the duration of continuous treatment with the initially prescribed medication [1].

In a clinical setting, physicians are trained to diagnose a disorder and select an appropriate medication based on pharmacokinetic (e.g., absorption, metabolism, elimination, and interaction) and pharmacodynamics (e.g., adverse effects) properties. However, if the patient does not follow the medication appropriately, even the most scrupulously chosen and optimal treatment cannot work. Compliance or adherence to treatment is the degree to which the patient respects mainly the prescriptions, dosage, and frequency [2].

Medication compliance is different from medication persistence; this one refers to the act of continuing the treatment for the prescribed duration. It may be defined as "the duration of time from initiation to discontinuation of therapy" [3]. Moreover, compliance is measured over a period of time and reported as a percentage, whereas persistence is reported as a continuous variable in terms of number of days for

A. Ozge, M.D.
Department of Neurology, Mersin University School of Medicine,
Çiftlikköy Kampusü, Yenişehir, 33430 Mersin, Turkey

G. Natalucci (✉)
Department of Pediatrics and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, Via dei Sabelli, 108, Rome, Italy
e-mail: natalucci.giulia@gmail.com

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which the therapy was available. Clinical outcomes are affected not only by how well patients take their medications but also by how long they take them [4].

Better compliance depends first of all by the relationship with the physician. Patients must completely understand why they are taking drugs and why it is important to respect dosages and frequencies, and they must learn about possible complications if they do not take medication. Furthermore, physicians have to explain why they have chosen that kind of therapy and, especially with children, explain in the most clear and simple way every step they must take because it is important to know that the responsibility for fulfillment of the prescribed regimen lies with the patient. Secondly, treatment adherence also expresses, in a broad sense, the will of cooperation with the various structures of health organization in the path of a default regimen.

Compliance is a complex and multifaceted issue that is still poorly understood, but there is a guideline for physician to help them to deal with this problem [5].

Optimum diagnostic and management goals are the main scope in headache in children and adolescent (HCA) process. Combining the various modalities will improve the chances for successful treatment. This includes increasing quality of life, optimizing mood, minimizing stress, practicing good sleep hygiene, and avoiding triggers. All comorbid factors should be addressed, including atopic disorders, sleep and mood disorders, chronic neck pain, epilepsy, and obesity. Preventive treatment is necessary in the majority of patients, and a plan for "rescue" approaches is essential. Avoiding medication overuse and increasing academic and social life expectations are advisable. Additional options for treatment including Onabotulinum toxin A, and more invasive modalities, together with adjunct treatment including supplements and relaxation may also be considered. Keeping a headache diary (in print or electronical) is almost mandatory in management with attention to particular headache triggers, patterns and medication overuse headache (MOH). This age group, a trusting physician–patient–parent relationship is also very important more than adults and will enhance compliance and foster communication. Patients and parents often lapse from the management plan, and the treating physician should be open-minded about continuing care [6].

The efficacy of drug treatment in children and adolescents with headache is partly determined by medication adherence. The adherence literature has focused almost exclusively on the behaviors required to optimally use medications that are taken on a fixed schedule, as opposed to medications taken on an as needed basis to treat acute episodes of symptoms, such as headaches. It is known that only 50–75% of patients performing the behaviors required to optimally using medication. Defining and solving of compliance and adherence problems could increase success of the management [7, 8].

19.1.1 Compliance, What Does It Mean?

Compliance and concordance are terms that stress the amount of patient involvement in the structuring and following of treatment recommendations. While compliance implies passivity on the part of the patient, and can be defined as how well a

patient "follows the doctor's orders," concordance implies patient agency and assumes the patient's desires have played a role in the structuring of the treatment regimen.

Treatment nonadherence in migraine can best be understood as deviation from an optimal cycle of provider and patient behaviors designed to enhance the patient's health. Main barriers to reduce compliance of headache in children and adolescents are difficulty recognizing headache types by physicians, lack of knowledge about headache and medication, forgetting medications, side effects of the drugs, perceived inefficacy of the management by patients or parents with nonrealistic expectations, role conflicts of the patients or parents, social influences of headache attacks, and management procedures and preference. Difficulty recognizing headache types and role conflicts were among the most commonly described barriers to optimal use of acute headache medication [ibidem].

19.1.1.1 Definition of Compliance and Adherence Treatment

There are many challenges to a childhood headache definition. Like with migraines, there are no biological markers on most of the subtype, and criteria are largely based on satisfying treatment paradigms and optimizing comorbid factors changing by gender and increasing age of the children [6]. Not only diagnostic process but also abortive and preventive managements of headache attacks in children and adolescents have challenging issues. Although it is not supported by evidence based data, researchers suggest that optimal use of fixed schedule medication requires three medication-taking behaviors (establishing medication taking as part of a regular routine, keeping medication accessible at scheduled times for administration, and communicating relevant information to the prescriber); using acute medications optimally appears to require successful performance of more complicated sequences of behaviors, which are contingent on multiple symptom- and situation-specific factors. Therefore, optimal use of acute medication may be more challenging and more problematic than optimal use of fixed-schedule medication especially in children and adolescents [8].

19.1.1.2 Red Flags for Noncompliance in Childhood and Adolescence

Patients can be classified into one of three general compliance categories: (1) full compliers, who take adequate amounts of medications to control the disorder; (2) partial compliers, who take many doses, but not regularly enough to control the disorder; or (3) noncompliers, who take few or no doses and whose disorder is unaltered [2].

Nonadherence to prescribed treatment regimens is an important and widespread behavioral health issue especially in chronic conditions, in particular when prescribed with a self-administered medication. Rates of noncompliance range from 50 to 60% across adult chronic illness population and from 50 to 88% across pediatric population [9].

These high rates between children are due to different reasons. First of all, noncompliance can depend on disease categories and age group. In fact, it is most prevalent during the adolescent years when the process of transition from parental dependency to autonomy produces confusion as to who is responsible for administration of medication [10, 11].

A second reason involves children's family and their attitudes toward different treatments. When children have to start and follow a strict drug therapy, parents are often reticent and skeptic because of the possible side effects and the long-term effects on their children. It is not uncommon that patients and parents deliberately choose not to follow the doctor's recommendations and consequently there may be a non-improvement or even worsening of the patient's symptoms. Furthermore, maternal control style seems to affect noncompliance behavior on children: children whose mothers are more controlling and less guiding exhibit more aversive styles of noncompliance and less committed compliance [12]. Moreover, there could be non-intentional barriers to medication compliant that are related to family routines, to child-raising issues, and to social issues such as poverty [13].

Atreja and colleagues [14], in response to enhance patient adherence, grouped adherence-promoting interventions into categories that can be remembered by the mnemonic "SIMPLE": (1) simplifying regimen characteristics, (2) imparting knowledge, (3) modifying patient beliefs, (4) leaving the bias, (5) provide communication and trust, and (6) evaluating adherence.

Noncompliance does not only lead to worsening patient symptomatology but also to an increase in costs related to inefficient management of the disease (Table 19.1).

Table 19.1 Positive and negative factors influencing compliance [15]

Positive and negative factors influencing compliance in headache children
Positive factors
Understanding the disease and possibilities about chronification
Absence of personality disorders
Good patient–parent–physician relationship
Involvement of the family and school counselors or teachers
Negative factors
Occurrence of side effects or no improvements
Psychiatric comorbidity (anxiety, depression, school problems, etc.)
Co-occurrence of other disease like sleep disorders, obesity, atopic disease, cardiovascular disease, etc.
Irregular appointment attendance and declining headache diary use
Substance abuse
Adolescence hormonal changes

19.1.1.3 How to Evaluate Compliance?

Qualitative research is a standardized form of inquiry of headache compliance that is designed to gather in-depth, holistic information about a phenomenon utilizing detailed study of a few participants. At an early stage of inquiry, such as the current state of the literature on optimal use of headache medications, qualitative (as opposed to quantitative) studies can provide detailed information about little-studied phenomena and minimize reliance on researcher assumptions and biases which can overlook important information about a phenomenon. Qualitative studies are an important foundation upon which a program of empirical research can build, allowing the program of research to avoid "Type 3 errors," or the error of asking unnecessary or inconsequential empirical questions according to most of the authors [8, 16].

There are many interpretative models regarding treatment adherence in literature. One of the most famous was formulated by Leventhal and Cameron [17]. They identified five main theoretical perspectives related to adherence: (1) biomedical, (2) behavioral, (3) communication, (4) cognitive, and (5) self-regulatory.

The biomedical perspective incorporates the biomedical theory in which patients are assumed to be passive recipients of doctors' instructions from which they receive the diagnosis and therapy. The behavioral theory emphasizes the importance of positive and negative reinforcement as mechanisms to influence patient behavior; these have proved to be of immediate impact on adherence to treatment. The communication perspective suggests that improved provider–client communication will enhance adherence, and it also places emphasis on the timing of treatment, instruction, and comprehension. Communication is said to be "the cornerstone of every patient-practitioner relationship" [18]. The cognitive perspective includes theories such as the health belief model (HBM), the social-cognitive theory (SCT), the theories of reasoned action (TRA) and planned behavior (TPB), and the protection motivation theory (PMT). These theories focus on cognitive variables as part of behavior change and share the assumption that attitudes and beliefs are major determinants of health-related behavior [19]. Finally, the self-regulation perspective integrates environmental variables with cognitive patient's responses, according to a self-regulation model. It is necessary to examine individuals' subjective experience of health threats to understand the way in which they adapt to these threats [20].

Although these theoretical models explain to us why patients do not adhere to treatment and what methods are most effective in reducing this phenomenon, the assessment of medical compliance is still complex. In general to assess compliance it is necessary to take into account several indicators such as: (1) health outcomes (e.g., blood pressure), (2) direct indicators, (3) indirect indicators (e.g., pill count and refill records), (4) subjective report (e.g., patients or others' reports), and (5) utilization (appointment making and keeping and use of preventive services) [21].

Concerning HCA it is possible to evaluate adherence treatment through different indicators. For example, the compilation of the headache diary is a sign of good self-monitoring and is fundamental for optimal diagnosis and headache

management. Also appointment attendance is very predictive of treatment adherence, and parent's report sometimes is the only feedback physician can have, especially with little children. Regarding statistical instruments on adherence, there are some questionnaire utilized in clinical setting, but all of them have some limitation. The most used are the Medication Adherence Questionnaire (MAQ), the Self-efficacy for Appropriate Medication Use Scale (SEAMS), and the Brief Medication Questionnaire (BMQ) [22].

19.2 Children with Headache and Their Adherence to Treatment

19.2.1 Compliance in Children with Chronic Headache

Chronic headache disorders define as headache problems occurring more than 15 days a month and disturb daily living activities of sufferers. The most common problems in children and adolescents are chronic migraine, chronic TTH, and chronic cluster headache with or without medication overuse headache (MOH). Intracranial pressure changes, vascular malformations, intracranial space occupying lesions, and other secondary causes of chronic headaches in children and adolescents are always kept in mind. Following variables should revise on the chronification process [23–25]:

- Increased frequency of attacks
- Obesity: A specific risk factor for episodic migraine to transformation to chronic migraine. It is also related to side effect of some medication like divalproex sodium and some secondary causes of headache disorders like idiopathic intracranial hypertension.
- Stress: A specific risk factor for chronification and decreased the compliance independently. After management of comorbid mood disorders it could be optimized.
- Medication overuse headache (MOH): A specific reason of decreased compliance and daily living activities. It is required a strict headache diary study and taking into account for prophylactic management.
- Sleep disorders: Sleep and headache are intimately related. Over or under sleeping may cause headache, and yet, often, sleep relieves headache. Screen for sleep disorders, and, if indicated, evaluate with a polysomnogram. Insomnia is the most common sleep disorder associated with headache and may reflect anxiety.
- Caffeine excess: Caffeine is present in coffee, teas, soft drinks, and chocolate. Caffeine is also present in many OTC analgesics and energy drinks. Caffeine excess and chronic headache disorder association is controversial.
- Comorbid mood and personality disorders: It should be revise both of the diagnostic and management process, and physicians should be ask specifically about

tics, anxiety, worrying, panic disorder, depression, attention deficit hyperactivity disorders, or bipolar disease. A psychiatric consultant can facilitate appropriate diagnosis, initiate psychiatric treatment, if indicated, and serve as a valued collaborator (make certain the psychiatrist is interested in working with headache patients; many psychiatrists are not). Art therapy, biofeedback, and other relaxation techniques can be incorporated into treatment.
– Regularly screen for abuse and maltreatment: Childhood emotional, sexual, or physical abuse is associated with an increase in headache frequency and changes headache phenotype. Prior or ongoing abuse is associated with comorbid mood disorders. Abused patients should receive appropriate resources and referrals.
– Education of patient, families, and school counselors: In addition the known awareness studies drawing a picture of headache attacks, taking video records, or using complicated headache networks are suggested.

A physician–patient–parent's relationship, based on mutual respect and trust, is essential for successful diagnosis and treatment process in HCA. This relationship has to include always families and partially school counselors as well. The physician should remain supportive yet set patient "limits" and emphasize reasonable expectations supported by required educational materials [6].

There are several therapeutic strategies in children and adolescents with chronic headache both pharmacological and non-pharmacological. The success of multidisciplinary treatment programs for children who suffer from frequent or chronic headache is well established [26].

Generally, treatment regimens for headache often require development of acute strategies, preventative treatments including medications and behavioral lifestyle changes, self-monitoring of symptoms and treatment, and attending medical appointments related to the diagnosis and treatment of headache [27]. Adherence to acute treatment strategies requires an understanding of how and when to use acute medication as well as the behavioral skills to organize and to plan for differing medication regimens [7].

19.2.2 How to Evaluate Compliance in HCA

A method of evaluating compliance to headache managements required to optimally use headache medications is prerequisite to developing instruments to assess performance of behaviors, as well as interventions to increase the probability of successful performance of these behaviors. However, specific medication-taking behaviors people with headache are utilizing to manage headaches in the moment have not been elucidated. Most of the children and adolescent behaviors depend on the parent adherence. Apart from adult headaches, children and adolescent headache managements should include always some strategies for parents and/or counselors [8].

19.2.3 What Treatment Is the Best? Pharmacological, Non-pharmacological, or Their Combination?

Chronic headache patients have often been on several prior acute and preventive medications with different prescriptions. Before eliminating past treatments, be sure that they were taken in adequate doses for a reasonable period of time with the correct diagnosis. Abortive management of headache attacks in children and adolescents is a challenge because of the short attack duration in this age group. In case of frequent emergency room visit, a specific combination with an antiemetic drug might be a rescue medicine. Early taking of the drugs is essential for management success. Patients should limit most acute therapy to 2–3 days a week at most. Acute and prophylactic pharmacological choices mean finding a balance between efficacy, tolerability, and side effects on the growing body [25, 28].

Abortive management options are as follows (for detailed information please refer to related sections of the book):

- Nonsteroidal anti-inflammatory drugs
- Triptans
- Dihydroergotamine and ergotamine
- Dopamine antagonists
- Steroids
- Opioids

Prophylactic pharmacological treatment options are as follows (for detailed information please refer to related sections of the book):

- Anticonvulsants
- Tricyclic antidepressants
- SNRI antidepressants
- Other nonprescription agents

Prophylactic interventional procedures are as follows:

- Peripheral nerve blocks
- Botulinum toxin injections
- Occipital nerve stimulation

Non-pharmacological procedures are as follows: lying down, avoiding light and sound, eating, or drinking and, less commonly, using empirically supported behavioral headache management skills (such as relaxation training, biofeedback, cognitive behavioral therapy, and stress management training) [29].

Andrasik and colleagues [30] conducted a follow-up study in which they compared pharmacological treatment to behavioral treatment in children with tension-type headache. Despite both group had significant clinical improvements, in behavioral treatment group, the percentage of dropouts was lower than in the pharmacological treatment group.

Other studies have demonstrated that compliance decreases with more frequent or complex dosing regimens [31]; however there are no studies that correlate the number of medications prescribed with adherence in the preventive treatment of headaches. In fact it seems that there were no differences between adherence to treatments in monotherapy and in combination of medications, suggesting a rate even higher of adherence among those patients who received three or four drugs, when compared with those who received two drugs [32].

There are also new options for management of headache disorders in children and adolescents like CGRP antagonists. In the next future, we learn more knowledge about it.

19.3 How Clinicians Can Improve Medication Adherence and Compliance in Children with Headache?

19.3.1 Compliance to Prophylaxis and/or Acute Headache Treatment

Abortive attack management of the children and adolescents' headache disorders is required in limited conditions mentioned above. Choosing appropriate drugs, route, and duration is essential to achieve optimum compliance of the patients and families. Prophylactic management is the main procedure for chronic headache disorders using appropriate medical, interventional, and/or non-pharmacological agents depending on headache diagnosis, age, and comorbid medical problems of the patients. Optimum duration of the prophylactic medication is a mandatory decision for the physician. Reduced duration of the prophylaxis is among the main reasons of the failed patient compliance. Physicians may choose one of the procedures for the patient or combined some of them according to requirements [25, 28] (Table 19.2).

Key Features

- Any secondary cause of the headache should always be considered and evaluated accurately.
- Recognize signs and symptoms of the little patient before quality of life is impaired.
- Headache diary compilation is important for both diagnosis and management of headache and also for identify Medication overuse headache (MOH).
- Most of the patients becoming pain-free may be unrealistic. Lessening disability is a reasonable goal, and this knowledge should be shared with parents and patients on each step of the process.
- In each step you should have another plan for management. Interventions and non-pharmacological options should be revised strictly.

Table 19.2 Treatment adherence model for headache in children and adolescents (Adapted from [1])

1. Evaluation
• Patient self-report, parents' report
• Interview and history including drawing a picture of headache or video imaging of headache attacks
• Physical and neurological examination on each application
• Laboratory and imaging if necessary
2. Treatment planning
• Collaborative goal setting including family plans and explanation of all options
• Establishment of priorities depending on quality of life
• Choosing among available treatment options including non-pharmacological procedures and some interventions
3. Implementation
• Provider interventions
• Shared interventions
• Patient interventions
• Follow-up appointments
4. Monitoring and evaluation
• Adherence monitoring using qualitative and quantitative methods
• Health status monitoring adapted for age and sociodemographic variables
• Side-effects of the drugs and interventions
• Protective factors for not stopping therapy

– Set limited restriction for the life and say physician not a management. Compliance is a multifactorial problem, and good compliance increases quality of life not only to patients but also to families and physicians.
– It is known that children with headaches are at risk for poor health-related quality of life; it is likely that improved self-management and adherence to headache treatment recommendations may not only decrease headache frequency and severity but also improve health-related quality of life and headache-related disability.

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Chapter 20
Pharmacological Treatment of Headache and Comorbidities

Omer Karadas and Pierangelo Geppetti

20.1 Introduction

The term "headache" encompasses primary conditions and those secondary to other illnesses. This chapter describes the pharmacotherapy of primary headaches in children affected by additional diseases. As in the adult population, the most common primary headaches in children are migraine and tension-type headaches. Overall, the international prevalence of migraine among children and adolescents is in the range of 7.7–9.1%. Migraines are more prevalent in girls than boys when the age is 12 years or older, and migraine with aura is less common than migraine without aura [1–3]. Chronic migraine in US adolescents aged 12–17 years was 0.79, and 2% when including medication overuse [4]. Using a dedicated questionnaire, a population of children from 6 to 17 years of age exhibited the following 1-year prevalence: headache 89.3%; migraine 39.3%; and tension-type headache (TTH) 37.9%. Headache prevalence ≥15 days/month was 4.5% [5]. Cluster headache (CH) is a rare condition in adults and even rarer in children, with prevalence in the pediatric population estimated as 0.03–0.09% [6, 7]. In particular, attention is paid to pharmacotherapy of comorbidity of migraine with other diseases. Comorbidities affect treatment strategy and follow-up, especially when pharmacologic treatment is needed. In this chapter, we summarize pharmacologic options for migraine and tension-type headache treatment with specific attention to comorbidities.

The therapy of childhood migraine is based, like that for the adult population, on algorithms including behavioral approaches, abortive drugs, and preventative strategies, as well as non-pharmacological options (alternative and complementary

O. Karadas (✉)
Department of Neurology, Gulhane Education and Research Hospital, Ankara, Turkey
e-mail: dromerkaradas@gmail.com

P. Geppetti
Headache Center, University Hospital Careggi, University of Florence, Florence, Italy

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medicines) such as vitamins, supplements, and drugs. Pharmacotherapy is rather complex as the use of some medicines is not based on formal randomized clinical trials, and, therefore, in clinical practice, most choices are "off label." However, in this respect, comorbidities may increase the appropriateness of treatment as certain drugs may be approved not for migraine but for the comorbid condition.

20.2 Abortive Migraine Treatment

Comorbidities do not significantly impact abortive migraine treatment, which is mainly based on the use of analgesics (paracetamol), nonsteroidal anti-inflammatory drugs (NSAIDs), and triptans. Abortive (rescue) medications are taken during acute headache attacks, with the goal of providing quick relief from headache pain. The use of these medications should be limited to not more than 10 or 15 (depending on the type of drug) doses per month, to avoid medication overuse headache. Early recognition and treatment, and resting in a quiet location after drug intake, are key points for successful treatment of migraine attacks. All medications have a better chance of relieving symptoms if given as early as possible in the attack. Gastroparesis frequently occurs as migraine sets in, limiting the absorption of oral medications.

For some pediatric patients, over-the-counter (OTC) analgesics provide sufficient relief, are well tolerated, and have little or no side effects. Acetaminophen and ibuprofen are more likely than placebo to reduce headache intensity at 2 h posttreatment, are safe and effective in migraine, and are recommended as first-line therapy, especially when doses are weight based [8]. Other nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen, may provide relief from migraine pain, especially for prolonged attacks. NSAIDs are not recommended or must be used carefully in patients with gastrointestinal (such as inflammatory bowel syndrome or gastric ulcer), cardiovascular (arterial hypertension), or severe allergic (asthma) comorbidities.

Among abortive medicines, triptans have been the most extensively studied. They might work by reversing the cranial artery dilation (via $5HT_{1B}$ receptor activation on vascular smooth muscle) that occurs during migraine or by inhibiting the release of calcitonin gene-related peptide (CGRP) (via $5HT_{1D}$ receptor activation on nerve terminals) from trigeminal nociceptors. Triptans are migraine-specific acute abortive agents and are considered to be most effective when given early in the course of the headache. While in adults all triptans have level A evidence for efficacy [9], the same level of efficacy has not been reported in children [10], probably because of a higher placebo response and the shorter duration of attacks in the pediatric population. They are typically administered by the oral route, although nasal sprays are also available. The intranasal route may be preferable in patients who have significant vomiting with their migraines. Sumatriptan is available in an injectable preparation; however, it is seldom used in pediatric practice. Triptans approved for treatment of pediatric migraine are rizatriptan (6–17 years old), almotriptan (12–17 years old), and a combination of sumatriptan and naproxen (12–17 years old).

A multicenter, randomized, double-blind, placebo-controlled study found no difference in pain relief at 2 h when comparing oral sumatriptan to placebo [11], but another study found that a sumatriptan (20 mg nasal spray) provided greater rates of relief at 30 min and 2 h post-dose compared to placebo [12]. Zolmitriptan has been shown to provide fast relief when given in nasal spray form, with onset of pain relief often apparent within 15 min [13], whereas oral ibuprofen provided rates of pain relief at 2 h similar to placebo [14]. Eletriptan and placebo do not differ significantly in headache improvement at 2 h, although eletriptan reduced headache better than placebo in the 24 h post-dose [15]. When using triptans, patients and their parents should be advised of possible adverse effects, such as chest tightness, drowsiness, dizziness, and, rarely, serotonin syndrome (mostly in children taking SSRIs or SNRIs) [16].

Dihydroergotamine is a nonselective vasoconstrictor agent mainly used before triptans were available. Side effects, mainly due to their nonselective agonist action on 5-HT1 and 5HT2 receptors and dopamine D2 and alpha-adrenergic receptors, are more common and severe than with triptans. In children, a spray formulation of dihydroergotamine might be considered if triptans are ineffective. Butalbital-containing medications are rarely used because of the risk of development of medication overuse headache if taken more than twice weekly [17]. There are no randomized controlled trials in adults or children to support the efficacy of opioids in migraine, so they should not be used in the treatment of primary headaches, also because they are associated with the risk of medication overuse headache and with the transformation from episodic to chronic form. Steroids, such as dexamethasone, should be used (administered for a few days) for terminating a status migrainosus. In addition to analgesic medication drugs for nausea, including ondansetron (used principally in the emergency room), metoclopramide and prochlorperazine can be considered [18].

20.3 Preventive Migraine Treatment

Preventive medications are usually taken when the headaches occur more than once per week, causing frequent disability. The goal of preventative medication is to relieve pain and reduce disability from headache. Parents should be informed about the aims of this therapy (e.g., a 50% reduction in headache frequency and severity), the duration of the treatment (a positive effect will not be appreciated in a short time but rather after weeks or months), and the appropriate regimens of drug administration associated with lifestyle modifications. Notably, a high placebo response rate in adolescents makes interpretation of the limited available evidence rather difficult. It should be clarified that to reduce overall migraine frequency and severity, maintenance therapy should usually be taken on a daily basis. It is also important to set realistic expectations as maintenance therapy usually does not eliminate headaches completely. The combination of daily prophylactic therapy, periodic use of an abortive medication, and lifestyle modification seems to achieve better results [19].

Vitamins, minerals, and supplements have been proposed as prophylactic agents, popular with parents who believe them to be safer than drugs [20]. Riboflavin (vitamin B2), used in adults for migraine prophylaxis, has limited and mixed evidence in the pediatric population. One randomized, double-blind, placebo-controlled study reported a similar proportion of 50% or greater reduction in headache frequency by both riboflavin (400 mg/daily) and placebo groups, with some side effects of riboflavin (strong odor/color of urine and mild gastrointestinal upset) [21]. Magnesium, which regulates cellular and neuronal homeostasis, is frequently used for migraine prevention in children at a dose of 9 mg/kg/day [22], with diarrhea as the most frequent adverse effect. Coenzyme Q10 is an electron carrier involved in mitochondrial energy production and is used in children and adults, usually at 1–3 mg/kg/day. Butterbur extract (*Petasites hybridus*) is recommended in adults for migraine treatment for its anti-inflammatory and perhaps neuromodulatory effects. In an open-label study, 108 children and adolescents between 6 and 17 years of age were treated with 50–150 mg of butterbur root extract; 77% of them reported a reduction in the frequency of migraine attacks by at least 50%. Undesired effects (7.4%) included mostly eructation [23]. Feverfew (*Tanacetum parthenium L.*) belonging to the Asteraceae family is an herbal remedy for migraine [24, 25] that may act via several mechanisms of action, including inhibition of nociception and neurogenic vasodilatation in the trigeminovascular system by targeting the transient receptor potential ankyrin (TRPA1) channel [26]. However, no trials report the safety or efficacy profile of feverfew for pediatric headache [27]. Vitamin D supplementation, associated with migraine prophylaxis, has been shown to reduce headache frequency [28]. Currently, among the various preventive pharmacological treatments in adults, only topiramate is approved for migraine prevention in children. This anticonvulsant agent reduced mean monthly headache frequency and school absenteeism better than placebo and produced a greater reduction in headache-related disability, measured by the Pediatric Migraine Disability Assessment Scale (PedMIDAS) [29]. In another study, topiramate resulted to be more effective than propranolol in reducing headache frequency, severity, duration, and disability [30]. Possible adverse events are cognitive slowing, weight loss, and paresthesias. However, a very recent large study (Childhood and Adolescent Migraine Prevention, CHAMP) [31] comparing the effectiveness of amitriptyline, topiramate, and placebo showed no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline, topiramate, or placebo over a period of 24 weeks, but the active drugs were associated with higher rates of adverse events. The calcium channel blocker flunarizine significantly reduced frequency and duration of migraine attacks in two double-blind trials after treatment, respectively, of 4 and 8 months [32, 33]. Other studies confirmed the efficacy of this drug at a dose of less than 5 mg oral/day in children 6–11 years of age [32]. Other medications that are commonly used for migraine prevention, such as cyproheptadine and divalproex sodium, do not have sufficient evidence to be recommended for children. Pizotifen is widely used as prophylaxis in children with migraine, but there are no trials assessing its efficacy [32].

Both valproate and propranolol, a nonselective beta-blocker, have been shown to be effective in reducing monthly headache frequency by >50% and to cause a statistically significant reduction in headache severity and mean headache duration per week, as well as an improvement in response to rescue medications [32]. Propranolol should be avoided or used with great caution in patients with asthma, as it can cause bradycardia and hypotension. Valproate should be avoided in young women of childbearing age due to its potential teratogenicity and weight gain. While gabapentin has not been extensively studied in the pediatric population, it may be helpful in the management of selective subpopulations. There are anecdotal reports of some benefits in patients treated with low doses of amitriptyline, with a warning of possible drowsiness, QT prolongation, and suicidal ideas. The antihistamine cyproheptadine in a syrup form might be useful in younger migraineurs with the advantage of easy use in children unable to swallow pills. Possible side effects are weight gain and drowsiness [32]. Verapamil, levetiracetam, pregabalin, and zonisamide have also been used in the treatment of migraine, but there is little evidence supporting their use in the pediatric population [34, 35].

Generally, treatment should be started with a low dose that may be gradually increased for a trial of 4–6 weeks at a target dose. If there is no change in headache burden by that time, a change to an agent of a different class should be adopted. Combination of two or more prophylactic drugs is uncommon. Should a good control of headaches be attained, treatment can be continued for at least 3–6 months before considering its tapering [36, 37].

20.4 Psychiatric Conditions and Headache

Depression and anxiety are not as rare as once thought in children. Mood disorders, attention-deficit/hyperactivity disorder, and obsessive-compulsive disorder can increase migraine severity, and, vice versa, migraine can exaggerate mood disorders [38–40]. For both chronic migraine and chronic tension-type headache, in addition to psychological interventions, such as cognitive behavioral therapy, antidepressants, including selective serotonin reuptake inhibitors (SSRIs), especially fluoxetine, sertraline, and fluvoxamine, can be used for treatment. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are not as effective as SSRIs. Amitriptyline is one of the most widely used prophylactic medications in pediatric migraine, although its efficacy has not been assessed in randomized controlled trials. Starting doses of 5–12.5 mg once daily may be gradually increased to 1 mg/kg/day. Due to its side effects, most notably somnolence, amitriptyline must be titrated slowly over a period of 8–12 weeks, increasing by 0.25 mg/kg/day every 2 weeks or so. Nortriptyline, with its less sedating effects, is sometimes used to replace amitriptyline, although it does raise the concern for increased risk of arrhythmia, and regular electrocardiograms may need to be performed. Beta-blockers are not good options for long-term treatment of migraine coexisting with depression.

20.5 Sleep Disorders and Headache

The coexistence of sleep disorders and headache, particularly migraine, is related to common anatomical structures and neurochemical processes. Treatment of sleep disorders, including insomnia, sleep apnea, sleep bruxism, and restless leg syndrome, often decreases the frequency and intensity of migraine [41]. Dietary changes and sleep hygiene, stress management, reassurance, biofeedback, and behavioral therapies are non-pharmacologic preventive methods in children with migraine. Antihistaminics, melatonin, and serotoninergic drugs are the first options in pharmacologic treatment. Cyproheptadine, an antihistamine with anti-serotoninergic properties, has been widely prescribed for pediatric migraine since the 1980s, although efficacy data are limited. It is often prescribed in doses of 0.2–0.4 mg/kg/day and is considered a first-line option for children under the age of 6 years. It has the added benefit of coming in a liquid form for those who have difficulty swallowing pills. The most commonly encountered side effect, which is sedation, can be used to treat children with concomitant sleep disorders. Drugs containing caffeine are not recommended in the pediatric population.

20.6 Epilepsy and Migraine

The migraine-epilepsy continuum covers a fascinating array of disorders that share many clinical similarities but also differ fundamentally in pathophysiology. Both conditions are episodic neurological disorders, can be triggered, and have similar attack evolution stages. Treatment of migraine and seizures with antiepileptic drugs as topiramate and valproic acid is effective [42]. The effective dose of topiramate in the pediatric population has not been established, but a dose of 2–4 mg/kg/day appears to be effective. To achieve this dose, however, it must be titrated slowly, typically increasing the dose by quarter steps over a period of 8–12 weeks. The most commonly observed side effects include drowsiness, paresthesias, memory or language dysfunction, decreased appetite and anorexia, metabolic acidosis, hyperthermia, dizziness, and abdominal pain. Valproic acid is another migraine prevention considered first-line in adults, and several open-label and retrospective studies have suggested that it may be effective in children and adolescents. Doses of 15–20 mg/kg/day appear to be effective and must be titrated over a period of 8–12 weeks to avoid unwanted side effects. Adverse effects include dizziness, drowsiness, alopecia, weight gain, thrombocytopenia, lymphopenia, potential hyperammonemia, and elevated pancreatic enzymes that make laboratory surveillance critical.

Gabapentin, pregabalin, zonisamide, and levetiracetam can also be used as second-line treatments. In particular, levetiracetam (500–1500 mg bid), in view of its relatively desirable safety profile, with irritability, aggressiveness, and mild memory issues as the most reported adverse effects, has been considered a reasonable alternative option. As tricyclic antidepressants (TCAs) can decrease the seizure threshold, the use of drugs such as amitriptyline, imipramine, mianserin, clomipramine, and maprotiline requires caution if an epileptic disorder is present.

20.7 Atopic Disorders and Migraine

Trigeminal nociceptors can be activated by allergens by releasing inflammatory chemicals from dural mast cells, and this can trigger a migraine attack. We know that glyceryl trinitrate (a donor of nitric oxide (NO)) and histamine (which probably activates endothelial NO formation) both cause a pulsating dose-dependent headache with several migrainous characteristics. Sinus pathologies can coexist with migraine and tension-type headache, and their diagnostic criteria sometimes overlap [43, 44], making differential diagnosis difficult. Antihistaminics, steroids, and antibiotics can be added to the standard treatment procedure in headaches coexisting with atopic disorders. Beta-blockers must be excluded from the treatment because of their capacity of obstruction at bronchial level.

20.8 Obesity and Headache

Childhood obesity can be associated with many medical disorders, such as diabetes, cardiovascular disease, and mood disorders. Tension-type headache and migraine can also coexist with obesity. Research data have highlighted that there is a relationship between headache physiopathology and central and peripheral mechanisms responsible for food assumption. In this regard, neurotransmitters such as serotonin and peptides such as orexin and adipocytokines (adiponectin and leptin) seem to play a key role both in food assumption and in headache pathogenesis. Therefore, those therapeutic strategies aiming to decrease body weight may represent a model of useful treatment to understand whether weight loss reduces the incidence and the severity of headache in obese children [45]. Weight loss, regular diet, and physical exercise (although sometimes intense exercise can trigger migraines) are the first line of treatment. Having a weight loss side effect, topiramate is a good option for overweight and obese migraine patients. Norepinephrine dopamine reuptake inhibitor (NDRI) antidepressants can cause weight loss, and bupropion can be used in both migraine and tension-type headache treatment.

20.9 Cardiovascular Disease, Ischemic Stroke, and Headache

The mean annual incidence of stroke in children is about 2.5 per 100,000 [46]. The causes of cerebral infarction in children may include: heart disease, vascular disease, blood disorders, primary hypercoagulable states, or congenital metabolic disorders, but 50% of strokes are considered idiopathic [47]. In children, the diagnosis of stroke caused by migraine is still questioned; in fact, until now, only a few cases have been reported in subjects under the age of 16 years [48, 49]. A history of migraine with aura seems to be more common among victims of ischemic stroke than among controls, and an acute attack of migraine may precede, accompany, or follow a

thromboembolic transient ischemic attack or a stroke, this seems to occur more often among migraineurs compared with patients without migraine [50, 51]. Adults suffering from migraine with aura are at increased risk of cardiovascular disease and stroke [52], but it is necessary to consider that in adults, the analysis of this association is complicated by a frequent presence of additional risk factors such as smoking, hypertension, and diabetes mellitus. In children, these and other potential confounding factors are much less common. There are relationships arising from small clinical samples of pediatric age who demonstrate the association of migraine with dyslipidemia [53], hyperhomocysteinemia, and genetic variants related to homocysteine which appear to be risk factors for the development of stroke in children [54]; for this reason, these risk factors should be kept under control. Beta-blockers, most notably propranolol with suggested dosing ranging from 0.5–2 mg/kg/day, are the first option for migraine patients having arrhythmias. Its usefulness in this population is limited by a drop in blood pressure as well as exercise-induced asthma and depressive side effects, but it can be useful if there is a heart rhythm disorder. Tricyclic antidepressants can cause arrhythmias, so TCAs must be excluded from treatment.

20.10 Brain Tumors and Headache

A careful history and physical examination remain the most important aspects of headache assessment, enabling the specialist to decide if any further studies are necessary. Imaging of headache patients for tumors, if they have primary headache disorders, such as migraine and typical cluster, generally is not cost-effective but is necessary if there are any atypical features. However, only a minority of patients who have headaches have brain tumors; however, recognition of the headaches characteristically associated with tumors is most important. Some locations are more likely to produce headache (e.g., a posterior fossa tumor causes headache more often than a supratentorial tumor). Rapidly growing tumors are more likely to be associated with headache. Uncommon headache presentations can occur with tumors, including paroxysmal cough, cluster headache, and TACs. The classic brain tumor headache is not as common as a tension-type presentation or migraine. Patients who have prior primary headaches may have more headache symptoms if they have a tumor and of course they still have their primary headache disorder. Mass lesions progress and inevitably develop other symptoms and signs besides headache, and these new symptoms and signs must be sought and found. Treatment of headache in patients who have metastatic brain tumors should be aggressive in terms of pain and symptoms control. Treatment of primary CNS tumors is dictated by the kind of neoplasm and site, but control of headache should not be ignored; for this reason, standard treatment protocols can be combined with steroids and antiemetics. Antiepileptic drugs may be a first choice in patients with migraine and brain tumor to reduce seizure risk. Conversely, TCAs must be excluded from treatment because of their capacity of lower seizure threshold.

20.11 Movement Disorders and Headache

Tourette syndrome is one of the most common childhood movement disorders. It is characterized by motor and phonic tics. Neurotransmitter dysregulation, particularly involving the serotonin system, has been implicated in the pathogenesis of Tourette syndrome, obsessive-compulsive disorder, and migraine headache. The rate of migraine in this group of patients is four times more, and tension-type headache is five times more [55]. Antiepileptics (carbamazepine, phenytoin, valproate), beta-blockers, and SSRIs can be used in the treatment of patients with Tourette syndrome and migraine, whereas TCAs are the option for tension-type headache treatment. Antiemetics are not recommended.

20.12 Autism Spectrum Disorders and Headache

Autistic children that are overreactive to sensory input also have anxiety behaviors and frequently experience both migraine headaches and tension-type headaches. Both migraineurs and autistic individuals have elevated levels of serotonin [56].

Antidepressants (SSRIs), antiepileptics (carbamazepine, valproate), propranolol, and melatonin can be used for the treatment of migraine, and antidepressants (SSRIs) can be used for the treatment of tension-type headache.

20.13 Fibromyalgia and Headache

Many people who have fibromyalgia may also have tension-type headache, migraine, anxiety, and depression [57]. Similar to migraine, changes in the levels of serotonin may contribute to the increased excitation in fibromyalgia. Also, levels of substance P are high in patients with fibromyalgia. Amitriptyline and SSRIs are the first line of treatment in both migraine and tension-type headache.

20.14 Learning Disabilities and Headache

Learning disabilities and attention-deficit/hyperactivity disorder (ADHD) can frequently be observed in children and adolescents and often coexist with primary headaches [58]. Dopaminergic system dysfunction, brain iron deficiency, and sleep disturbance may play a role in both conditions. Antidepressant drugs and melatonin are the first options in pharmacological treatment.

20.15 Rheumatic and Autoimmune Diseases and Headache

There is a higher prevalence of migraine and tension-type headache in patients with juvenile idiopathic arthritis and familial Mediterranean fever. This can be due to the nonspecific result of stress associated with the disease chronicity, or headache can be triggered by the immune-mediated disease activity [59]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids can be used alone or in combination with the standard treatment protocols.

20.16 Emerging Therapies

Both physicians and patients are often frustrated with the current therapeutic options for primary headache and particularly for the chronic forms that represent a major unmet medical need. Moreover, approximately 3% of pediatric migraineurs fall into the chronic migraine category, many of whom are intractable and have failed two or more preventive medications.

Onabotulinum toxin A was approved by the FDA in 2010 for use in chronic migraine in adults, but data on effectiveness and tolerability in the pediatric population are limited. In a retrospective case series to assess tolerability and efficacy of onabotulinum toxin A in 10 patients aged 11–17 years, four patients reported subjective but clinically meaningful relief consisting of a decrease in headache intensity, with two patients additionally noting a decrease in headache frequency. The four responders also reported improvements in quality of life [60]. In another retrospective review of pediatric patients receiving onabotulinum toxin A for chronic migraine, a statistically significant improvement in monthly headache frequency was found [61]. A 30-point improvement in the pediatric disability scoring between first injection and follow-up injection was also observed, with a change from severe disability to moderate disability on PedMIDAS.

Eventually, the current large number of clinical trials with monoclonal antibodies against CGRP (the pro-inflammatory and vasodilator neuropeptide released from terminals of trigeminal neurons) or against its receptor [62] will provide final data regarding this innovative approach to treat migraine and cluster headache. The expectation is that this therapy may also be applied to the pediatric population soon (Table 20.1).

Table 20.1 Summary for recommended treatment of comorbidities

Comorbidity treatment	Recommended	Unrecommended
Psychological conditions	SSRIs	Beta-blockers
Sleep	Antihistaminics, melatonin, seratoninergic drugs	Caffeine
Epilepsy	Antiepileptics	TCAs
Atopic disorders, allergic rhinitis	ST with antihistaminics, steroids	Beta-blockers
Obesity	Topiramate, NDRIs, SSRIs	TCAs, mirtazapine
Cardiovascular disease, ischemic stroke	Beta-blockers, antiplatelet agents	TCAs
Brain tumors	Antiepileptics, SSRIs	TCAs
Movement disorders	Antiepileptics, antidepressants, beta-blockers	Antiemetics
Autism spectrum disorders	ST	
Fibromyalgia	SSRIs	
Learning disabilities	SSRIs	Antiepileptics
Chronic rheumatic disease	ST with NSAIDs and/or steroids	

ST standard treatment

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Chapter 21
Non-pharmacological Treatment in Headache with Comorbidity

Noemi Faedda and Vincenzo Guidetti

21.1 Introduction

To date there are no therapies that are fully effective in paediatric migraine. Treatment of headache requires a multidisciplinary approach that combines pharmacotherapy with non-pharmacological therapy such as psychoeducational and behavioural interventions. Furthermore pharmacological options for paediatric populations have been largely based on evidence originating from adult studies [1]. Only two triptans (almotriptan and rizatriptan) have been approved by the Food and Drug Administration (FDA) to be safe and effective for the abortive treatment of paediatric migraine [2]. With regard to prophylactic treatments, only one antiepileptic drug (topiramate) and one antidepressant (trazodone) have been shown to be more effective than placebo [3]. So the majority of placebo-controlled clinical trials that have been performed to assess the effectiveness of candidate migraine pharmacological treatments for children have failed to demonstrate effectiveness of active drugs over placebo [1]. These findings emphasize the importance of non-pharmacological therapy in headache treatment. Some non-pharmacological therapies seem to have effects that are similar to those of most drugs used for the prevention of migraine and tension-type headaches [4]. These therapies, also known as behavioural therapy, often do not have dangerous adverse effects and are much less expensive than pharmacological therapies both in children and adolescents than in adults [5, 6].

N. Faedda, Ph.D. • V. Guidetti, M.D. (✉)
Department of Paediatrics and Child and Adolescent Neuropsychiatry, Sapienza University of Rome, Via dei Sabelli, 108, 00185 Rome, Italy
e-mail: vincenzo.guidetti@uniroma1.it

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21.2 The Placebo Effect in Treatment of Headache in Children and Adolescents

A very famous definition describes the placebo effect as: "Any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties" [7].

Theories regarding the placebo analgesic effect uniformly acknowledge the interplay between environmental information and their perception and integration by the individual's organism to induce a positive (placebo) or negative (nocebo) response. The presence of these interactions implies the involvement of higher-order, central nervous system (CNS) associative processes in the production of analgesic placebo effects [8]. Placebo analgesia seems to be associated with patterns of cerebral-blood-flow activation (particularly rostral anterior cingulate cortex) similar to those seen after injection of an active opioid [9, 10]. Furthermore placebo analgesia seems to be related to a reward dopaminergic system [11], and the endocannabinoid system seems to have a pivotal role in placebo analgesia.

Placebo response rates are known to be high in paediatric migraine trial [1]. An inverse relationship between age and placebo response rates has been reported in migraine. This inverse relationship has been suggested to continue into adulthood. Younger adults appear to be more likely to respond to placebo as compared with older adults who are more likely to respond to pharmacotherapy [12]. In short-term clinical trials, about 30–50% of children and adolescents have been reported to improve while receiving placebo [13, 14].

Another very interesting phenomenon is the *nocebo effect*, which is opposite to the placebo effect and whereby expectations of symptom worsening play a crucial role [15]. Amanzio et al. [16] conducted a systematic review of adverse events in placebo groups of anti-migraine clinical trials and they found, in accordance with the expectation theory of placebo and nocebo effects, that the adverse events in the placebo arms corresponded to those of the anti-migraine medication against which the placebo was compared. For example, anorexia and memory difficulties, which are typical adverse events of anticonvulsants, were present only in the placebo arm of these trials.

The high placebo response rates, found in paediatric migraine trial, lead the way to new therapeutic approach based on non-pharmacological and behavioural interventions.

21.3 Behavioural Therapy

Behavioural treatment strategies derived from cognitive behavioural therapy (CBT) [17]. CBT is not defined as a specific treatment but rather an umbrella term for a diverse group of treatments that all have in common the application of cognitive and behavioural techniques, aiming at promoting symptom reduction and behaviour change [18].

Behavioural strategies have in many cases been shown to be as effective as pharmacological treatment [19], not only for headache management but also to maintain a lifetime response to the headache treatment [4, 20]. The presence of particular factors makes it preferable the use of non-pharmacological strategies rather than pharmacological intervention for headache treatment in children and adolescents [21]:

- Patient preference for non-pharmacological treatment
- Poor tolerance or poor response to pharmaceuticals
- Negative side effects of medication
- History of overuse of acute care medication
- Significant stress
- Inadequate ability to cope with stress or pain
- Comorbid psychological disorders [22]

Some of the goals of behavioural treatments are to reduce the frequency and severity of pain, increase the patients' control of their headaches, reduce related disabilities and symptoms and limit reliance on poorly tolerated or unwanted medications [4, 23]. Several researches found that the behavioural approach maximizes adherence to the prescribed headache treatment regimen, improves child or adolescent's quality of life and reduces disability and psychological comorbidities [24].

21.3.1 Three Components of Behavioural Therapy

Behavioural therapy consists of three components [25]:

1. Treatment adherence
2. Adjustment of lifestyle management
3. Psychological intervention

21.3.1.1 Treatment Adherence

Non-adherence to prescribed treatment is an important factor in the management of headache [26], poor adherence to prescribed treatment regimens can indeed compromise the efficacy of medical treatments and the health and quality of life of patients, and it can increase health-care costs with an overuse of the health-care system [27]. The literature about this topic in children and adolescents is poor [28, 29], but non-adherence to headache treatment is estimated at 50–88% in this population [26, 30]. Treatment adherence involves educating the patient and his/her family about the importance of following assigned treatment regimen, identifying factors that may affect the effectiveness of the interventions and discussing any barriers or obstacles to adherence that patients may have [31].

The factors that may limit the adherence to treatment can be divided into three categories: (1) regimen characteristics (e.g. difficulty of lifestyle changes),

(2) disease characteristics (e.g. younger age of onset, frequency and severity of headache attacks) and (3) patient or family characteristics (e.g. premorbid/comorbid behavioural, psychopathology or dysfunctional family) [4, 23, 32].

Furthermore other important determinants of non-adherence can be categorized as patient-related factors (demographic, sociocultural and behavioural factors) and external factors (disease characteristics, medication properties and system components) [31, 33–35].

Factors identified as having a positive effect on adherence are positive family functioning, close friends, internal locus of control, treatment with immediate benefits and a positive and trusting collaboration between doctor and patient [4, 36].

Verbal and written instructions could be used to increase knowledge of patients and their family about the management of headache symptoms and the importance of the proposed treatment [23].

In this way coping and control strategies could be improved and fear and negative emotions could be reduced [37, 38]. Visual reminders (alarms on watches or phones), self-monitoring and rewards could be used to help children to comply with the assigned treatment [23].

Based on a comprehensive literature review, Julius et al. [39] recommend the following strategies for addressing adherence problems:

1. Focus on strengthening the therapeutic alliance.
2. Devote time in treatment specifically to address medication adherence.
3. Assess patients' motivation to take prescribed medications.
4. Identify and address potential barriers to treatment adherence.

21.3.1.2 Adjustment of Lifestyle Management

Lifestyle interventions are focused on the acquisition and maintenance of healthy lifestyle habits that have a great influence on medical outcomes [23]. Changing unhealthy habits and behaviours can significantly improve quality of life [40].

Numerous lifestyle factors are recognized triggers of headache attacks. Triggers reported most frequently are stress, sleep disorder, weather, lights, odours, sounds, foods and drinks [41–43].

Source of *stress* in children and adolescents can relate to family and housing conditions (divorce, parental styles, etc.), school problems (relationship with teachers, learning disability, etc.) and relations in the peer group (bullying, integration difficulties, etc.).

A vast body of literature supports the existence of interactions between *sleep* and headache, mediated by time (headache occurs during sleep, after sleep and in relationship with sleep stages) or quantitative (excess, lack, bad quality or short duration of sleep may trigger headache) relationships and by a reciprocal connection: noxious stimuli and painful disorders interfere with sleep, and sleep disturbances affect pain perception [44].

Connelly et al. [45] conducted a study to evaluate if fluctuations in *weather* predict increased likelihood of headache occurrence, recording data on weather

variables (temperature, dew point temperature, barometric pressure, humidity, precipitation and sunlight) in the child's geographic location. Of the weather variables, they found that relative humidity and presence of precipitation were significantly predictive of new headache onset, with nearly a threefold increase in probability of headache occurrence.

An abnormal sensitivity to or intolerance of *light* (photophobia) is reported as a trigger by 52.9% of children and adolescents with headache [43], a hypersensitivity to *odours* (osmophobia) by 55% and an intolerance or hypersensitivity to *sound* (phonophobia) by 47% [4, 46].

Some *foods* and *drinks* can be a trigger for headache attacks (chocolate, caffeine, etc.); others can be effective in treating migraines in children and adolescents [47]. These foods are called *nutraceuticals* and they include magnesium, riboflavin, coenzyme Q10, the herbal extracts of butterbur, feverfew and ginkgolide B. Several researches showed that these substances are able to reduce the frequency of headache attacks in children and adolescents [48–51].

21.3.1.3 Psychological Intervention

Headache is commonly associated with several psychiatric comorbidities, in particular depression, anxiety and attention-deficit/hyperactivity disorder [52]. Teaching relaxation techniques, stress reduction, increasing physical activity and other psychological interventions should be considered standard management options for children with headache and other comorbidities [38]. In management of primary headache, psychological treatments include [53]:

- Relaxation skills
- Biofeedback
- Cognitive behavioural therapy

Relaxation skills include progressive muscle relaxation (PMR), autogenic phrases, self-hypnosis, guided imagery (GI) and diaphragmatic breathing [54]. These techniques have been shown to be as effective as pharmacological treatment in child, adolescent and adult, improving the frequency, intensity and duration of headache [55, 56]. Using PMR, patients learn and recognize the difference between the feelings of tension and relaxation [54], and they incorporate a series of relaxation exercises into their daily routines. Autogenic phrases are focused on several parts of the body such as "my arms and legs are heavy" or "my heart is calm and regular"; the patients must concentrate on these phrases in order to achieve a deep relaxation. Self-hypnosis is a form of autogenic relaxation that reflects an active coping and self-regulation [57]. Guided imagery techniques require the use of imagination; the patient must concentrate on images related to feelings of safety, warmth and tranquillity [54] to evoke feelings of well-being and relax mind and body. Further, GI has been associated with increased brain plasticity [58]. With the diaphragmatic breathing techniques, the patient learns to take a deep breath, using diaphragm, with minimum possible movement of the chest [59]. The aim of this technique is to decrease hyperventilation and to achieve relaxation [54].

Biofeedback is useful in paediatric headache to understand and address the mind-body connection [23, 60]. In particular thermal biofeedback, teaching to take under control skin temperature, has been recommended for migraine in children and adolescent [61].

Cognitive behavioural therapy (CBT) consists mainly of cognitive and behavioural techniques that help the patient to modify dysfunctional thoughts, interpretations of events, assumptions and typical behavioural patterns of responding to stressors or events, increasing patient's ability to cope with the pain and to reduce headache-related distress [23]. CBT gradually re-exposes the patients to everyday activities, including school, sports and leisurely activities [54]. Indeed children and adolescent with headache often engage in avoidance behaviours in order to try to avoid headache attacks [53]. In table 21.1 are reported some relevant studies that showed the effectiveness of behavioral intervention in children and adolescents with headache and other chronic pains.

Table 21.1 Effectiveness of behavioural intervention in literature

Author	Study design	Sample	Diagnosis	Conclusions
Eidlitz-Markus et al. [62]	Empirical study	92 children aged 3.8–17.2 years	Migraine	A non-pharmacological regimen is recommended also in preschool children younger than 6 years
Bennett et al. [63]	Systematic review	Ten studies (209 children, including 70 in control groups)	Chronic physical illness	Children may benefit from cognitive behavioural interventions for depression and anxiety in the context of a comorbid chronic physical health problem
Fisher et al. [64]	Meta-analysis	35 studies (children and adolescents of ≤18 years of age)	Chronic pain	Psychological therapies can significantly reduce pain
Powers et al. [6]	Randomized clinical trial	135 youth aged 10–17 years	Chronic migraine	The use of CBT plus amitriptyline is associated with greater reductions in days with headache and migraine-related disability compared with the use of headache education plus amitriptyline
Chen et al. [65]	Randomized clinical trial	90 children	Migraine	Preventive treatment of behavioural therapy plus oral flunarizine had better clinical efficacy than oral flunarizine alone
Blume et al. [66]	Retrospective study	132 youth aged 8–18 years	Headache	A 58 and 43% reduction in headache days with biofeedback therapy
Trautmann et al. [67]	Meta-analysis of randomized controlled studies	23 studies (patients aged 7–22 years)	Recurrent headache	Relaxation, biofeedback and CBT are highly effective in treating headache symptoms, both in frequency and severity

21.3.2 Strengths and Limitations of Behavioural Therapy

Behavioural therapy, like any other therapeutic intervention, presents some limits that need to be addressed [4, 68–72]. But it is possible to contrast strengths and limits, so that they are balanced:

- It takes time to change same behaviours, so parents and teachers may find this frustrating, but behavioural therapy is a cost-saving treatment.
- To teach parents how to work more effectively with their children can result in a poor compliance, but a behavioural therapy maximizes and ensures therapeutic alliance and compliance.
- The focus of this approach is "here and now", but behavioural therapy maximizes long-term therapeutic benefit.
- Therapist must maintain a sense of control and awareness, but this approach does not report negative side effects of medications.
- The aim of the behavioural therapy is to teach new alternative ways of thinking and behaving, but patterns of behaviour may change over the course of life.
- Behavioural therapy reduces headache severity and frequency, but it is not effective for people with severe mental disorder.
- Behavioural therapy can reduce pain and disability, but it does not always take into account individual differences.

21.4 Conclusion

The vast impact of environmental factors on headache has led to consider this disorder as a biopsychosocial condition, caused by cognitive, emotional and environmental factors, as well as biological [73, 74]. So it is critical to use a multidisciplinary approach that combines pharmacotherapy with behavioural and psychoeducational interventions in the treatment of headache. Non-pharmacological therapy would seem to maximize long-term therapeutic benefit, ensure compliance with pharmacological treatment, reduce costs and do not have dangerous adverse effects, especially in children and adolescents.

Paediatric data is limited and further studies are needed to identify the better treatment for children and adolescents that are not merely small adults.

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Chapter 22
Cognitive Therapy for Comorbid Disorders in Children and Adolescents with Headache

Elisa Salvi and Vincenzo Guidetti

Headaches are a very diffuse problem in children and their incidence is growing steadily [1]. This increase is alarming and probably reflects changes in the lifestyle of children that are negative [2]. A review of epidemiological data collected by Abu-Arafeh and Hamalainen [3] on studies done between 1990 and 2007 has shown that the estimated prevalence of headaches in children and adolescents, for periods ranging between 1 month and the entire life, cycle is 58.4%, with an increased incidence in females [3]. Recurrent headache prevalence in the school age population has a growing trend, varying between 5.9 and 82%, reaching a peak in the group aged 11–13 years old and that for both sexes [4]. Headaches are observed in 3–8% of children aged 3 years old, in 19.5% of the those aged 5, and in 37–51.5% of those aged 7. Between the age of 7 and 15 years, the prevalence fluctuates between 26 and 82% [5]. Studies based on the IHS (International Headache Society) criteria in the general population revealed a prevalence oscillating between 3 and 11% [6]. On the first assessment, the persistence of primary headaches prior to age 10 seems to be a predictor of their increased incidence in adulthood, mostly for migraines.

Guidetti et al. [7] have found that migraines would demonstrate a slighter remission tendency compared to tension headaches. Concerning headaches, the frequency and duration of the attacks will allow us to distinguish a chronic form and an episodic form. Generally, in cases presenting headaches during at least 15 days on a monthly basis and this for a period of at least 3 consecutive months, we talk about chronic headache (ICHD-III, 2013). This ultimate condition seems to be more frequently associated to psychiatric comorbidity [8]. If they are screened and treated

E. Salvi (✉)
Association of Cognitive Psychology, APC, Viale Castro Pretorio 116, 00185 Rome, Italy
e-mail: elisa.salvi11@gmail.com

V. Guidetti
Department of Pediatrics and Child and Adolescent Neuropsychiatry, "Sapienza" University of Rome, Rome, Italy
e-mail: vincenzo.guidetti@uniroma1.it

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adequately, headaches in children have a positive prognosis with high remission probability (around 30% of cases) and high clinical improvement probability (around 50% of cases), independent of the type of headache. A deterioration of the clinical picture and of the stability of the symptomatology is respectively recorded in 5 and 15% of cases [9]. Female gender and the presence of psychopathology seem to be factors associated with worse prognosis. The versatility and the many determinants that are at the base of common headaches always require adequate insights, from an organic or psychological point of view. Generally speaking about "stress" or "nervousness" as causes of headaches that finally refer to "clichés," can be quite counterproductive in engaging "self-healing" mechanisms, which thus become in the long run responsible for the chronicity of the crisis themselves, as it has been demonstrated with excessive analgesics use [10]. Many studies have shown a relationship between migraines or headaches and psychopathologies in children. Depression is the most frequent. Recently, Pavone et al. [11] investigated the frequency of different comorbidity in children having primary headaches. Therefore, they have conducted a study on 280 children suffering from headaches (175 boys and 105 girls) of age ranging from 4 to 14 years. The authors have found a significant concurrence between primary headaches and anxiety and/or depression. In 2000, Masi and collaborators surveyed, in a psychiatric setting, the prevalence of somatic symptoms in a sample of 162 subjects suffering from behavioral or emotional disorders. The authors have found that headaches are the somatic symptom most frequently observed in children and adolescents with anxiety, depression, and behavioral disorders. Guidetti [8] defined migraines as a subtype of headache having a particular interest in psychiatry, since a relationship was identified between migraines, psychiatric disorders, personality traits, and stress. The nature of this relationship is still unclear and it has not yet been established if this was specific to migraines or if it was related to the frequency of the attacks. While phobic disorders on their own seem to be a predictor for the onset of migraines, mostly in men, anxiety, more than depression, provides for the long-term persistence of migraine and reduces the perception of effectiveness of the acute treatment [9]. The increased risk of encountering anxiety and depression in children and adolescents with migraines, compared to patients who do not suffer from such conditions, is confirmed in many studies. Very often in young patients suffering from headaches, a high level of perfectionism was noticed. Perfectionism is defined as setting oneself to high, almost impossible to attain standards, emphasizing only the accomplishments and the fact of achieving all the set objectives. Perfectionism can be conceptualized in due types: adaptive and maladaptive. The first has little clinical relevance; in subjects with maladaptive perfectionism, failure, no matter how small, becomes unacceptable and the urge to avoid it threatens the ability to succeed. In children suffering from headaches, perfectionism reflects a maladaptive process that causes them distress. In addition to the concept of adaptive and maladaptive linked to perfectionism, the literature adds other defining elements such as unidimensional trait or a multidimensional one. This last notion considers perfectionism as characterized by a component that can be both intraindividual and interindividual: a self-orientated

perfectionism (SOP), referring to self-imposed requirements to be perfect; socially perceived requirements (SPP), requirements perceived as coming from others, to attain perfection; and the perfectionism prescribed on others (OPP), requirements imposed by a subject on other people, to achieve perfection. Through our clinical experience, we have noticed that in children and young people with high standards of perfectionism, self-criticism is their reaction if the goals are not reached, while they will rate their performance as insufficiently brilliant, if the target has not been achieved at the top level. Such processes are often observed on patients suffering from headaches. According to the Model of Social Expectations proposed by Flett and Hewitt [13], the parents who are perfectionists also set high standards for their children. With such behaviur, the parents can transmit to the child that in order to receive their affection, he must be perfect and that failure is intolerable, thus generating distress in them.

22.1 Homework

Already from the first meeting, the therapist can start assigning activities to be carried out in-between meetings (e.g., exercise the skills learned in social skill training, do what was planned as pleasant activities, keep a journal to write down thoughts, sensations, and significant events). Obviously, everything that the patient must do as assignment at home must be carefully planned during the previous session and analyzed during the following one; this also allows the therapist to appreciate the level of motivation/involvement of the young patient and to monitor the progress of the therapy. It can be essential to involve the parents of the younger patients to help them perform as assigned.

22.2 Therapeutic Alliance

A therapist working with children and adolescents should display a mindset with a fair amount of collaborative skills and abilities to decode and integrate information, as well as the capacity to teach through engaging activities. Indeed the cognitive behavioral therapy is based on an ongoing collaboration between therapists, that is, on a teamwork to help them understand the emotions, the thoughts, and the behaviors that accompany the patient's malaise. In the motivational intervention with the child/young patient, the therapist should give information about the distinction between his own role and that of the other adults involved; this will help the young patient understand that collaboration between the therapist and himself is a central element that will allow a progressive improvement in his suffering. One must be able to create intrinsic motivation for change and reinforce the positive aspects but also strengthen the commitment to change.

22.3 Motivation

As Friedberg and McClure [14] observe, the choice of intervention strategies should be guided by such factors as the age of the patient, his level of cognitive development, the severity of depressive symptoms, the previously integrated skills, and obviously the context in which the young patient evolves. Secondly, one needs to determine the cognitive level and the language development of the child in order to understand which psychotherapeutic interventions could be useful and eventually elaborate a therapeutic plan taking into account the child/young patient's abilities. Since young patients often arrive in therapy with little motivation, few problem solving skills, and a profound state of despair, it might be useful to initiate therapy using basic techniques, easier to deal with. Once we have chosen the type of approach, it is a good practice to present the first interventions through simple, gradual tasks respectful of the patient's abilities, so that the success in fulfilling them can raise his sense of self-efficacy and therefore his motivation. Taking into account which current issues create most discomfort to the young patient, Dacomo and Pizzo [15] suggest to select those easier to deal with in the initial treatment phase. Especially with children of school age, drawings and cartoons can be used to identify the situations that generate their negative emotions as well as the things that make them feel happy. We can start planning enjoyable activities, these potentially being a valuable tool against anhedonia, social isolation, and the sense of fatigue of the young headache patients.

22.4 The Treatment of Perfectionism

There are evidences to suggest that perfectionism affects the psychotherapeutic treatment in children. In adolescents with high level of perfectionism, less improvements are observed during the period of therapy, independent of the type of treatment. Indeed perfectionism influences the response to therapy, reducing its beneficial effects; for this reason the reduction of the "perfectionist trait" remains an essential element of the protocol that we use in cognitive therapy for headache treatment. In a sample of children aged 9–12, who have been submitted to a preventive intervention of anxiety symptoms inspired from CBT, perfectionism influenced treatment outcomes of both anxious and depressive symptoms, since it also interferes with the development of a strong therapeutic alliance; therefore low levels of perfectionism allow better therapeutic improvement. The perfectionist subjects are less likely to engage in cognitive therapy because of the commitment required; for example, problem solving ability, a CBT element in anxiety disorders, is a challenge. The perfectionist subjects tend to postpone the tasks and this could interfere with the completion of the CBT exercises. Finally, high perfectionism levels can interfere with the therapeutic alliance and with the quality of social relations, which in turn influence the therapy outcomes.

In our protocol, there are three essential points to overcome perfectionism:

- Identify the areas in which the perfectionism is expressed.
- Evaluate the consequences, paying attention not only to the short-term advantages (as temporary improvement of one's own assessment, better sense of self-control, simplification of life in general, etc.) but also to the long-term ones (negative evaluation of oneself).
- Increase the importance of other assessment domains (identification of new activities to be undertaken).

22.5 The Treatment of Depression

When patients suffer from depression, it is not easy to have them tell us what they enjoy, so it might be useful to go back to what they used to like. Once the activity has been identified, it is important to record the emotions, the thoughts that emerge prior to and after the planning, and actualization of the activity. This recording can provide valid information on the patient's mood and on the activities prone to improve the situation; it also allows the patient to understand that the depressed mood is a temporary state and that it can change.

This should help in challenging thoughts such as "nothing will ever be interesting," "everything is boring," and "when I have an headache, I cannot do anything interesting." Elaborating a form of plan representing the patient's weekly program can be useful and stimulating, and we can consider using colors, newspaper cuttings, and photos. We must ensure that the selected activities can be initiated by the children on their own and we must be careful as to facilitate their successful evolution; these can be games, reading an amusing story, or meeting friends. It is also essential to involve the parents in the treatment, since they can collaborate with the children in the realization of the identified enjoyable activities. Adolescents are more autonomous both in the choice and completion of the pleasurable activities related to treatment and this, even without the parents' support. At the same time, a depressed adolescent can be so isolated that it is difficult for him to create viable social opportunities or interesting activities; often such a subject has few friends, doesn't belong to any organized group, and doesn't participate in any team sport. Therefore, the therapist must play an important role and be active in the planning; he needs to be creative to personalize his proposals; in our clinical experience, we have noticed, for example, that acting lessons or theater courses can often be very effective in promoting socialization but also self-expression and improvement of self-confidence. The identification of the emotions and thoughts linked to the planned activity, either prior to or after its completion, is fundamental, since the therapist can then initiate to work on the patient's associations between his negative automatic thoughts and his emotions. Through the course of these pleasurable activities, the young person must learn that his depressed and sad feelings are temporary and mutable sensations. Monitoring his own moods during the enjoyable activities

allows the patient to challenge the typical convictions of depressed young people, referring to being hopeless. Assessing and improving the patient's ability to recognize his emotions and express them is a fundamental aspect of treatment concerning children. The therapist helps them to recognize and classify their own emotions and to understand the relationship between situations and thoughts associated to them. Practically, using various media as drawings, cutouts, and movies will allow the child to understand the link between the situations, the thoughts, and the sentiments and to recognize how these are also related to somatic sensations. With the younger children, it is useful to have them understand that emotions can have various intensities, not functioning in terms of "all or nothing"; using for this purpose different synonyms of one emotion, we can help the child elaborate some links with associated antecedents and thoughts. Social skill training is a fundamental intervention with young patients suffering from headaches and having psychiatric comorbidity. Making friends and engaging in a social interaction often represent a great challenge for them. The therapist must ensure that the young patient has basic social skills as to successfully interact with his peers, so to avoid rejection that would increase his depressive dynamics and his social withdrawal. It can be useful to teach them how to ask and answer questions or how to share their interests with their peers. We are referring here to learning abilities such as assertiveness, maintaining visual contact, the adapted facial expression, how to offer and receive compliments, how to converse, and how to resolve conflicts and ask someone to put an end to an annoying behavior [16]. Such abilities are taught through direct instructions, modeling, role-playing games, and stories or books. In practice, we notice how some children, often only children, grown among adults and with little peer contact, have some difficulty to share their interests and therefore to interact with their peers; in such cases, it can be useful to explore with them the possibility of developing some issues in order to facilitate conversation and information exchange such as becoming expert in a football team, making an album of football players cards, watching a television program popular among many of his peers, etc. For a young depressed patient, the difficulty in making decisions and the impression of hopelessness can make problem solving look like an insurmountable task. The thoughts that they are unable to solve the problems and that they will fail any attempt are examples of dysfunctional beliefs. Identifying the obstacles and challenging these dysfunctional beliefs will therefore facilitate the problem solving process. During the middle phase of treatment, cognitive strategies will be more specifically adopted. With an auto-monitoring perspective, we will ask the patient to register his own automatic thoughts, identifying his own beliefs and his dysfunctional cognitive patterns. The patient must deliberately observe himself and the situations in which he is involved and record his observations (e.g., evaluate the frequency of occurrence of some thoughts). As Friedberg and McClure [14] have noticed young depressed people are not always able to gather their emotions and their thoughts and to express them. Some of them feel embarrassed; others are worried that their emotions and thoughts could become distressing leading them to feel overwhelmed. They believe that talking about it could lead them to feel worse and to lose control. In these cases, to verify the presence of such beliefs is a good strategy: "What do you think might

happen if you tell me what you are presently thinking of?" gradually encouraging them to share what is disturbing them. During the therapy sessions, we must ensure that the patient completes the headache journal assigned by the neuropsychiatrist with information such as his states of mind, the events, his emotions, and his thoughts. The negative distortions are habitual ways of interpreting information that alter the reality in such a way to generate an excessively negative vision of oneself, the future, the world; in therapy, it is fundamental for the patient to recognize and give a name to his cognitive distortions. The therapist must lead his patient in figuring out what kind of distortion his thinking belongs to, using a list of the most common ones, to be used as a reminder; such an intervention helps him to appreciate to what extent these distortions can have an impact on his emotions. With time, the patients start to figure out which cognitive distortions characterize their way of analyzing what happens and how they feel when it occurs. In an advanced stage of therapy, we work on a reassignment, a questioning, and a verification of the dysfunctional thoughts. If we are in the presence of a patient who tends to feel excessively responsible of what happens around him, the therapist can help him perceive more accurately the situations through alternative explanations. This technique consists in elaborating a list of all the factors that might have contributed to the event. In a perspective of attributing responsibility, the young patient then assigns to each factor a portion of the pie so to quantify their impact. This is useful since adolescents often consider themselves responsible in situations over which they have no control, for example, family disagreements or the parents' separation. In many headache patients, the natural tendency is to blame themselves for the occurring adverse events as well as for their own condition. When this happens, it is good to support them with the "detective" technique so to encourage them to collect the pros and cons on the automatic negative thoughts, recording their observations and the changes in their thoughts and in their sentiments during the various exposures. The results of such experiments, recorded in a journal, graphically represented, help the patient appreciate that he can question his own automatic negative thoughts, leading him to feel better.

22.6 The Treatment of Anxiety

The principal goals are to learn new skills for the management of anxiety and reduce the avoidance of the feared situations. The specific procedures include psychoeducational techniques, the cognitive restructuring (the "realistic" thinking or "detective thinking"), a gradual exposure to anxiety-inducing stimuli ("the ladder"), and management techniques for the parents. Also there are optional modules dealing with other problems often relevant in anxious children, including social skills, assertiveness, and school phobia that is a growing disorder among children and young people suffering from headaches. As for depression, it is useful to provide the parents the information on the nature, the causes, and the maintenance factors of anxiety. This helps clarify the difference between "normal" and "pathological"

anxiety, explaining the physiological, cognitive, and behavioral aspects and how they will be addressed with the various treatment procedures. We have already discussed that in our interactions with children, in order to help them feel comfortable, we can alter the names attributed to the chosen cognitive techniques. The cognitive restructuring can be presented as "realistic thinking" to adolescents and "detective thinking" to younger children. The children choose their own superhero or favorite detective that will help them find the "clues" or the "proofs" against their own anxiety-inducing thoughts or against their own predictions of possible negative events when they are in feared situations or stimuli. With adolescents, the expression "realistic thinking" is used aiming at modifying only the nonrealistic negative convictions in positive ones. The young people are encouraged to weigh all evidence for and against their negative predictions, to generate calming thoughts that are credible. The explanation of the cognitive restructuring begins by introducing the young person, through examples, to connections between situations, thoughts, and sentiments. At the beginning of treatment, we ask the young people to monitor the situations, thoughts, and levels of anxiety (on a scale of "preoccupation"). The goal of this exercise is to practice in identifying the anxiety-inducing thoughts for them to be challenged. The therapist then concentrates on the two main cognitive distortions present in anxious individuals: overestimating the possibility that an unpleasant event might happen and overestimating the negative consequences of that event, if it were to actually occur. We teach young people various techniques to collect proofs against the likelihood of their own predictions that something bad is going to happen, based on their own past experiences and general knowledge. Afterward, the adolescents go a step further, learning to identify and question the consequences of the feared event. We ask them to record, on modules, the situations that generate anxiety in them, the negative predictions related to the situation, and the proofs against such predictions. Then they learn to generate "calming thoughts" based on a realistic evaluation of the anxiety-inducing event. Cognitive restructuring can be an important tool in anxiety reduction; however, those who try to educate children using this technique often come across common obstacles. For example, some children become so anxious when confronted to a feared situation that they forget to turn to the detective technique. In such cases, "clue" cards can be used to remind them of their own calming thoughts for this situation. If the family identifies the coming of a difficult situation, the child can use the detective thinking prior to the event. Another common problem is that some children have difficulty in understanding the concepts behind cognitive restructuring. It is therefore important for them to be able to identify their own anxiety-inducing thoughts and understand the connection between thoughts and sentiments prior to questioning them. With children that have difficulties with cognitive restructuring, alternative techniques in anxiety management can be applied, among which inner dialogue modification [17] and relaxation exercises [18].

Another fundamental element is the exposure that has the goal of encouraging children to face the situations they fear and usually avoid. This is done in a gradual way (the ladder), starting with the less threatening situations in order to encourage compliance. The gradual exposition allows the children to learn that the situation is not threatening and that they can deal with it [19, 20]. Exposure is probably the most

efficient treatment strategy aiming at anxiety reduction in children and adults [18]. In our protocol, we teach cognitive restructuring prior to introducing gradual exposure—so, in situation, the young person has already identified evidence against the alleged negative impact of certain events and he is now able to reinforce it through direct experimentation. We often add relaxation techniques to exposure in order to help the children control the excessive anxiety in feared situations. The anxiety associated with the exposure technique can be dealt with in assigning the child some control over the process. Telling the children that they will start with easier situations, they choose the fears they wish to overcome first, before going to the next step only when they feel ready for it. The children will need encouragement and motivation to face the feared situations. Often anxious children have high and unrealistic performance standards which contribute to their reluctance toward new or difficult activities. We assign them numerous exercises to encourage them to praise themselves after having dealt with their own fears. Rewards should be used to reinforce the attempts of the child to face his fears; they may take the form of activities, praise, material objects or points to convert in rewards when a certain amount is reached.

In the final phase of treatment with headache patients, the therapist analyzes conjointly with the child/adolescent, the objectives that were identified at the beginning of the treatment, confronting them to those that have been reached. Together they identify the objectives that have been partially achieved or that require further work by the young patient and that can be successfully managed in an independent way. The ideal moment to end the treatment should coincide with clear agreement on the outcome achieved between the various parties involved, with supporting empirical data, allowing a period during which the results are stable and in which there is a constant tendency toward improvement. Clarity in providing information concerning the treatment modality and time frame allows the child and the adolescent to understand that he is in a precise time-limited process. Treatment doesn't end in an abrupt way, at any moment; the sessions in the final phase should rather be gradually reduced in frequency. Assuming that initially there were weekly sessions, we can choose to outdistance them for 2 weeks and then further decrease until the last follow-up sessions. The therapist should spend some time clearly discussing the modalities and the terms of the conclusion, thereupon addressing concerns and questions. In the planning of the schedule and modalities of the final sessions, the therapist should put emphasis on the positive impact of the achieved results, confronting them with the initial clinical reality and emphasizing the subject's active role as well as the level of competence he has reached. At the end of the treatment, the therapist should organize a final meeting with the parents' participation, in which the highlights of intervention would be reiterated, allowing at the same time to emphasize the importance of their role in the improvement of their child's situation.

Since we work every day with children and young people who are suffering from headaches, for us, the work on psychiatric comorbidity is fundamental; a good psychotherapy allows the therapist, and indirectly the neuropsychiatrist, to intervene precociously on "the pain," reducing its potential evolution to chronicity, a component that is seen more and more frequently in our practice.

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