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Original Article

Hyperventilation During Routine Electroencephalography: Are Three Minutes Really Necessary?

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ABSTRACT

OBJECTIVE: Hyperventilation induces absence seizures in children with absence epilepsy, and routine electroencephalography studies include three minutes of hyperventilation. We aimed at determining the duration of hyperventilation required to provoke a first absence seizure to establish whether three minutes of the procedure are indeed necessary. **METHODS:** Electroencephalography records of children who experienced absence seizures during hyperventilation were reviewed. The time from hyperventilation onset to a first and further seizure(s) was measured, and the occurrence of absences during the posthyperventilation phase was also noted. **RESULTS:** Sixty-two studies were evaluated. Mean time from hyperventilation onset to a first absence was 52 seconds (median 32 seconds). The vast majority (85.5%) had an absence within 90 seconds. Most (68%) children sustained a single event. All eight children with posthyperventilation seizures had experienced at least one event during hyperventilation. **CONCLUSIONS:** Our findings suggest that current guidelines for routine pediatric electroencephalography recording requiring three minutes of hyperventilation may not be clinically necessary. We found that the vast majority of children referred for suspected absence seizures experience a seizure less than 90 seconds after hyperventilation onset, and even more so by 120 seconds. Hence, a larger prospective study is warranted to establish more accurate hyperventilation duration parameters. We also suggest that once an absence seizure has been recorded at any time during hyperventilation, this procedure could be stopped, thus reducing the amount of discomfort for the child.

Keywords: absence seizures, EEG, time-to-event, hyperventilation, child, electroencephalography

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Introduction

Absence seizures are a common seizure type in childhood. They most commonly occur as the main seizure type in childhood absence epilepsy and as a major component of juvenile absence epilepsy. The average attack lasts 9-12 seconds (range 3-40 seconds).[1,2] The ictal electroencephalographic correlate of the absence seizure consists of high amplitude, bilateral, synchronous, symmetrical 3-Hz spike-and-wave discharges, with the highest voltage observed in the anterior regions.[1-4]

Hyperventilation (HV) is a well-recognized trigger for absence seizures in children with absence epilepsy,[2-4] provoking the seizures in virtually all children when performed correctly.[2] Long-standing recommendations for minimal technical standards for routine electroencephalograph (EEG) established by the American Clinical Neurophysiology Society include three minutes of HV followed by at least 1 minute of postventilation recording.[5,6] The European Commission of the International League Against Epilepsy also recommends for standard EEG performance to include three minutes of recording during hyperventilation with a continued recording for at least 2 minutes after cessation of HV.[7]

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HV can be safely performed in the office setting.[8] If HV is well-performed, our clinical experience suggests that most children with a history of absences will experience at least one episode in this situation. In this setting, it appears that most patients sustain the absence event within less than 90 seconds of starting HV. Therefore, we aimed at determining whether this clinical observation is correct and at establishing whether performing HV for a full three minutes was really necessary to elicit an absence seizure in children during routine EEG recording. Because HV is a relatively uncomfortable procedure, usually accompanied by dizziness and headaches, shortening this routine EEG activation procedure may also reduce the amount of discomfort for these patients.

Methods

This study was performed under the authorization of all three medical centers' institutional review boards.

Records of all routine EEGs of children who experienced at least one absence seizure during hyperventilation were reviewed at our three medical centers. All studies were done using the 10-20 system for electrode placement[5,6] and included two standard activation procedures: three minute hyperventilation followed by at least 10 minutes of post-HV recording and photic stimulation.

All records were reviewed by one of the authors (M.H., M.F., T.S.) and the findings compared with the official EEG report from the actual time of the study. Demographic data of all cases were obtained from the EEG report/study request. Clinical information on patients included: indication for study, past EEG records (if any), and current antiepileptic drug regimen (if any). Only records in which the child succeeded in performing the full three minutes of HV were included.

The time (in seconds) from the onset of HV until the occurrence of an electrographic generalized spike-and-wave seizure lasting a minimum of 5 seconds was measured. Also, the time to a second and to further absences from HV onset was recorded. Finally, whether electrographic absences appeared during the 2 minute post-HV phase was also noted and the time of occurrence with respect to HV ending was determined. Clinical correlation of the EEG seizure was obtained from the EEG technician's annotations, where available.

Statistical analysis

Because data were not distributed normally (Shapiro-Wilk test), continuous variables are described as mean ± standard deviation, median and minimum-maximum (min-max). Nominal parameters were shown as numbers and percentage. Comparison between two parameters was done—for nominal parameters—by chi-square or Fisher's exact test. For continuous data, Mann-Whitney nonparametric test was done, and among three hospitals, by Kruskal-Wallis nonparametric test and Bonferroni post-hoc comparisons. Difference was considered statistically different when $P < 0.05$. All differences were two-tailed when appropriate. All analyses were performed with SPSS-21 software.

Results

Sixty-two records were reviewed. Most (59.7%) patients were girls. Age range was 4-15 years (average 9.3 years, median 8.5), of whom almost 60% were younger than age 10. The geographical distribution of the records was 58% Israeli and 42% Turkish children (Table 1).

The time elapsed between HV onset and EEG seizure occurrence is depicted in Table 2. The average time to the first episode was 50.16 ± 73.3 seconds (median 32 seconds [min-max 2-130]). Twenty-four children sustained a second event (mean 105.88 ± 51.5 seconds, median 100 seconds [min-max 28-180]), whereas only four experienced a third absence. In the vast majority of the records (85.5%), the first EEG seizure occurred within 90 seconds from HV onset. Among the remaining 14.5%, the first event took place after an average of 110 seconds (median 100 seconds). In three of the 62 cases, the first event occurred between 120 and 130 seconds. When comparing by age groups, we found that the average time for first event was 47 seconds for those younger than 10 years of age, and 55 seconds for those older. Nevertheless, this difference was not statistically significant. Eight children experienced absences during the post-HV period. All had sustained at least one event during HV itself.

Seventeen of the 62 children had EEG performed while receiving antiepileptic medications (10 of the 17 had also had an EEG on no medications). No significant difference was noted in the time to first event between treated and untreated children.

Discussion

Generalized spike-and-wave discharges, the EEG correlate of childhood absences, are believed to represent a pathological phenomenon because of the malfunction of any of several specific voltage- or ligand-gated mechanisms in the thalamocorticothalamic network.[9] This allows burst activation of the cortex, normally seen only in a sleeping state, to occur during wakefulness, resulting in the EEG appearance of rhythmic spike-and-wave discharges and interrupting responsiveness to external stimuli.[10] In particular, the thalamic reticular nucleus and the frontal cortex appear to play a major role, suggesting that absence seizures may not be truly generalized, but may involve selective networks.[1]

Alkalosis resulting from reduction of blood carbon dioxide levels has been suggested as the mechanism behind the occurrence of absence seizures during hyperventilation. Thus, forced hyperventilation, by virtue of provoking alkalosis, induces absences.[11] This conclusion is supported by the fact that children with absence epilepsy do not sustain absences during physical exercise, when hyperventilation occurs as a compensatory mechanism to eliminate carbon dioxide and to raise blood pH.[12] Nevertheless, one study showed that low carbon dioxide levels may not entirely explain the induction of absences because some children did not sustain the seizures despite critically low end-expiratory carbon dioxide values.[13] Blood alkalinization from hyperthermia-induced hyperventilation causes

TABLE 1.
Characteristics of Israeli and Turkish Patients

Gender (%)	Age (years)	No. of Patients by Age (%)	Country (%)
Female: 37 (59.7)	Range 4-15	4-10 years: 37 (59.7)	Israel: 36 (58)
Male: 25 (40.3)	Mean 9.3	11-15 years: 25 (40.3)	Turkey: 26 (42)

TABLE 2.
Time in Seconds From Onset of Hyperventilation to Occurrence of Absence Seizures

	First Seizure $n = 62$	Second Seizure $n = 24$	Third Seizure $n = 4$
Mean	50.16	105.88	105
Median	32	100	109
Range	2-130	28-180	72-128

seizures in a rat model of febrile seizures.[14] These seizures can be prevented by ventilating carbon dioxide and avoiding alkalosis. Indeed, a recent study has shown that breathing 5% carbon dioxide while hyperventilating suppresses hyperventilation-induced absence seizures in children.[15]

Both HV and intermittent photic stimulation significantly increase the diagnostic yield of routine EEG. These procedures are frequently associated with an increase in interictal epileptic discharges and even with de novo appearance of epileptiform activity, especially in patients with generalized epilepsy but also in those with partial seizures.[16,17] The yield of HV and intermittent photic stimulation is higher in EEGs of children and young adults because generalized epilepsies are more common in this population.[18] Nevertheless, some studies suggest that the yield of hyperventilation in eliciting interictal epileptiform activity may be somewhat lower.[19]

As mentioned in the introduction, current guidelines for routine EEG recording, both in Europe and in the United States, recommend performing hyperventilation for at least three minutes. Interestingly, despite the fact that absence seizures are most common in childhood and the adopted practice of performing three minutes of HV in routine pediatric EEG, HV is not specifically included in the current Clinical Neurophysiology Society requirements for pediatric EEG (it only states that “the basic principles of clinical EEG outlined in the general EEG recommendations also apply to the very young and are reaffirmed” and that “where a subject is not covered, the recommendations of Guideline 1 remain appropriate and should be consulted”). Conversely, the need for photic stimulation in pediatric EEG is specifically mentioned in the requirements for pediatric EEG.[6]

A review of the literature on the scientific basis for the recommendation for a minimum of three minutes of hyperventilation does not provide a clear explanation for this protocol. Detailed reviews on EEG findings associated with generalized epilepsies do not address the scientific foundation for this specific recommendation.[20] However, some studies have assessed the effects of HV on ventilation values. To induce EEG slowing (not epileptiform activity) in healthy children, the optimal conditions were: a respiratory rate of 30/minute, a three-fold elevation of expiratory volume/minute, and HV duration of 4 minutes.[21] Decreases in partial pressure of carbon dioxide and cerebral blood flow appear to be responsible for EEG slowing during HV.[22] Using the same methodology in children with epilepsy, EEG slowing was found to occur earlier than among healthy individuals. Cerebral blood flow decreased earlier in epileptic children than in controls, possibly explaining the earlier EEG slowing.[23]

The requirement of a full three minutes of HV during routine EEG to elicit absence seizures has not been questioned in the literature. Studies pertaining to the EEG characteristics of absence epilepsy describe the yield of HV in provoking the seizure rather than the time elapsed until the appearance of a first absence.[1-4,9,21-23] A recent study measured the time to first absence seizures for the whole EEG record, but did not address the time elapsed from HV onset to the appearance of an absence.[24] In the 1980s, Konishi published two studies on the standardization of HV during routine pediatric EEG recording. Conversely from our study aims, the author’s objective was to determine the amount, intensity, and duration of hyperventilation-related parameters to elicit EEG slowing in neurologically asymptomatic children. The author found that the parameters previously mentioned (a respiratory rate of 30/minute, a three-fold elevation of expiratory volume/minute, and HV duration of 4 minutes) were optimal for provoking EEG background slowing, arguably the electrographic expression of effective HV.[25]

In the present study, 85.5% of children experienced the first absence within less than 90 seconds from HV onset. The median time for seizure appearance among the remaining 14.5% was 100 seconds. Hence, our evaluation of EEG records from two different populations (Turkey and Israel) suggests that, if an absence seizure does not occur within 90-120 seconds from HV onset, the chances of its appearance upon continuing this activation procedure are very small.

Another issue to be addressed is the justification for continuing HV once an absence has been captured in the EEG. Because HV is often uncomfortable for the child, when a suspicion of absence epilepsy is the indication for an EEG, following the detection of an absence seizure at any time during HV this procedure could probably be stopped without completing the three minutes.

Our study has some limitations. First, we only evaluated EEG records of children referred for suspected absence seizures who sustained at least one electroclinical event during HV. Therefore, some children with absence seizures may not have been included in the study, because events may not have occurred during hyperventilation. As previously mentioned, studies indicate that HV, if performed correctly, can provoke absence seizures in the vast majority of children with petit mal. Therefore, we feel that our sample is quite representative of children with childhood absence epilepsy that will experience at least one absence seizure during hyperventilation, and that more than 85% sustained the first event within 90 seconds is of practical significance. Second, an important yet unanswered question that was not addressed by our study remains unanswered: the percentage of EEG records of children with absence seizures that do not sustain electroclinical events during HV but do experience absences within other periods of the routine EEG recording. Third, although in our patient series all records with post-HV absences had sustained at least one seizure during HV, the possibility

exists that some children may have an event only during the post-HV period.

In summary, our findings suggest that current guidelines for routine pediatric EEG recording requiring three minutes of hyperventilation may not be clinically accurate. We found that the vast majority of children referred for suspected absence seizures experience a seizure less than 90 seconds from HV onset, and even more so by 120 seconds. Hence, a large-scale prospective study is warranted to establish more accurate HV duration parameters. We also suggest that, once an absence seizure has been recorded at any time during HV, the procedure could be stopped, thus reducing the amount of discomfort for the child.

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