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A Review of Hyperventilation Activation in Diagnosis and Management of Childhood Absence Epilepsy

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Abstract

Childhood absence epilepsy is one of the most prevalent pediatric epilepsy syndromes, but diagnostic delay is common and consequential. Childhood absence epilepsy is diagnosed by history and physical examination including hyperventilation with electroencephalography (EEG) used to confirm the diagnosis. Hyperventilation produces generalized spike-wave discharges on EEG in >90% of patients with childhood absence epilepsy and provokes clinical absence seizures consisting of brief loss of consciousness typically within 90 seconds. Child neurologists report a high volume of referrals for children with "staring spells" that strain already limited health care resources. Resources are further strained by the use of EEG for monitoring antiseizure medication effectiveness with unclear benefit. In this review, we examine the safety and efficacy of hyperventilation activation as a tool for the diagnosis and management of childhood absence seizures.

Keywords

absence seizures, childhood absence epilepsy, electroencephalogram, hyperventilation, staring spells

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Staring spells are a frequent presentation in children[1] resulting in significant use of both electroencephalography (EEG) resources and child neurologists' time. The differential diagnosis for staring spells includes absence epilepsy, focal seizures with alteration of awareness, and nonepileptic paroxysmal events such as daydreaming, ocular tics, and inattention.[2,3] The literature[4-6] and child neurologists anecdotally report a high rate of referral of nonepileptic staring spells. As a result of limited encounter time and poor-quality referral data, most child neurologists receiving referrals for staring spells have adopted the practice of performing a routine EEG before the initial clinical visit. Most centers report that it is easier to get a routine outpatient EEG than a new patient clinic appointment with a child neurologist, with typical average wait times of 1-2 months and upward of 4 months in university settings and certain regions in the United States.[7] The EEG is used to screen for epileptiform activity or seizures that may prompt sooner evaluation by a child neurologist.

Childhood absence epilepsy is one of the most common pediatric epilepsy syndromes, accounting for 12% to 18% of epilepsy diagnoses in school-aged children, and affecting girls more frequently than boys.[3,8] Childhood absence epilepsy is characterized by absence seizures, which are brief episodes of behavioral arrest and impaired recall, as well as rarely generalized tonic-clonic seizures.[3] Despite their high frequency, absence seizures are subtle, and easily missed by caregivers, resulting in delayed diagnosis. Childhood absence epilepsy is diagnosed by careful history and physical examination, including hyperventilation then confirmed by EEG. Although childhood absence epilepsy was previously considered a benign epilepsy, it is now clear that the epilepsy itself and the comorbidities including attentional difficulties and mood symptoms can result in poor psychosocial outcomes even when appropriately treated.[9] Additionally, there is evidence to support improved cognitive outcomes when the absence seizures remit.[10] Currently, the sensitivity of pediatricians' referrals for evaluation of staring spells for childhood absence epilepsy is low.[11] Additional clinical data at the point of care could identify children at high risk, shortening the time to diagnosis and initiation of appropriate therapy, and reducing the strain on child neurology resources.

As in other genetic or idiopathic generalized epilepsies, EEG can be a useful diagnostic tool, but its use for the management

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of childhood absence epilepsy is highly variable. EEG is well accepted to confirm seizure freedom; however, the utility of EEG in management is debatable when there is ongoing seizure activity. Hyperventilation was defined as an activation procedure for epileptiform discharges in 1930 and has been standardly used in combination with EEG. Apart from EEG, hyperventilation alone has not been well studied but is frequently used in clinic visits, with more than 80% of pediatric neurologists using hyperventilation to guide clinical decision making.[12]

In this review, we provide an overview of the evidence base for the use of hyperventilation as a tool in the diagnosis and management of childhood absence epilepsy. In this era of increasing health care costs and limited resources, there is great need for the adoption of a clinical tool that is inexpensive, accurate, and easy to implement. Hyperventilation, although widely used among neurologists as a binary tool to identify ongoing seizures, has the potential to improve referral efficiency if used by pediatricians and may allow for additional information to be gleaned regarding antiseizure medication management.

The Problem With Staring Spells

Staring spells in children is a common reason for referral to pediatric neurologists. Overreferral for EEGs among nonneurologists contributes to inefficient use of health care resources. In a retrospective analysis of 100 pediatric EEG referrals by pediatricians at Kaiser, 77% were found to be normal.[11] Nonepileptic EEG findings are present in a higher percentage of children with attention-deficit hyperactivity disorder (ADHD) who frequently present with staring spells associated with daydreaming or inattention, leading to additional unnecessary testing.[13] A recent single-center retrospective chart analysis of children referred with staring spells found that in the 3- to 13-year age group, 72% were found to be attributed to ADHD, normal behavior, or sleep apnea, whereas <12% were attributed to epilepsy.[14] The authors concluded that additional clinical history and testing could significantly aid in epilepsy diagnosis. One such clinical test that can be performed during an office visit is hyperventilation.

Hyperventilation's Role in Diagnosis of Childhood Absence Epilepsy

Capturing a typical absence seizure provoked by hyperventilation is standardly part of the criteria for diagnosis of childhood absence epilepsy.[3] The childhood absence epilepsy study found that clinical absence seizures had on average a duration of 10.8 seconds.[15] The clinical phenomenology of absence seizures is recognizable, consisting of a pause/stare, and the semiology can be categorized with excellent interrater reliability for motor automatisms and eye involvement.[16] This is consistent with the clinical practice that neurologists have a high sensitivity and specificity in identifying absence seizures whether spontaneous or provoked by hyperventilation.[17] Hyperventilation triggers absence seizures in >90% of patients with drug-naive absence epilepsy, with the majority occurring in the first 90 seconds of hyperventilation.[9,15,18-20] The International League Against Epilepsy (ILAE) recognizes that in resource-limited regions, childhood absence epilepsy can be diagnosed in children who meet clinical criteria if they have a witnessed typical absence seizure with hyperventilation without confirmatory EEG.[3] When access to EEG was further limited during the COVID-19 pandemic, children with childhood absence epilepsy were evaluated with telemedicine and hyperventilation.[21] In a retrospective case series, clinical history and results of hyperventilation were used to make treatment decisions without confirmatory EEG. There were no significant adverse events, and the authors concluded that initiation of therapy does not need to be delayed for an EEG confirmation if the diagnosis is supported by physician observation of seizure activity on hyperventilation.[21] These studies contribute to a growing body of evidence indicating the potential value of hyperventilation in clinic settings as well as in home settings by means of live telehealth or other video recording when interpreted by a neurologist or other trained clinician. Hyperventilation should be used as an adjunct but not replacement for patient/family-reported history including seizure diaries.

Hyperventilation During EEG for Enhanced Epileptic Discharge Detection

Hyperventilation is an activation procedure routinely used during an EEG to provoke or enhance epileptic discharges, aiding in the diagnosis and classification of seizures, particularly in patients with predisposition. Hyperventilation is defined as a respiratory rate of at least 18 to 24 breaths per minute.[22] This causes a chemical shift of O_2 and CO_2 to $H^+ + HCO_3^-$ in the blood, resulting in blood pH increasing into the alkalotic range above 7.4.[23] Numerous studies have shown that including hyperventilation in routine EEGs improves diagnostic sensitivity by eliciting or enhancing interictal epileptiform discharges and ictal discharges, namely, absence seizures when a patient is predisposed to having seizures such as in childhood absence epilepsy.[9,15,18-20] Hyperventilation not only induces physiological slowing of brain rhythms but also promotes paroxysmal synchronization.[24] Therefore, hyperventilation can be helpful in diagnosing epilepsy and characterizing epilepsy type.

Hyperventilation Guidelines for EEG Diagnostic Testing

The American Clinical Neurophysiology Society (ACNS) recommends routinely using hyperventilation during EEG for diagnostic purposes unless patients have contraindications such as recent intracranial hemorrhage or significant cardiopulmonary disease, which are discussed in further detail below.[25] Hyperventilation should be performed for a minimum of 3 minutes, with a 1-minute recording after its cessation. Longer durations may be considered for improved seizure provocation.[26] An important limitation to the sensitivity of hyperventilation for absence seizures in children is the risk for false negative results when the patient is unable to properly perform the hyperventilation technique as instructed. Young children may require encouragement using pinwheels or facial tissues to improve effort. The quality of the patient's effort during hyperventilation should be assessed for potential repetition and greater yield, as set forth by the Association of Neurophysiological Scientists and the British Society of Clinical Neurophysiology.[27] Patients and caregivers should be informed of the possibility of hyperventilation and other provocative maneuvers, such as intermittent photic stimulation, which may elicit epileptiform discharges or seizures in susceptible individuals.

Contraindications and Safety of Hyperventilation During EEG

Although hyperventilation is generally safe, some contraindications should be taken into consideration. Absolute contraindications for hyperventilation during an EEG include recent (within the prior 12 months) stroke or myocardial infarction, significant cardiac disease, pulmonary disease, sickle cell disease, and moyamoya disease.[28] Relative contraindications include stable cerebrovascular ischemic heart disease, respiratory problems, brain tumors, and severe anxiety. These contraindications are important to consider in the context of risks that may occur from hyperventilation, such as hypocapnia, which could result in cerebral vasoconstriction and potentially increase the risk for cerebral ischemia or other hypoxic organ injury. However, a study of 3475 patients including adults undergoing EEG in the United Kingdom found low rates of adverse events, with only 2 patients experiencing self-limited symptoms related to asthma and tachycardia during hyperventilation.[28] Regarding hyperventilation risk for provoking seizures that could result in injury, there is no literature evidence to support absence status epilepticus resulting from hyperventilation. Although there is a small risk of provoking a focal or focal to bilateral tonic-clonic seizure with hyperventilation (0.07% of 9919 EEG reports in a retrospective study), this is rare in children[28,29] and more likely to occur in persons with known focal epilepsy in the setting of antiseizure medication withdrawal for seizure capture[30] or in adults with autoimmune encephalitis.[31] There is also a small risk for hyperventilation eliciting a generalized tonic-clonic seizure (0.03% of 3170 patients studied prospectively).[28] Furthermore, the overall risk of generalized tonic-clonic seizures is less at the time of diagnosis of childhood absence epilepsy and increases as the child nears puberty[32,33] and is possibly evolving into another generalized epilepsy syndrome such as juvenile myoclonic epilepsy.

Factors Influencing the Activation of Seizures during Hyperventilation in EEG

There are a few factors that have been studied to determine when hyperventilation during EEG is most likely to activate seizures. The research by Craciun et al[26] found that 5 minutes of hyperventilation yielded a significant increase in both seizures and interictal abnormalities compared with 3 minutes. Another study conducted by Rozenblat et al[34] in 2020 showed that the sitting position, as opposed to supine, may improve diagnostic sensitivity during hyperventilation in children with childhood absence epilepsy, although this was not consistent across age groups. Additionally, a study of the safety and efficacy of hyperventilation during EEG by Kane et al[28] in 2014 found that patients aged 1-10 years had the highest yield for seizure provocation, whereas the appearance and exacerbation of interictal epileptiform discharges remained relatively high across older age groups. Adams and Luders[35] found that hyperventilation was less sensitive to the state of the patient than prolonged EEG recording and, as a result, a better objective index of epileptogenicity.

Monitoring Treatment Efficacy in Childhood Absence Epilepsy

Children with childhood absence epilepsy are treated with ethosuximide or valproic acid as first-line agents.[3,15] In epilepsy management, physicians typically assess treatment efficacy based on patient and family reports. Although patient self-report is a limited tool even in epilepsies with motor seizures, in childhood absence epilepsy, the subtle nature of absence seizures renders self-reporting even less helpful unless parents report seizure freedom. As a result, clinical studies such as the childhood absence epilepsy study have focused on "freedom from failure, which is defined as the absence of clinically apparent seizures based on parent report or electrographic seizures at 16-20 weeks of treatment."[15] Although EEG has long been the primary tool for the diagnosis of childhood absence epilepsy, the use of EEG for the monitoring of antiseizure medication effectiveness in childhood absence epilepsy is more nuanced. The lack of generalized spike-waves (GSWs) or absence seizures on EEG strongly suggests seizure remission, and the capture of absence seizures on follow-up EEG can indicate the need to escalate antiseizure medication regimens. There remains significant practice variability, with many child neurologists anecdotally reporting that they are aiming for the child to do well overall, for example, in school, and less focused on complete seizure freedom if the family reports rare seizures. Further complicating matters are ongoing or prolonged generalized spike-wave discharges without clinical features, which can imply ongoing seizure risk but do not always clearly translate into actionable management steps such as increasing or changing antiseizure medications. Occasional brief generalized spike-wave discharges are often disregarded but are of unclear significance in seizure risk recurrence.[17] When generalized spike-waves are present and a person is of driving age, there remain no clear guidelines for distinguishing the EEG signature of "safe" versus "unsafe" driving for a person with childhood absence epilepsy. Furthermore, there is no clear standard for comparing one EEG to another to determine if there is a decrease in seizure burden or a trend toward improvement. Patient-specific variables such as “state of alertness, time of day, blood glucose levels, and anxiety” can impact the quantity of generalized spike-waves or seizures at the time the EEG is performed.[35]

The use of EEG in management remains ambiguous even before antiseizure medication withdrawal. EEG is frequently used for evaluation of the presence and burden of generalized spike-wave discharges as a broad indicator of unreadiness for antiseizure medication discontinuation. As in antiseizure medication management, whereas the capture of an absence seizure is conclusive, the threshold for generalized spike-wave burden indicative of increased relapse risk is unclear. Moreover, EEG’s role after antiseizure medication withdrawal in predicting absence seizure relapse is of equivocal utility. As in most childhood idiopathic epilepsies, guidelines support a trial of antiseizure medication withdrawal after 2 years of seizure freedom; however, unless 1 or more absence seizures are captured on EEG, it is unlikely to provide sufficient information to restart an antiseizure medication or continue off.

Hyperventilation in Childhood Absence Epilepsy Management: Clinical Practice Insights

A 2013 study examined survey responses from 96 board-certified or board-eligible child neurologists trained in US residency programs (Figure 1).[12] Of the respondents, 77 (80%) child neurologists used hyperventilation to assess seizure control, whereas 19 did not. Among those who used hyperventilation, 43 (56%) obtained EEG to evaluate control, with 29 of those respondents adjusting medication if discharges lasted longer than 3 seconds. Among the child neurologists who did not use hyperventilation, 8 still obtained EEG for control assessment, with 5 adjusting medication for discharges longer than 3 seconds. The findings highlight differing practices and approaches in medication adjustments based on EEG results in childhood absence epilepsy management.

Mimics of Absence Seizures in Children: Differentiating Features

In the discussion of hyperventilation-induced absence seizures in children, it is important to consider hyperventilation-induced high-amplitude rhythmic slowing (HIHARS) as a mimicker of absence seizures in children, as was described by Nasreddine et al[36] in 2020. Similarly to absence seizures, hyperventilation-induced high-amplitude rhythmic slowing results in loss of awareness, or altered awareness, following hyperventilation activation procedure and often results in an accompanying EEG change, although quite different from the classical frontocentral-predominant 3-Hz generalized spike-wave discharges seen accompanying typical absence seizures in childhood absence epilepsy. This study included 116 children with a mean age of 9.8 years and found that symptomatic features such as blinking, staring, smiling, manual automatisms, and fidgeting were useful in distinguishing between the 2 conditions.[36] Although blinking and staring were more indicative of absence seizures, smiling, manual automatisms, and fidgeting favored hyperventilation-induced high-amplitude rhythmic slowing. Hyperventilation-induced high-amplitude rhythmic slowing clinically did not manifest until later in hyperventilation, at 139 seconds, suggesting that the clinical alterations in hyperventilation-induced high-amplitude rhythmic slowing are related to a cumulative physiological change occurring during hyperventilation.[37] Although findings from these studies suggest that hyperventilation can be helpful in clinically differentiating hyperventilation-induced high-amplitude rhythmic slowing from absence seizure, it is important to note that EEG remains the gold standard in differentiating these 2 clinical entities. As the acronym HIHARS implies, EEG is expected to show high-amplitude rhythmic slowing, characterized by ≥3 seconds of 2.5- to 5-Hz diffuse rhythmic slowing above 100 μV.[37,38]

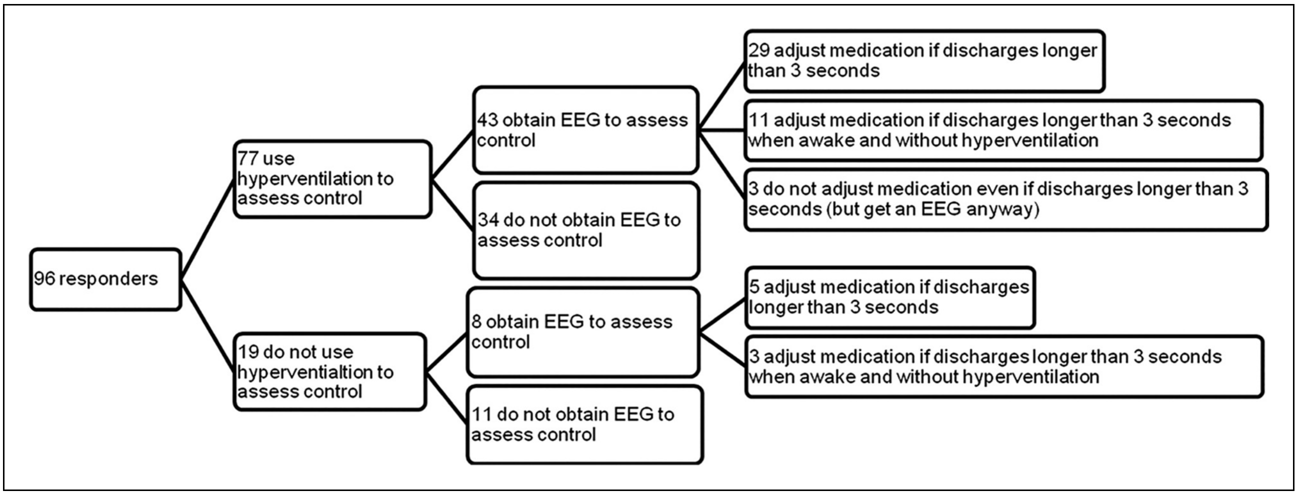

Figure 1. Responses from 96 board-certified or board-eligible child neurologists trained from a residency program in the United States. EEG, electroencephalogram. Adapted from Desai J et al in *Journal of Child Neurology* 2013;12. .

Advances in the Management of Childhood Absence Epilepsy

Studies show that self-reporting by patients or caregivers is not accurate in assessing absence seizure frequency.[39,40] In a small case series, Adams and Lueders[35] found that a 5-minute period of "rigidly standardized HV [hyperventilation] was an excellent objective index of seizure frequency and superior to 6-hour EEG recording." Hyperventilation has proven to increase yield in a follow-up routine EEG more than longer EEG duration without hyperventilation activation.[28] Beyond EEG, however, there is a need for further evaluation tools for the management of childhood absence epilepsy and specifically assessing the effectiveness of antiseizure medication treatment. This is evidenced by the lack of new antiseizure medications to treat childhood absence epilepsy despite only 60% of children obtaining seizure freedom after the first medication.

There remain few markers for guiding management and prognosis in childhood absence epilepsy. Recent reviews have emphasized the lack of clear EEG markers for determining long-term outcomes.[41] Concurrently, research has illuminated the potential of clinical features—such as seizure duration at diagnosis, presence of generalized tonic-clonic seizures, and myoclonic features—to predict pharmacoresistance in childhood absence epilepsy.[42]

The pivotal childhood absence epilepsy study provided class 1 evidence for the use of ethosuximide as the optimal initial treatment for childhood absence epilepsy.[15] In addition, a Cochrane review that considered 8 randomized trials found that ethosuximide is the preferred initial monotherapy for children and adolescents with absence seizures because of its favorable balance of efficacy and tolerability.[43] Additions to our pharmacopeia of antiseizure medications have long focused on severe epilepsy, with no new medications for childhood absence epilepsy since the 1990s. A substantial hurdle has been the difficulty in assessing seizure frequency in childhood absence epilepsy management; without accurate measures of seizures, monitoring seizure response during antiseizure medication trials becomes a barrier. Furthermore, up to 30% of children with childhood absence epilepsy face pharmacoresistance, and 10% to 15% will go on to develop juvenile myoclonic epilepsy, a prime opportunity to assess the efficacy of antiepileptogenic drugs after safety testing. Ongoing seizures and higher seizure burden also increase the risk of cognitive impairment.[44] Ultimately, the children with the most common idiopathic childhood epilepsy are left with few options for treatment once first-line therapies have been exhausted.

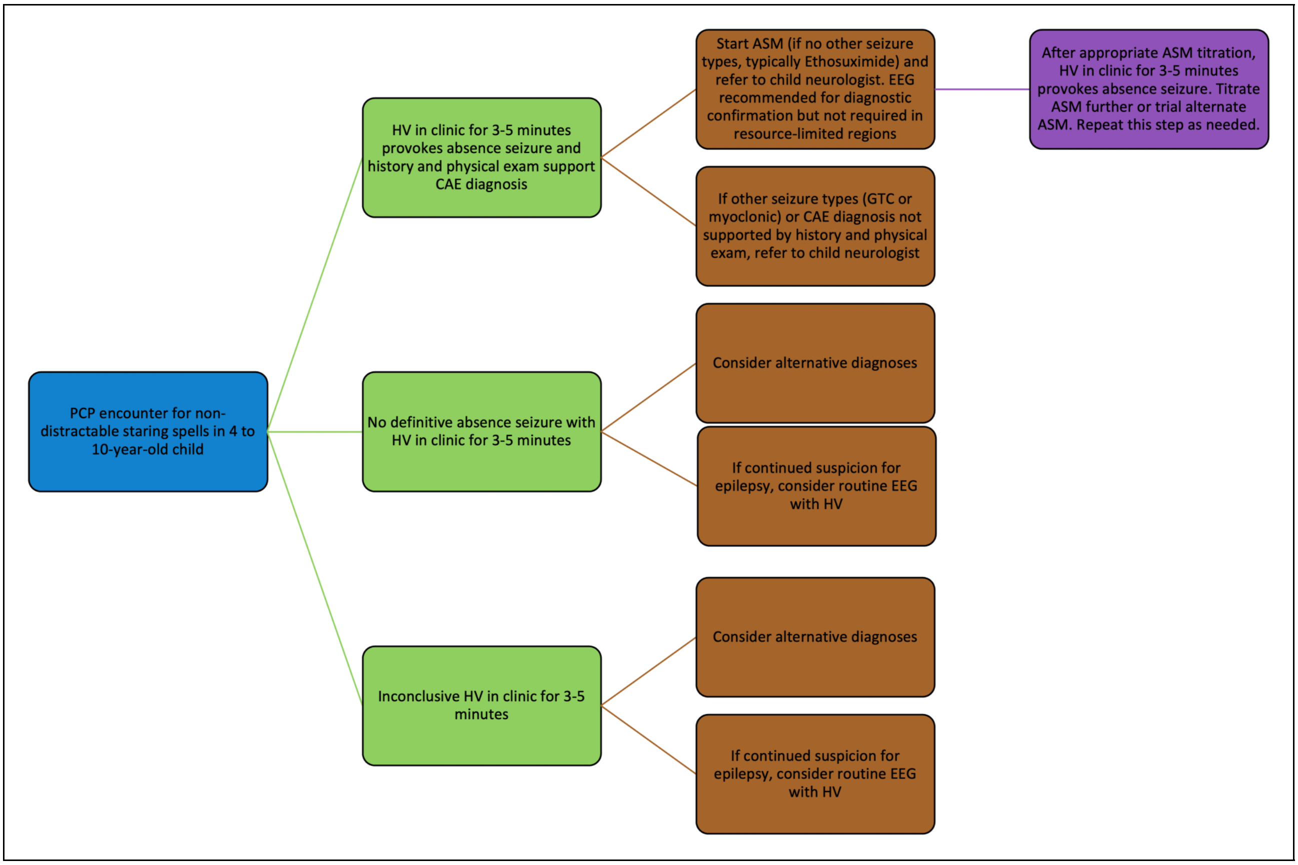

Figure 2. Decision tree for the proposed integration of hyperventilation (HV) in the clinical diagnosis and management of childhood absence epilepsy (CAE). PCP, primary care physician; HV, hyperventilation; CAE, childhood absence epilepsy; EEG, electroencephalogram; ASM, antiseizure medication; GTC, generalized tonic-clonic.

Next Steps

Although hyperventilation is commonly used for diagnosis and management, EEG is still viewed as a primary tool even though it has significant limitations. To decrease the burden on patients and caregivers and decrease time to seizure freedom, more research on the utility of hyperventilation is needed. From a diagnostic perspective, the use of hyperventilation in the pediatrician's office at the time of referral would significantly improve the time to diagnosis. Pediatricians can additionally identify patients at high risk for absence epilepsy by, for example, adding simple questions to the Vanderbilt assessment for ADHD including "non-distractible staring off," "lip-smacking," and/or "complaining about brief lapses in time" to screen for children more likely to have absence seizures. There is a dearth of literature demonstrating how frequently pediatricians and other primary care physicians use hyperventilation. Significant barriers to adoption include limited encounter time, discomfort with the procedure, and misperception of risks. As pediatricians in the United States are not required to undergo neurology training as part of their residency programs, additional education on the safety and efficacy of hyperventilation for absence seizure screening during office visits is needed. In Figure 2, we propose a decision tree to help guide the appropriate use of hyperventilation in the diagnostic and management pathway of childhood absence epilepsy. As noted in Figure 2, when appropriately performed in-clinic hyperventilation does not trigger an absence seizure or is inconclusive, alternative diagnoses should be considered such as hyperventilation-induced high-amplitude rhythmic slowing, focal seizures with alteration of awareness, and nonepileptic paroxysmal events including daydreaming, ocular tics, and inattention. Although hyperventilation triggers absence seizures in >90% of patients with drug-naive absence epilepsy, this is not a perfect screening tool. As such, comprehensive diagnostic workup including EEG with activation procedures and pediatric neurology consultation should be strongly considered despite no or inconclusive response to in-clinic hyperventilation if school-aged children have continued brief but frequent events of staring and behavioral unresponsiveness.

From a clinical management perspective, more evidence is necessary to standardize the use of hyperventilation to assess treatment effectiveness more comprehensively beyond only determining if seizures are present or not. Standardizing and quantifying the effort of hyperventilation may allow for greater determination if different sessions of hyperventilation can be compared. Absence seizures are known to have a circadian quality, with early studies showing that seizures are more frequent in the mornings after arousal, after lunch, and during monotonous situations.[45] The circadian effect on hyperventilation-provoked seizures is currently unknown.

Children with absence epilepsy have a significant rate of antiseizure medication failure.[15] Although EEG has not been shown to predict who will respond to antiseizure medications, perhaps early response to hyperventilation can be trialed to determine which patients are likely to respond to a particular antiseizure medication. This would allow clinicians to rapidly titrate medications and identify the nonresponders sooner, transitioning them to a higher level of care as it is understood that the worst psychosocial outcomes occur in children with ongoing seizure activity.[9,46]

Conclusions

Hyperventilation is an economical and informative tool that, if more widely used and studied, has the potential to decrease costs and improve outcomes in patients with childhood absence epilepsy. Although hyperventilation is commonly employed by neurologists as a binary tool for detecting ongoing seizures in patients with childhood absence epilepsy, its utilization by pediatricians could enhance the efficiency of referrals. Furthermore, incorporating hyperventilation in child neurology clinic follow-ups could provide additional insights for managing antiseizure medications in patients with childhood absence epilepsy following medication failure and prior to antiseizure medication withdrawal.

Author Contributions

RK conceived the idea for the topical review. CKR and RK conducted the literature search and analyzed relevant data to be included in the review. CKR wrote the initial draft of the manuscript with input and revisions from RK. Both authors reviewed and approved the final version of the manuscript.

Declaration of Conflicting Interests

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