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Editorial

Hyperventilation-induced EEG slowing with altered awareness: Non-epileptic, epileptic or both?

Hyperventilation (HV) is one of the oldest methods of activation used during an EEG. Indeed, the seizure-inducing effects of HV were known even before the discovery of EEG itself. Hans Berger, the pioneer in recording EEG in humans, was also the first to describe the effects of hyperventilation on EEG. Subsequently, a number of studies provided more detailed information and established the value of HV in provoking epileptiform activity on EEG and clinical seizures, particularly in patients who have generalized epilepsy with typical absence (TA) seizures.

HV also evokes physiological EEG responses that manifest as a buildup of theta and delta activity, with differences related to age, effort, posture and blood sugar. Children tend to have a more robust response and the slowing is usually most prominent in the occipital region, whereas adults have less pronounced effects and the delta activity is often frontally predominant. The term hyperventilation-induced high amplitude rhythmic slowing (HIHARS) has been used when the EEG shows >100 microvolts, 2.5–5 Hz, generalized rhythmic slowing lasting ≥3 s (Epstein et al., 1994; Lum et al., 2002).

The epileptiform discharges induced by HV may or may not be associated with impairment of consciousness, which can be assessed using a variety of simple (word recall or response to simple commands) or sophisticated (e.g. mathematical tasks, subject clicking a button in response to an auditory signal by the technologist) methods. The physiological EEG slowing is usually not associated with a change in consciousness, but this may occur in some patients. Reduced consciousness with HV was initially reported by Davis and Davis in 1939 (Davis and Davis, 1939), and hyperventilation-induced high-amplitude rhythmic slowing with altered awareness (HIHARSAA) has been increasingly recognized and studied in the last four decades.

The prevalence of HIHARSAA in the general population is not known. Most articles on this topic have been retrospective studies of small numbers of children, but in a recent prospective study, Nasreddine et al. (2020) observed HIHARS in 34% of 5–15 year old children, with altered awareness (AA) in 77% of this group. These authors also confirmed that AA was related to EEG slowing. In addition, they noted that a longer duration of HIHARS was associated with a greater likelihood of developing HIHARSAA and that patients ceased to perform HV when they had AA. AA generally begins several seconds after the onset of HIHARS and lasts for a mean of 10–15 s, but whether patients regain consciousness with, before or after the end of HIHARS is not clear (Epstein et al., 1994; Lum et al., 2002; Barker et al., 2012). We did not come across any studies in adults, and it is possible that due to a lower incidence of EEG slowing with HV, HIHARSAA is not observed as often in older age groups as it is in children.

HIHARSAA has been variably interpreted as being non-epileptic or epileptic in nature. Several attempts have been made to identify clinical features that can distinguish between HIHARSAA and seizures, such as staring, automatisms, fidgeting and yawning (Epstein et al., 1994; Lum et al., 2002; Barker et al., 2012; Nasreddine et al., 2020), but the consensus appears to be that EEG is the most reliable way to distinguish between this phenomenon and TA seizures. Currently, most investigators consider HIHARSAA to be non-epileptic in nature and do not recommend anti-seizure medicines, as most patients have isolated spells of altered awareness without interictal epileptiform discharges or other abnormalities in the baseline EEG (Epstein et al., 1994; Lum et al., 2002; Barker et al., 2012). HIHARSAA can also occur in people with epilepsy, as demonstrated by a history of clinical seizures and/or interictal epileptiform discharges, but it is unclear if the HIHARSAA itself is epileptic even in this situation.

The literature has generally focused on the comparison of groups of children with HIHARSAA with others who have TA seizures, but in this issue of *Clinical Neurophysiology Practice*, Mattozzi et al. (2021) describe 5 children with both HIHARSAA and TA seizures. However, they found that both the phenomena did not occur at the same age or time in these patients. TA seizures occurred first, with a mean age at diagnosis of 4.6 years, followed by HIHARSAA diagnosed at 8.0 years. HIHARSAA developed only after TA seizures were controlled with anti-seizure medicines.

Although other authors have noted a history of not only TA but also a variety of other seizure types including atypical absence, myoclonic, generalized tonic-clonic, focal motor and febrile seizures in patients with HIHARSAA (Lum et al, 2002; Barker et al, 2012), this is the first study describing a sequential temporal relationship between TA seizures and HIHARSAA. It is unclear if the evolution from TA seizures to HIHARSAA reflects a developmental process in terms of brain maturation, an effect of anti-seizure medicines, or if it suggests that HIHARSAA is somewhere on the ictal-interictal continuum in these children. The small number of patients studied and the short duration of follow-up make it difficult for the authors to address these possibilities. It would be interesting to continue to follow these patients further to see if and when HIHARSAA ultimately disappears. In other studies of HIHARSAA, spontaneous resolution was seen after a variable period with or without anti-seizure medicines (Lum et al., 2002; Barker et al., 2012).

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Another interesting observation made by Mattozzi et al. (2021) is that the two phenomena did not occur at the same time i.e. children either had TA or HIHARSAA but not both. This could indicate that TA seizures suppress or preclude HIHARSAA, as the authors suggest, or that HIHARSAA represents an evolution from TA seizures.

The exact mechanism of HIHARS has not been clearly established, but likely involves hypocapnic cerebral vasoconstriction, the direct effect of hypocapnia on nerve cells, and some effect of cerebral alkalosis (Yamatani et al., 1994). Most authors believe that hypocapnia, either by leading to vasoconstriction and subsequent cerebral ischemic hypoxia (Davis and Wallace, 1942) or from its direct effect on the brainstem (Patel and Maulsby, 1987) or thalamocortical projections (Sherwin, 1984), is the most important factor (Fisch and So, 2003).

The contribution of each of these mechanisms to and the specific pathways involved in HIHARSAA and TA seizures remain uncertain. Mattozzi et al. (2021) suggest a common mechanism, speculating that TA and HIHARSAA are both genetically determined and age-dependent and occur due to an underlying dysfunction of the same cortico-thalamo-cortical network. They emphasize the role of alkalosis in inducing absence seizures in experimental settings in animals and humans, and its effects on upregulating excitatory neurotransmitter receptors and ion channels. They also comment on the findings from a murine model where increased NMDA-receptor excitatory activity enhanced thalamic oscillatory rhythms without inducing epileptic activity (Lacey et al., 2012), and suggest this may be significant in the origin of HIHARSAA. Their ideas are interesting and provocative, but would have been strengthened with objective supportive evidence beyond the clinical findings from their small sample of patients. As they acknowledge, considerable additional work with a larger sample of patients is necessary.

Conversely, some clinical observations suggest that the mechanisms of HIHARSAA and TA seizures may be different. Niedermeyer (1972) reported that intravenous diazepam administration prevented epileptiform discharges induced by HV but not slowing. Also, altered awareness occurs much earlier after HV in TA (shortly after starting HV and development of 3 Hz SWC) than with HIHARSAA (>2 min after HV, and >1 min after onset of slowing) (Lum et al., 2002). Mattozzi et al. (2021) also describe similar findings. Further, in their subjects, TA and HIHARSAA did not occur at the same time, and the mean age of onset was later for HIHARSAA. Although alkalosis may be important, it is not clear to us how their clinical observations support their assertion that it is "the core of the HIHARSAA biochemical mechanism." Blood gas studies along with HV, as performed in some early studies, could be helpful to assess acid-base changes. The role of hypocapnia, if any, in the genesis of both HIHARSAA and TA seizures also needs to be studied.

In conclusion, HIHARSAA is an intriguing phenomenon that has been reported in relatively few children so far, but may be more common than initially thought. Its identification may depend on rigorous performance of HV, and subtle forms may go unnoticed if the level of consciousness is not observed or assessed. With increasing awareness among clinicians, larger studies, and greater effort and more detailed testing of consciousness during HV, we will obtain a better understanding of its true prevalence and mechanisms. Although HIHARSAA is likely non-epileptic in nature, its clinical and pathophysiological relationship to epilepsy also needs to be clarified further.

Conflicts of interest and funding sources

None.

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