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Case report

Occurrence of hyperventilation-induced high amplitude rhythmic slowing with altered awareness after successful treatment of typical absence seizures and a network hypothesis

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ABSTRACT

Background: Typical absence seizures (AS) are epileptic phenomena typically appearing in children 4–15 years of age and can be elicited by hyperventilation (HV). Hyperventilation-induced high-amplitude rhythmic slowing (HIHARS) represents a paraphysiological response during HV and may manifest with alteration of awareness (HIHARSAA). To date, HIHARSAA has mostly been described in patients without epilepsy.
Aim: To describe five patients with treatment-responsive typical AS who, after becoming seizure free, presented with HIHARSAA.
Methods: By using video-electroencephalographic recording (Video-EEG), we describe differential clinical characteristics and ictal electrophysiological patterns of both typical AS and HIHARSAA.
Results: We demonstrate that when HIHARSAA occurs in patients with typical AS there is a temporal window between the two phenomena. This suggests that the presence of typical AS precludes the appearance of HIHARSAA.
Conclusions: We hypothesize that alkalosis and dysfunction of the same neural network are involved in both typical AS and HIHARSAA and that their distinct electroclinic manifestations are due to the involvement of different ion channels.
Significance: A better understanding of the characteristics of typical AS and HIHARSAA and of the role of alkalosis in both, can help avoiding misdiagnosis and identifying more suitable therapies for typical AS.

1. Introduction

Typical absence seizures (AS) are epileptic generalized non-convulsive seizures characterized by staring, arrest of activity and transient loss of awareness (Hughes, 2009). Typical AS are, sometimes, accompanied by simple (lip licking) or complex automatisms (blinking, rubbing hands or touching the face) (Kessler et al., 2017). Typical AS commonly occur in children aged 4–15 years, with an estimated annual incidence of 7 new cases per 100,000 population (Sidenvall et al., 1993; Lum et al., 2002) and a prevalence range from 0.4% to 0.7% cases per 100,000 population (Olsson, 1988; Loiseau et al., 1990; Jallon and Latour, 2005). The Epileptic Syndromes classified by the International League Against Epilepsy (ILAE) as Idiopathic Generalized Epilepsies (IGE) (Scheffer et al., 2017), i.e. Childhood Absence Epilepsy, Myoclonic Absence Epilepsy and Juvenile Absence Epilepsy, are all featured by typical AS.

The ictal electroencephalographic recording (ictal EEG) consists in regular 3 Hz (range 2.5–3.5 Hz) generalized spike-waves complexes (SWc) with abrupt on- and offset, and an average duration of 10.2 s (s) (Hughes, 2009), that are evoked by voluntary hyperventilation (HV) in over 90% of patients with typical AS (Hughes, 2009). In typical AS, the beginning of clinical symptom (loss of awareness) is synchronous with the appearance of the first SWc on the ictal EEG; usually, the 3 Hz generalized SWc appears with an average latency of 75 s from the beginning of HV.

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In some epileptic and non-epileptic individuals, HV can also elicit high-amplitude, slow and rhythmic non epileptic brain activity (Kessler et al., 2017), a phenomenon known as HV-Induced High-Amplitude Rhythmic Slowing (HIHARS). HIHARS occurs in children aged 4–14 years and spontaneously disappears around puberty; its prevalence in the general population is mostly unknown (Scheffer et al., 2017). During episodes of HIHARS, specific automatisms may appear (e.g., smiling, eyelid myoclonus, yawning and mild motor restlessness), sometimes accompanied by clinical alteration of awareness (HIHARSAA) (Barker et al., 2012). The clinical manifestations always resolve spontaneously. Although it may clinically mimic AS, HIHARSAA is not considered an electroclinical epileptic phenomenon. The ictal EEG is characterized by generalized 2.5–5 Hz slow-wave complexes with an average voltage of 357 microvolts (μV) (range 100–900 μV) and an average duration of 14 s (range 3–36) (Lum et al., 2002). The first slow-wave complex appears around 73 s (range 15–150) after beginning HV. Evidence of alteration of awareness in HIHARS tends to appear around after 139 s (range 37–230) (Lum et al., 2002). The inter-ictal EEG background activity is generally normal both in typical AS and in HIHARSAA (Kessler et al., 2017).

HIHARSAA has been reported both in epileptic and non-epileptic subjects. In those with epilepsy, HIHARSAA is associated with additional epileptic features and/or inter-ictal epileptiform abnormalities. In this paper, we describe the occurrence of HIHARSAA in patients with typical AS and outline their temporal succession.

2. Methods

Children with EEG and clinical features of typical AS and HIHARSAA were identified from the database of the Child Neuropsychiatric Unit, University of Sassari and the Pediatric Neurology Unit of Tor Vergata, University of Rome and were recruited for the study. Informed consent was obtained from the parents of all patients.

All patients underwent video-EEG recording: disc electrodes were applied to the scalp according to the ten-twenty electrode placement system.

The EEG criteria used to define typical AS were: amplitude of 100–900 μV and generalized regular 3 Hz SWc, while for HIHARSAA were: amplitude of 100–900 μV, and generalized 2.5–4 Hz rhythmic slow-waves activity associated with loss of awareness. Loss of awareness was defined as "being unaware of oneself and one's environment throughout the seizure" (Scheffer et al., 2017).

Loss of awareness was elicited with HV using a modification of previously published procedures (Barker et al., 2012). Prior to HV, each child underwent verbal skills test through recognition and denomination of common objects or by answering questions. Children were asked to repeat a sequence of 3 known words and told to remember the words and words sequence for later. HV was then achieved through repetitive forceful blowing. In between, the child had to count out loud the number of his own breaths, starting with the number 1 after the first blow, 2 after the second blow, et cetera for a minimum of 180 s to a maximum of 300 s. The length of HV was dependent upon the quality of performance, with longer times needed for patients who became distracted during the test. For younger children, HV was achieved by blowing on a pinwheel for 180–300 s, also based on performance. Clinical loss of awareness was confirmed by the interruption of repetitive forceful blowing and the inability of the child to repeat the 3 words in the correct sequence.

In patients with suspected absence seizures, we performed an ictal Video-EEG (time 0), necessary for the diagnosis of typical AS (Glauser et al., 2010).

After the first diagnostic Video-EEG, we introduced the most appropriate anti-epileptic drug (AED) among the first line treatments (Ethosuximide, Valproate or Lamotrigine) (Buchhalter, 2011). Good response to AEDs was defined as the disappearance of clinical seizures, with normalization of Video-EEG, 2 months after treatment initiation, and with no adverse events. In AED responders, Video-EEG follow up was scheduled every 6 months for 2 years, when a gradual drug tapering started (¼ of daily intake every two months), until complete AED discontinuation in the absence of seizures relapses. Transient add-on treatment was restricted to refractory patients up to the completion of the transition to a second effective AED; In some other non-responder patients, a direct switching to an alternative AED was preferred.

Exclusion criteria were Epileptic Syndromes other than Childhood Absence Epilepsy, Myoclonic Absence Epilepsy and Juvenile Absence Epilepsy. Other exclusion criteria were the presence of potentially causative genetic abnormalities and the diagnosis of intellectual disability or other neurodevelopment disorders.

2.1. Statistical analysis

Mean and relative range, as appropriate, were used to analyse the demographic and clinical features of the enrolled patients.

3. Results

Six AS patients exhibiting HIHARSAA were identified (five females; mean age 12.5 years, range 6.3–18.8). Of these, one was ruled out owing to the presence of a Xp22 duplication with intellectual disability. Of the 5 remaining children four were females (mean age 11.5 years, range 6.3–17.5; details on Table 1).

The mean age at diagnosis of typical AS was 4.6 years (range 2.9–5.7). Video-EEG showed both spontaneous and HV-induced typical generalized SWc (3 Hz, 100–900 μV) in all patients, associated with automatisms, staring and loss of awareness.

The mean age at diagnosis of HIHARSAA was 8.0 years (range 4.4–11.5). The generalized slow-waves had a frequency of 2–3 Hz, an amplitude range of 100–900 μV and were associated with restlessness of limbs, fidgeting, staring and loss of awareness, often with yawning and oral automatisms or blinking (Table 1).

In all patients, the presenting symptom of AS was staring spells (Scheffer et al., 2017). Mean follow-up duration was 6.5 years (range 7 months-11.5 years) and, in all cases, AS successfully responded to AEDs (details on Table 1).

In AS cases the mean latency between HV and the onset of SWc was 90 s (range: 60–110); the average ictal sequences length was 14.4 s (range: 12–23). Regular generalized 3-Hz SWc were recorded in all patients and the amplitude was higher than 100 μV. On ictal EEG, alteration of awareness synchronous with the appearance of the first SWc were detectable (Fig. 1).

As for HIHARSAA, it firstly occurred after an average 2.7 years (range: 0–6.5) following the successful treatment of typical AS; at HIHARSAA onset, 4 patients were below the age 10, and one was 11.5-year-old. The ictal video-EEG recording showed generalized sequences of 2–3 Hz slow-waves with a latency between 60 and 270 s (mean 122) after HV. Loss of awareness appeared after the first generalized sequence of slow-waves with a varying latency between 1 and 120 s (mean 55.8) and lasted for a mean 6.6 s (range 3–13). The average length of the ictal generalized slow-wave sequences was 31.4 s (range 10–60). The mean amplitude was 400 μV (range ~ 100–~900 μV) (Fig. 1). Inter-ictal EEGs were normal in all patients. The frequency of the paroxysms within the ictal generalized sequences ranged between 2 and 3 Hz in HIHARSAA and around 3 Hz in the typical AS (Table 1).

Table 1
Patients' demographic and clinical characteristics.

Patient	#1	#2	#3	#4	#5
Gender	F	F	M	F	F
Familiarity	CAE	NO	NO	JME; CAE	NO
Typical AS Onset Age (y/o)	2.9	4,8	5	4.9	5.7
Typical AS Latency from HV (s)	60	60	60	100	120
Typical AS Duration (s)	12	23	12	13	12
SWc Frequency Range (Hz)	3	3	3	3	3
SWc Voltage Range	100–900	100–900	100–900	100–900	100–900
Typical AS Daily Frequency	Multidaily	Multidaily	Multidaily	Multidaily	Multidaily
Anti Epileptic Drugs (AEDs)	VPA	VPA	VPA + LTG	VPA	VPA
Typical AS Control Time Since Drug Therapy Starting (y/o)	0,1	0,2	2,5	0,25	1
AEDs Therapy Suspension Age (y/o)	7,9	7,8	In Progress	In Progress	In Progress
HIHARSAA Onset Age (y/o)	4,4	9,1	11,5	5	7.1
HIHARS Latency from HV (s)	90	60	60	130	270
AA Latency Since HIHARS Starting (s)	60	120	60	38	1
AA Duration (s)	3	5	4	13	8
Max HIHARSAA Sequence Duration (s)	60	10	60	17	
HIHARSAA Frequency Range (Hz)	2–3	2–3	2–3	2–3	2–3
HIHARSAA Voltage Range	100–900	100–900	100–900	100–900	100–900
Comorbidities	None	None	Complex TICs; ADHD	None	None
Follow-UP (yrs)	11,5	6,5	11,5	0,5	2.5

Abbreviations: HV: Hyperventilation; Typical AS: Typical Absence Seizure; HIHARS Hyperventilation-Induced High Amplitude Rhythmic Slowing; HIHARSAA: Hyperventilation-Induced High Amplitude Rhythmic Slowing with Altered Awareness; SWc: Spike-Wave complex; AEDs: Anti-Epileptic Drugs; JME: Juvenile Myoclonic Epilepsy; CAE: Childhood Absence Epilepsy; VPA: Valproic Acid; LTG: Lamotrigine; ADHD: Attention-Deficit/Hyperactivity Disorder; Hz: Hertz; s: seconds; y/o: years old.

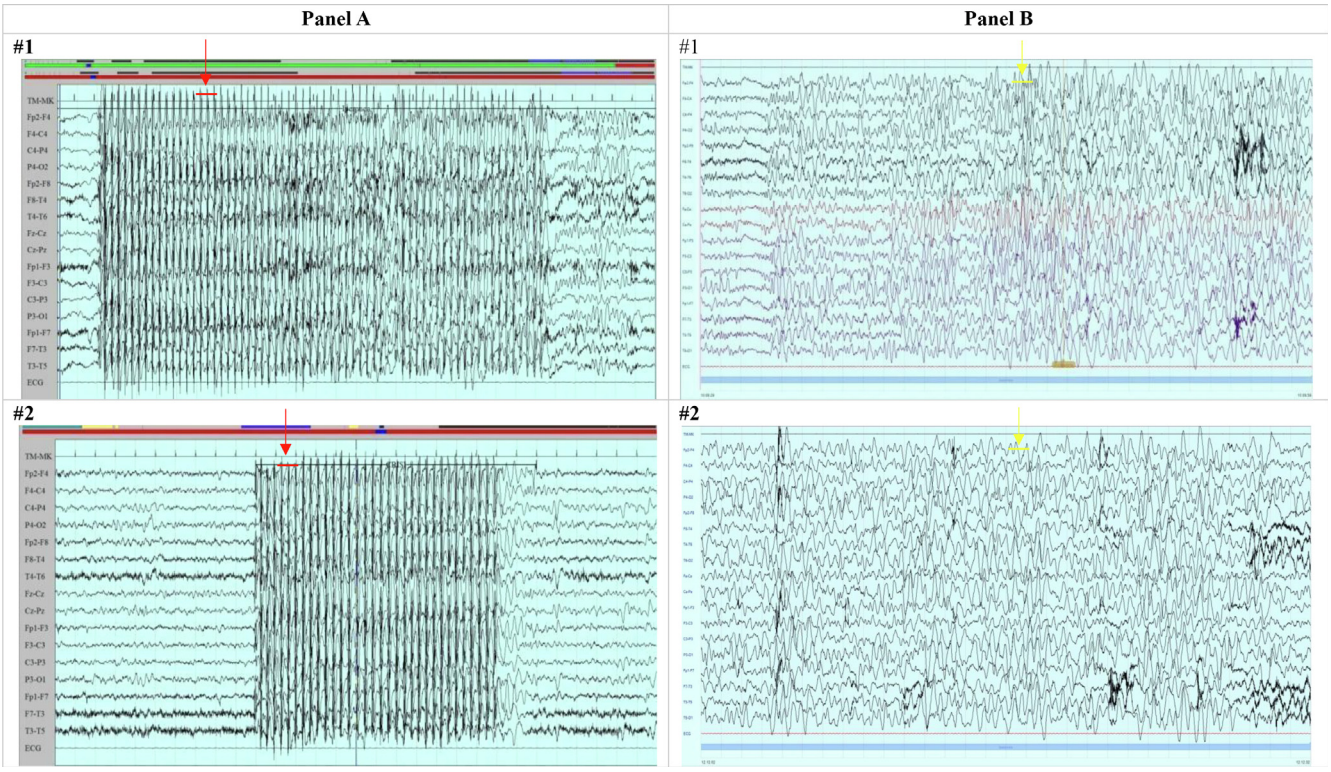

Fig. 1. The images show ictal electroencephalograms demonstrating typical AS and HIHARSAA patterns. Panel A shows the typical AS patterns of patients 1 and 2 respectively. Panel B shows the respective HIHARSAA patterns of patients 1 and 2. The red lines and yellow ones show the similar frequencies, in both phenomena. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Our study confirms that the frequency of paroxysms, within the ictal generalized sequences, is similar between HIHARSAA and typical AS and that both phenomena are elicited by HV (Epstein et al., 1994; Barker et al., 2012). However, we found HIHARSAA to occur in AS patients with a variable temporal window after their recovery from AS seizures. We may suggest that when it is clinically active (i.e. not yet controlled by AEDs or before their age-related disappearance), typical AS may limit or preclude the appearance of HIHARSAA.

Previous studies have demonstrated a role of the cortico-thalamic-cortical network in typical AS appearance, in which direct and indirect efferent projections from cortical pyramidal neurons to the thalamus, modulate the intrinsic oscillatory rhythm of the thalamic activity (McCormick and Huguenard, 1992; Huguenard and

McCormick, 2007). In a murine model, the selective ablation of the P/Q-type voltage gated calcium channels (VGCCs) of pyramidal neurons resulted in dysfunction of the cortico-thalamic efferent projections. This determined a dysfunction of the cortico-thalamic-cortical network for the appearance of generalized SWc (5–7 Hz at the thalamic level) associated with behavioral arrest, that could respond to ethosuximide (Huguenard and McCormick, 2007).

Although the role of HV in typical AS activation has not been clarified (Bomben et al., 2016), experimentally HV-induced alkalosis has been demonstrated to be a trigger of typical AS (Schuchmann et al., 2009; Lu et al., 2012; Salvati and Beenhakker, 2019) and humans (Yang et al., 2014). In murine models, alkalosis resulted in up-regulation of VGCCs, N-methyl-D-aspartate (NMDA)-type glutamate receptors as well as α-amino-3-hydroxy-5-methyl-4-isoxazo lepropionic acid (AMPA) receptors in cortical pyramidal neurons (Schuchmann et al., 2009; Lu et al., 2012). Concomitantly, a down-regulation of the same channels in the inhibitory cortical neurons was reported resulting in a generalised cortical hyperexcitability state. This process, which has not been exhaustively unfolded yet, suggests that base-sensitive ion channels may exist which are presumably similar to the already known acid-sensitive ion channels (ASICs) (Schuchmann et al., 2009).

Our cases, as well as those previously reported (Barker et al., 2012), confirm that in some individuals HV can cause HIHARSAA and suggest that alkalosis is the core of HIHARSAA-associated biochemical mechanism (Schuchmann et al., 2009; Lu et al., 2012; Yang et al., 2014; Salvati and Beenhakker, 2019).

In our study, typical AS and HIHARSAA occurred in a similar age range (Olsson, 1988; Loiseau et al., 1990; Sidenvall et al., 1993; Epstein et al., 1994; Lum et al., 2002; Jallon and Latour, 2005; Barker et al., 2012; Scheffer et al., 2017). Thus, we may hypothesize that HIHARSAA and typical AS are different phenotypes of the same genetically susceptible network to dysfunctioning, and that different age-dependent genetic mechanisms can modulate ion channels of the cortico-thalamic-cortical network resulting in non-epileptic (HIHARSAA) or epileptic (typical AS) phenotypes.

Results from a murine model study may support this idea as the increased NMDA-receptor excitatory activity was able to enhance oscillations of thalamic rhythm without inducing epileptic activity (Lacey et al., 2012). Phenomenologically, this may suggest the involvement of metabotropic receptors related channels, in the origin of HIHARSAA.

A larger patients' sample is desirable to confirm both the causal relationship between alkalosis and HIHARSAA elicitation and the temporal difference of onset between typical AS and HIHARSAA. Moreover, additional studies, aiming at identifying alternative or concomitant therapies for typical AS, are also required. Video-EEG recording with HV procedure is the gold-standard to differentiate these two phenomena and a correct diagnosis is crucial to appropriately treat typical AS and avoid overtreatment of the non-epileptic HIHARSAA.

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Conflicts of interest statement

None of the authors have potential conflicts of interest to be disclosed.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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