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BRIEF COMMUNICATION

Hyperventilation-induced focal seizures in adults: think autoimmune encephalitis

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Abstract

Case reports have described rare patients with autoimmune encephalitis in whom focal seizures could be reliably provoked by hyperventilation. With the hypothesis that this phenomenon may have diagnostic significance, all cases of hyperventilation-induced focal seizures identified during ~10,000 consecutive routine electroencephalography (EEG) studies were reviewed, and corresponding diagnoses established. Seven EEG recordings, in six patients, contained focal hyperventilation-induced seizures, each of temporal lobe onset. All patients were diagnosed with autoimmune encephalitis, in two cases after EEG; five had voltage-gated potassium channel complex autoantibodies. Although rare, a hyperventilation-induced focal seizure during EEG in an adult should raise concern for autoimmune encephalitis.

Introduction

Hyperventilation-induced focal seizures during electroencephalography (EEG) in adults are rare, described to occur in less than 0.5% of individuals referred for clinical EEG assessment.[1–3] In recent years, an unusual sensitivity to hyperventilation has been described in a small number of patients diagnosed with leucine-rich glioma-inactivated 1 (LGI1) autoimmune encephalitis, in whom focal temporal lobe seizures could be reliably provoked by hyperventilation.[4,5]

One of these patients, first reported by Steriade et al.,[4] was discovered at our hospital 9 years ago. In that case, referred for EEG assessment because of a 1-week history of altered behavior and a question of possible seizures, the search for LGI1 autoantibodies was precipitated by the observation of frequent subclinical temporal lobe seizures in the absence of interictal spikes, an EEG finding we had earlier noted to be associated with anti-LGI1 encephalitis.[6] In that patient, each of three epochs of hyperventilation, performed during two routine EEG recordings obtained 1 week apart, induced a left temporal lobe seizure.[4] Four years later, a different patient, diagnosed and treated for anti-LGI1 encephalitis 18 months earlier, was referred for EEG because of a question of possible focal seizures without loss of awareness. During an otherwise normal EEG recording, hyperventilation triggered one of the patient's typical pilomotor seizures, localized to the right temporal lobe. Subsequent continuous video-EEG monitoring confirmed that hyperventilation could reliably provoke the patient's seizures, which arose independently from either temporal region; overbreathing into a paper bag had no activating effect.[5]

Since the first description of these cases,[4] working with the clinical hypothesis that this rare EEG phenomenon may have an etiologically specific diagnostic significance with important treatment implications, all cases of hyperventilation-induced focal seizures reported during routine EEG at our institution have been reviewed, and the identified patients' corresponding clinical diagnoses established. Over the course of 9 years, the rarity of the EEG phenomenon was confirmed, as was the idea that the occurrence of a focal seizure provoked by hyperventilation during EEG in an adult should, in and of itself, raise the diagnostic possibility of autoimmune encephalitis.

Methods

The reports of all routine out-patient EEG studies performed in the Clinical Neurophysiology Department of the Toronto Western Hospital between January 2013 and January 2022 were reviewed by the author (laboratory director) to identify recordings that reported the occurrence of a focal seizure, subclinical or clinical, during or

directly following (within 90 sec) hyperventilation. All studies were performed in accordance with the laboratory's standard clinical protocol, and routinely included one 3-min epoch of hyperventilation, except in cases where individuals were unable or unwilling to perform the activation procedure, or if hyperventilation was considered medically contraindicated. If an initial epoch of hyperventilation induced an abnormality, a second round of hyperventilation was occasionally performed later during the same recording, at the discretion of the EEG technologist.

In total, 13,064 routine EEG recordings were acquired over the 9-year study period, 9919 of which contained hyperventilation. The most common relative contraindications to hyperventilation were heart disease, asthma or other respiratory problems, brain tumor or hemorrhage, age above 75 years, and pregnancy. The vast majority of referrals (~90%) specified a question of possible seizures or described a history of epilepsy. The study population was comprised entirely of adults. In-hospital video-EEG or continuous EEG recordings acquired in the epilepsy monitoring unit (EMU) or intensive care unit settings were not included.

Institutional research ethics board approval was obtained for the retrospective and prospective study of EEG in antibody-mediated encephalitis.

Results

From the 9919 EEG reports of studies including hyperventilation, seven (0.07%) were identified that contained descriptions of one or more focal seizures occurring during or shortly after hyperventilation. In total, eight hyperventilation-induced seizures were recorded in six different patients (five male), ranging in age from 43 to 71 years. All of the seizures were of unilateral temporal lobe onset; three propagated to the contralateral temporal lobe during seizure evolution (Fig. 1). Six of the eight

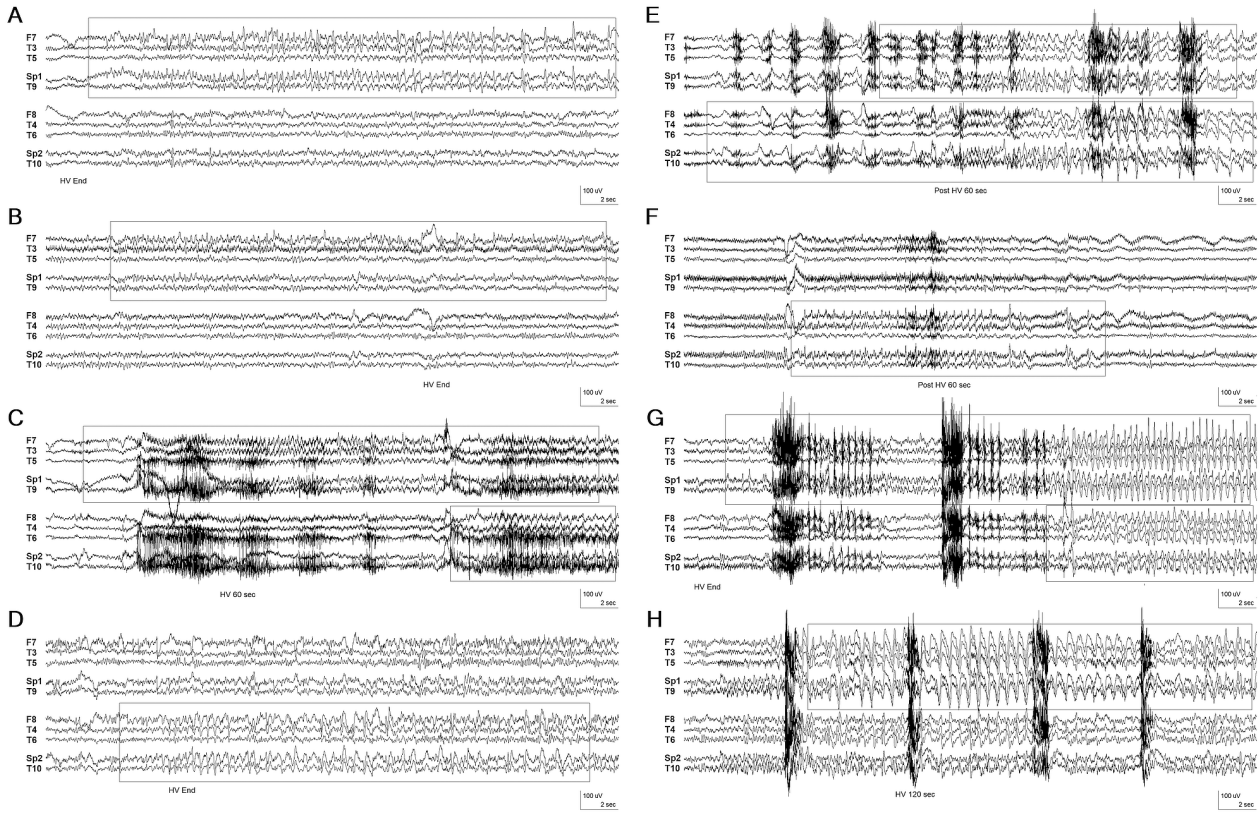

Figure 1. Hyperventilation-induced focal seizures. (A) Left temporal seizure, subclinical, patient 1 (seizure shown in Steriade et al.[4]). (B) Same EEG recording, left temporal subclinical seizure during second epoch of hyperventilation, patient 1. (C) EEG 1 week later, patient 1, left temporal seizure with propagation to right temporal lobe, subclinical. (D) Right temporal seizure, clinical (subjective sensation of chills), patient 2. (E) Right temporal seizure with rapid propagation to left temporal lobe, subclinical, patient 3. (F) Right temporal seizure, subclinical, patient 4. (G) Left temporal seizure with propagation to right temporal lobe, clinical (impaired awareness, postictal aphasia), patient 5. (H) Left temporal seizure, subclinical, patient 6. Rhythmic ictal discharges (seizures) highlighted by rectangular outlines. HV = hyperventilation. Digital filter bandpass = 1–30 Hz. Common average reference.

seizures were subclinical. There was one pilomotor seizure without impaired awareness, and one clinical event with ictal impaired awareness and postictal aphasia. Additional unprovoked subclinical temporal lobe seizures occurred in two of the EEG recordings (three seizures in two patients; Table 1).

No interictal epileptiform discharges occurred during any of the identified EEG studies, and six of the seven recordings were normal apart from the ictal electrographic events. Only one study showed interictal abnormalities in the form of intermittent polymorphic theta and delta frequency slow wave activity recorded independently over both temporal regions.

All six patients were ultimately diagnosed with autoimmune encephalitis. As the prevalence of autoimmune epilepsy is estimated at less than 10% of all adult epilepsies,[7] the observed association between hyperventilation-induced focal EEG seizures and a diagnosis of autoimmune encephalitis is highly unlikely to be due to chance ($p < 0.001$, Yates's chi-square test). The initial clinical presentation in all cases was the subacute onset of memory difficulties and behavioral changes. In two of the six patients, the findings on routine EEG led to the investigation for autoimmune encephalitis, which had not been suspected in either case (the patients' referring physicians were contacted by the EEG laboratory to alert them to the possible diagnosis). In these two patients the EEG studies were acquired within a month of illness onset. In the other four patients (all with hyponatremia at illness onset) a diagnosis of autoimmune encephalitis had been made months to years before the EEG studies were obtained at our hospital (Table 1).

Five of the six patients were found serologically to have autoantibodies directed toward proteins associated with the voltage-gated potassium channel (VGKC) complex: LGI1 in patients 1 and 2 (our two patients previously described[4,5]); LGI1 in patients 4 and 6; and contactin-associated protein-like 2 (CASPR2) in patient 5. In

Table 1. Routine EEG recordings with hyperventilation-induced focal seizures.

Patient (Age, y/Sex)	1 (61/M)	1 (61/M)	2 (35/F)	3 (66/M)	4 (49/M)	5 (71/M)	6 (43/M)
HV-induced seizures	2 L T subclinical	1 L → R T subclinical	1 R T clinical	1 R → L T subclinical	1 R T subclinical	1 L → R T clinical	1 L T subclinical
Spontaneous seizures	1 R T subclinical	0	0	2 L T subclinical	0	0	0
Interictal epileptiform discharges	None	None	None	None	None	None	None
Other EEG abnormalities	None	None	None	B T int theta/delta	None	None	None
Time from illness onset to EEG	1 week	2 weeks	18 months	4 years	10 months	1 month	9 months
Diagnosis before EEG	No	No	AE[a]	AE[b]	AE[a]	No	AE[a]
Diagnosis after EEG	AE[a]		AE[a]	AE[b]	AE[a]	AE[c]	AE[a]
Hyponatremia at illness onset	No		Yes[d]	Yes[e]	Yes[e]	No	Yes[e]
Anti-seizure medication at time of EEG	None	None	LVT 1500bid, CLB 10qhs	LVT 1500bid	LVT 500bid	None	LVT 1250bid
Immunotherapy before EEG	No	No	Yes[f,g,h,i,j]	Yes[f,g,h,k]	Yes[f,g,h]	No	Yes[f,g,h]
Immunotherapy at time of EEG	No	No	No	No	No	No	Yes[h]
Immunotherapy after EEG	Yes[h]		Yes[g]	Yes[f,g,k]	Yes[f,g,j]	Yes[f,h]	Yes[h,j]

Abbreviations: AE, autoimmune encephalitis; B, bilateral; CLB, clobazam; HV, hyperventilation; int, intermittent; L, left; LVT, levetiracetam; R, right; T, temporal lobe.

[a]Leucine-rich glioma-inactivated 1 (LGI1) autoantibodies detected.

[b]Autoimmune antineuronal antibodies not tested for at time of initial diagnosis; presentation fulfilled clinical diagnostic criteria for autoimmune limbic encephalitis.[8] Immunotherapy-responsive relapsing course prior to EEG referral. Autoimmune encephalitis panel negative (serum and cerebrospinal fluid) when tested 6 years after illness onset (under treatment with mycophenolate mofetil).

[c]Contactin-associated protein-like 2 (CASPR2) autoantibodies detected. Elevated serum levels of thyroid peroxidase (3440 IU/mL) and antithyroglobulin (450 IU/mL) antibodies.

[d]126–130 mEq/L.

[e]131–134 mEq/L.

[f]Intravenous methylprednisolone.

[g]Intravenous immunoglobulin.

[h]Prednisone.

[i]Plasmapheresis.

[j]Rituximab.

[k]Mycophenolate mofetil.

patient 3, testing for neural autoantibodies was not performed at the time of acute illness, 4 years prior to referral for EEG at our institution, but the patient had been treated successfully with immunosuppression for a clinical diagnosis of autoimmune limbic encephalitis[8] at the time, and then re-treated for two relapses (recurrence of behavioral abnormalities and memory difficulties) that occurred after discontinuation of immunotherapy (prednisone and/or mycophenolate mofetil), prior to the routine EEG acquired at our hospital.

All patients received immunotherapy (Table 1), with significant clinical benefit in terms of memory and behavior. Magnetic resonance imaging showed mesial temporal lobe abnormalities at some point in the course of each patient's illness: mild hyperintensities on fluid-attenuated inversion recovery sequences in five cases, and bilateral mesial temporal sclerosis in patient 3. Four patients (patients 1, 2, 3, and 6) developed clinical pilomotor seizures. Only patient 6 had a history of typical anti-LGI1 encephalitis motor spasms (faciobrachial dystonic seizures),[6,9,10] which resolved with immunotherapy prior to EEG.

Patients 2, 3, and 4 were later investigated as inpatients in the EMU, and the sensitivity to hyperventilation was confirmed in each case.

Anti-seizure medication treatment commenced with levetiracetam in all cases (started in patients 1 and 5 after the routine EEG studies) and was singularly ineffective. In contrast, phenytoin and/or cycling acetazolamide therapy, as previously described in patient 2,[5] provided excellent benefit when initiated. Seizure cessation in response to acetazolamide, before initiation of concomitant phenytoin, was confirmed during the EMU investigations of patients 3 and 4, and both remained seizure-free on the two medications (follow-up 6 and 3 years, respectively). In patient 1, pilomotor seizures first appeared 3 months after illness onset and were occurring multiple times per day 6 months later, ultimately resolving during a 6-month course of prednisone along with substitution of valproate for levetiracetam. Seizures stopped in patient 5 upon initiation of phenytoin and rapid weaning from levetiracetam, before immunotherapy was started. In patient 6, pilomotor seizures occurring multiple times per day despite levetiracetam and immunotherapy decreased abruptly (to 0–2 events/day) upon introduction of cycling acetazolamide therapy and discontinuation of levetiracetam.

Discussion

Recognition of the implications of hyperventilation-induced focal seizures in adults during EEG is clinically important. The phenomenon is rare, but has diagnostic specificity for autoimmune encephalitis, in particular VGKC-complex autoantibody subtypes, and the EEG findings may provide a referring physician with the first clue as to the etiology of their patient's illness.

The current study was not designed to assess the sensitivity of hyperventilation-induced focal seizures in the diagnosis of autoimmune encephalitis, which will be the subject of a future work. Sensitivity is potentially modifiable, dependent on patient effort and duration, factors that were not controlled in this observational study of unselected individuals. This likely accounts for the lower seizure incidence in this study compared to previous studies designed to investigate the effects of hyperventilation during EEG in patients with epilepsy[1–3] (see Appendix S1 for more discussion on the topic of sensitivity).

The mechanism by which hyperventilation can provoke focal temporal lobe seizures is obscure. Hyperventilation-induced hypocapnia causes acute systemic alkalosis, decreasing both cerebral blood flow (via pre-capillary vasoconstriction) and oxyhemoglobin dissociation (via the Bohr effect), although the acute neurophysiologic changes appear to be due to subcortical effects unrelated to cerebral tissue hypoxia.[11,12] Also unclear are the molecular mechanisms underlying (a) the ineffectiveness of levetiracetam in controlling temporal lobe seizures in VGKC-complex antibody-mediated encephalitis,[13,14] and (b) the comparative effectiveness of sodium channel blocking anti-seizure medications and acetazolamide.[5,14]

The propensity for temporal lobe seizures in VGKC-complex autoimmune encephalitis to have a pilomotor semiology, implicating the hypothalamus and central autonomic network,[15,16] combined with the susceptibility to hypocapnia and the therapeutic responsivity to sodium channel blockade and acetazolamide, is a combination of observations awaiting a unifying molecular explanation. For the time being, it is important to recognize hyperventilation-induced focal seizures during EEG for their clinical significance, because highly effective anti-seizure and immunotherapy options already exist.

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Conflict of Interest

The author has no potential conflict of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 Supplementary discussion material.

