Case Report

Alternating hemiparesis in the context of hemolytic uremic syndrome and COVID-19 positivity

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A R T I C L E   I N F O

A B S T R A C T

Hemiparesis has been reported in hemolytic uremic syndrome (HUS), however electrophysiological findings associated with this syndrome have not been well-characterized, and alternating hemiparesis presentations have not been reported. We present detailed electrophysiological and clinical findings in a case of alternating hemiparesis corresponding to alternating focal contralateral delta slowing on prolonged EEG monitoring in a case of HUS with COVID-19 positivity. A 24-year-old woman was admitted with bloody diarrhea, acute kidney injury, and focal seizures initially presumed due to Escherichia coli 0157:H7 Shiga-like toxin-related hemolytic uremic syndrome (ST-HUS). After admission, the patient tested positive for COVID-19. Continuous EEG monitoring revealed diffuse polymorphic delta slowing. Around 24 hours into the admission, the delta slowing became focal in the right hemisphere and was associated with a left hemiparesis. Around three days later, the clinical and EEG pattern reversed, showing left hemisphere slowing and an associated right hemiparesis. Additionally, 14 Hz positive spikes were observed throughout the recording period. Neuroimaging, including CT and MRI, was negative for acute ischemia throughout. The patient subsequently recovered over several days with no residual neurologic abnormalities.

1. Introduction

Hemolytic uremic syndrome (HUS) refers to a triad of clinical findings consisting of microangiopathic hemolytic anemia, thrombocytopenia, and acute oliguric renal failure. It is most typically associated with Shiga toxin-producing *E. Coli* or Shigella infections (and thus ST-HUS, or Shiga toxin-related HUS). These infections manifest with painful diarrhea that may be bloody, with or without fever. The HUS typically follows the diarrheal illness by several days. ST-HUS is mainly reported in children, and is uncommon in adults [1]. Neurological involvement in HUS is associated with severe disease and poorer prognosis [2], and may be a trigger for more aggressive therapies including plasma exchange or eculizumab.

Neurologic manifestations have been previously described in the setting of ST-HUS [2,3], and may include seizures, stroke, hemiparesis/hemiplegia, extrapyramidal syndromes, myoclonus, dysphasia, cortical blindness, altered mental status, and coma. While some of these impairments may be transient, some are not, resulting in persistent deficits, epilepsy, and even death. Magnetic resonance imaging (MRI) in ST-HUS has been reported to show symmetric subcortical T2 hyperintensities and diffusion abnormalities, and/or stroke [2,4]. Electroencephalographic (EEG) abnormalities, mostly identified on 20–40 minute routine recordings, that have been reported include generalized slowing, focal slowing, and interictal epileptiform activity [5,6], and status epilepticus in two cases [7,8]. EEG findings rapidly improved with plasma exchange in at least one case [8].

Neurological manifestations of COVID-19 infection have been published extensively over the last 12 months [9]. Altered mental state, headache, dysguesia, and anosmia are common clinical manifestations, whereas ischemic stroke and other serious manifestations (e.g. seizures, encephalitis, myelitis, Guillain-Barre syndrome) appear to be rare.

Here we present detailed clinical and EEG findings in a case of alternating hemiparesis in HUS and COVID-19.

2. Case report

A 24-year-old right-handed female with a past medical history significant for focal segmental glomerulosclerosis presented with acute onset nausea, emesis, bloody diarrhea and acute kidney injury. Diagnostic evaluation revealed Shiga toxin-producing

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E. coli 0157:H7. Over five days, she developed progressive oliguric renal failure requiring transfer to a tertiary care hospital for initiation of eculizumab. Her initial course was also notable for mild hypoxemia requiring oxygen 1–4 liters by nasal cannula.

While *en route* to our institution, she had two witnessed episodes of tonic posturing in both upper extremities suggesting focal seizures. She therefore received midazolam. On arrival to the Emergency Department, vital signs showed tachycardia and an oxygen saturation of 94% on 4 liters of oxygen by nasal cannula. She was stuporous and had anasarca. COVID-19 nasal swab PCR returned positive while serum antibodies were negative. Admission chest x-ray revealed right greater than left pleural effusions and hazy, perihilar infiltrates, suggestive of fluid overload. She did not receive COVID-19-directed therapy due to her renal failure (GFR < 15 mL/min) and concurrent use of eculizumab for HUS. After medical stabilization including initiation of levetiracetam (1000 mg IV loading dose), she was transferred to the medical intensive care unit (ICU) for further management.

In the ICU, she had a witnessed seizure involving left eye gaze deviation and tonic posturing of the bilateral upper extremities, requiring 2 mg of intravenous lorazepam, an additional dose of levetiracetam (2500 mg), and initiation of valproic acid (2000 mg IV loading dose followed by 250 mg tid). She continued to be stuporous and was placed on prolonged EEG monitoring to exclude ongoing electrographic seizures. Continuous EEG revealed diffuse medium amplitude (60–90 μV) 0.5–3 Hz polymorphic delta slowing. Over the first several hours of the recording, a marked asymmetry developed (Fig. 1A), with resolution of the left hemispheric slowing but persistent focal slowing in the right hemisphere. The slowing was initially intermittent, but then became continuous and was maximal in the right temporal head region (F8, T8, P8). Clinically, a left hemiplegia was present. She had a CT head and CTA head/neck that were negative for an acute cerebrovascular event. The EEG was subsequently discontinued as no seizures were recorded. She remained stable for 24 hours then experienced another seizure, described as left head turn, leftward gaze deviation, clonic activation of the right neck (sternocleidomastoid
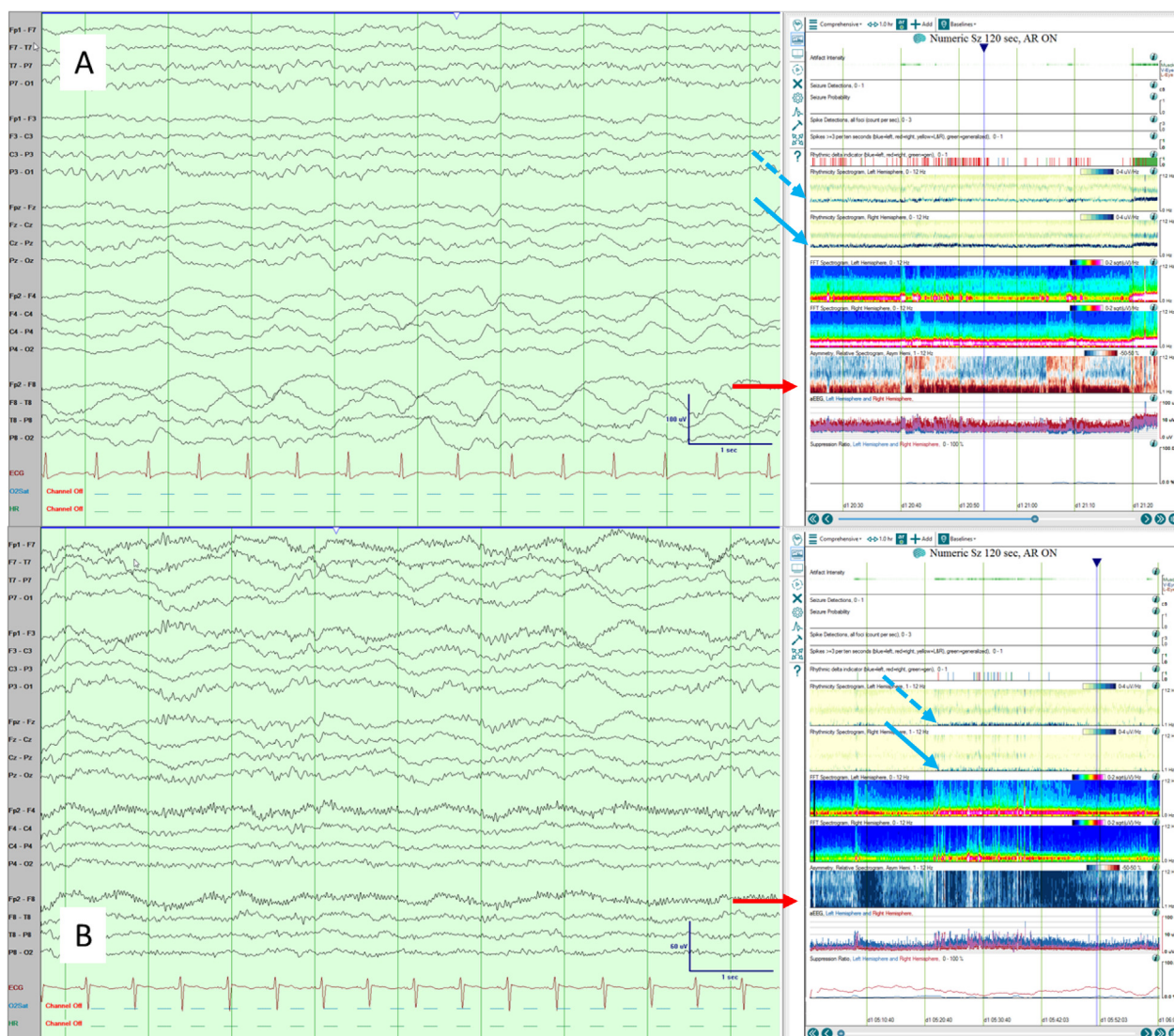
Fig. 1. EEG findings of alternating focal slowing. EEG during drowsiness, longitudinal bipolar montage (low frequency filter = 1 Hz, high frequency filter = 30 Hz). (A) During a period of left hemiplegia, continuous delta slowing was noted over the right hemispheric derivations, maximal in the right temporal head region (F8, T8, P8). Quantitative EEG (qEEG) showed accentuation of delta on the right on the asymmetry spectrogram tool (red arrow), and a denser delta band on the right on the rhythmicity spectrogram tool (blue arrows). (B) About 24 hours later, a right hemiparesis was noted. The EEG showed resolution of the right hemispheric slowing, and the presence of continuous delta slowing over the left hemispheric region, maximal in the left temporal head region (F7, T7, P7). QEEG shows increased left sided delta asymmetry (red arrow), and denser delta band on the left (blue arrows).

muscle), forced right elbow flexion, and partial right finger flexion. Following this event, she developed a right hemiparesis. An extra 1000 mg of IV valproate was given, and maintenance dosing increased to 500 mg tid. Prolonged EEG monitoring was restarted and showed asymmetric slowing involving the left hemispheric derivations greater than right (Fig. 1B). Again, the slowing was continuous and was now maximal in the left temporal head region (F7, T7, P7). MRI brain was performed and did not show any evidence of ischemic stroke, or any other definite cause for the symptoms. 14 Hz positive spike bursts (ctenoids) were also observed throughout monitoring (Fig. 2). Continuous EEG monitoring was discontinued as no seizures were detected and the patient was clinically improving.

Over the next 72 hours, the hemiparesis gradually resolved. The patient experienced no further seizures during the remainder of her recovery. She was discharged to an inpatient rehab facility 19 days after her initial admission, for further physical and occupational therapy due to deconditioning from her medical illness and prolonged hospitalization. After discharge, anti-seizure medications were gradually discontinued, and she showed no neurologic sequelae at last follow-up.

3. Discussion

Although HUS is rare, with an incidence of 0.5 to 6.1 per 100 000 (highest in children under 5 years, lowest in adults age 50–59) [1,10], neurological involvement is common, and generally reported in 25–50% [5,10]. The true incidence of neurological abnormalities may be even higher, as shown when detailed clinical testing was performed in one series of 42 patients (including cognitive and neuropsychological testing), demonstrating all 42 patients had some demonstrable abnormality [6].

A variety of neurologic findings have been described in HUS. In one study of 50 patients, 14 had neurological involvement, and hemiparesis was observed in two [5]. EEG in the 14 patients showed mostly diffuse slowing. When present, focal abnormalities on EEG (slowing or epileptiform discharges) did not appear to correlate with clinical exam findings. MRI revealed ischemic stroke in one patient and in the remainder non-specific symmetric T2 FLAIR and/or diffusion abnormalities in the basal ganglia, corpus callosum, and frontal white matter. In another study of 52 patients with HUS, paraparesis and tetraparesis were described, but not hemiparesis [6]. EEG abnormalities were limited to diffuse but frontal predominant 2–3 Hz delta slowing, with no focal abnormalities described. MRI abnormalities included bilateral symmetric T2 hyperintensities in the brainstem, basal ganglia, and corpus callosum. One patient had a syndrome consistent with PRES (posterior reversible encephalopathy syndrome). Another report described 52 patients with initial severe neurologic involvement [2]. In this series, 37 had seizures and seven had hemiparesis or hemiplegia. EEG findings were not described. MRI was performed in 29 patients, revealing abnormalities on T2 and diffusion weighted sequences in essentially all parts of the brain, as well as hemorrhagic lesions. None of these studies described alternating hemiplegia, and only a few described continuous EEG findings.

Ctenoids, also referred to as 14 and 6-Hz positive bursts, are a recognized benign variant without clinical significance [11,12]. However, ctenoids have been described in cases of Reye syndrome [13], a severe encephalopathy and hepatic dysfunction which is triggered by salicylates in the context of a predisposing inborn error of metabolism. The occurrence of ctenoids in our patient may have been a coincidence of no relevance to the patient's severe encephalopathy, in which case a follow-up prolonged EEG after recovery may be informative. However, their previously reported presence in Reye's raises the possibility as to whether this rare EEG finding could be an uncommon EEG feature in severe encephalopathies, and as an unexplained feature of this patient's EEG.
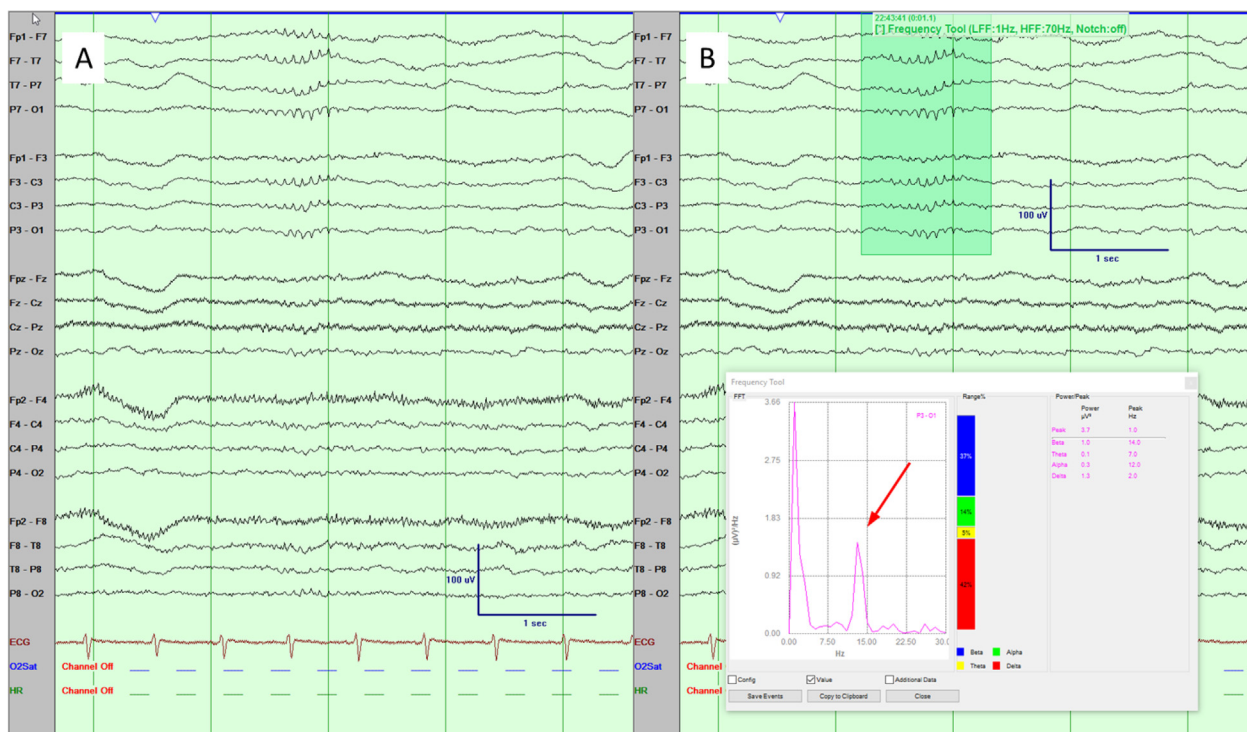
Fig. 2. EEG findings of 14 Hz positive spike bursts. EEG during drowsiness, longitudinal bipolar montage (low frequency filter = 1 Hz, high frequency filter = 30 Hz). (A) 14 Hz positive spikes ("ctenoids") were noted throughout the recording. These have also been seen in encephalopathies due to Reye syndrome. (B) Quantitative analysis, showing a sharp peak at 14 Hz (red arrow).

With respect to the COVID-19 positivity in our case, we note that respiratory manifestations of COVID-19 were mild (and perhaps also referable to fluid overload in the setting of oliguria) and other clinical findings typically associated with COVID-19 were absent. Hence while it is possible that COVID-19 infection contributed to the pathophysiology of the patient's neurologic presentation, ultimately its role is uncertain. EEG findings in COVID-19 have been well-described and range from diffuse slowing, to interictal discharges, periodic patterns, and seizures/status epilepticus [14,15]. A high incidence of seizures and status epilepticus has been reported [14,15], both of which have been associated with worse clinical outcomes [15]. However, in the absence of seizures/status epilepticus or stroke, focal slowing with corresponding focal neurological deficit (alternating or not) has not been described. It is worth noting that most of the patients included in the existing COVID-19 literature also suffered from severe hypoxia, which our patient did not have. Though speculative, hypoxia likely contributed to the severe abnormalities seen on EEG in this group of patients.

The specific pathophysiology of the neurologic presentation in our case is not clear. The alternating focal slowing on EEG suggests a lateralized physiologic disturbance in cerebral function. While the MRI did show some non-specific T2 FLAIR and diffusion abnormalities similar to those reported previously in HUS, no imaging abnormalities were present that would fully account for the clinical picture. The thrombotic microangiopathy and/or endothelial dysfunction associated with both HUS and COVID could perhaps account for the alternating hemiplegia presentation in this patient [16]. Cortical spreading depression (CSD), a wave of neuronal and glial depolarization associated with ion shifts and cerebrovascular changes, is another possible pathophysiologic mechanism that may have accounted for the transient deficits in this patient. CSD may be seen following subarachnoid hemorrhage and stroke, and has been posited to contribute to migraine aura, including the motor aura seen in hemiplegic migraine [17]. Of note, several paroxysmal hemiplegic migraine variants, including alternating hemiplegia of childhood, familial hemiplegic migraine type 2, and sporadic hemiplegic migraine are associated with mutations in the ATP1A2 gene, which codes for a sodium/potassium ATPase [18]. Other familial hemiplegic migraine types demonstrate associations with channelopathies secondary to CACNA1a and SCN1A gene mutations [19]. The patient had no prior history to suggest either of these mutations, however if further occurrences such as this were to develop, genetic investigations could be considered to determine if mutations such as these involving neuronal activation and suppression are present.

4. Conclusion

Alternating focal slowing with a corresponding reversible alternating hemiparesis or hemiplegia may occur in severe HUS complicated by COVID-19, though it is unclear if COVID-19 contributed to this finding or not. It is important for clinicians to recognize that such findings may occur in the absence of seizures or stroke, providing the basis for the possibility of a favorable prognosis when counseling patients and families in the acute setting. Ultimately, the pathophysiology of this phenomenon in this case remains unclear. The application of other diagnostic modalities in the future, such as FDG-PET and perfusion imaging, could be helpful in improving understanding of the underlying mechanisms in such patients.

CRediT authorship contribution statement

Hugh D. Simpson: Investigation, Data curation, Writing - original draft. **Erica Johnson:** Investigation, Writing - original draft. **Jeffrey Britton:** Conceptualization, Writing - review & editing, Supervision. **Sherri Braksick:** Conceptualization, Writing - review & editing, Supervision.

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