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A DAY IN THE LIFE OF A NEUROCRITICAL CARE TRAINEE

A Case of HIV Seroconversion Presenting Similarly to Anti-*N*-methyl-D-aspartate Receptor Encephalitis

Heather VanDongen-Trimmer[1], Kumar Sannagowdara[1], Binod Balakrishnan[2] and Raquel Farias-Moeller[1,2*]

Introduction

Continuous electroencephalogram (cEEG) monitoring is recommended in patients with acute supratentorial brain injury and altered mental status, such as patients with encephalitis. This practice may help facilitate prompt treatment of non-convulsive seizures and status epilepticus as well as assess the severity of encephalopathy [1]. As more critically ill patients with encephalopathy are being monitored with cEEG, experience is gained in recognizing EEG background patterns that can aid in prognostication, prediction of illness trajectory, and in a few occasions as biomarkers for specific disease processes [1].

Patients with *N*-methyl-D-aspartate receptor encephalitis (NMDARE) usually present with amnesia, seizures, psychiatric symptoms, dyskinesias, and autonomic dysfunction. Since the discovery of this antibody-mediated encephalitis in 2005 [2, 3], significant advances have been made in the description of the pathophysiology, clinical presentation, biomarkers, and treatment of NMDARE both in children as well as in adults [4, 5]. Approximately 75% of all patients with NMDARE require intensive care support [6] and are usually monitored with cEEG.

In 2012, a characteristic EEG pattern of continuous rhythmic to semi-rhythmic delta frequencies with bursts overriding beta activity termed extreme delta brush (EDB) was described [7]. This pattern was termed unique to NMDARE, usually guides to its diagnosis and has been explored as a potential biomarker [7–9]. More recently, EDB has been recognized in a few other disease processes. We present a case of a patient with acute human immunodeficiency virus (HIV) seroconversion and encephalitis whose presenting clinical picture resembled NMDARE including the presence of EDB, highlighting the importance of comprehensive evaluation of a critically ill encephalopathic febrile patient with seizures.

Presentation of Case and Management

A 16-year-old male with a history of attention deficit disorder and mild intellectual disability presented to the emergency department (ED) after a 7-min generalized tonic–clonic seizure following a 3-week prodrome of fever, malaise, and upper respiratory infection symptoms. Upon arrival to the ED, Glasgow Coma Scale was noted to be 10. He received a total 8 mg of lorazepam for presumed seizure and post-ictal agitation. He was admitted to the pediatric intensive care unit (PICU) for further treatment and evaluation.

In the PICU, his physical examination was significant for a temperature of 40 °C, heart rate of 180 bpm, respiratory rate of 40 bpm, blood pressure of 140/80 mmHg and oxygen saturation of > 98% on room air. He was profusely diaphoretic. There was absence of lymphadenopathy or pharyngeal exudates. Cardiovascular, abdominal, and genitourinary examinations were normal. Piloerection was noted as well as a fine macular rash was noted on the face and bilateral upper extremities. Neurologic examination revealed encephalopathy with irritability, inability to follow basic commands, scant albeit fluent speech, and bradykinesia. Cranial nerve examination was normal except for pupillary dilation with sluggish response. Strength was antigravity in all extremities. Diffuse hypertonia with hyperreflexia was noted as well as a right foot plantar extensor response. He had near

*Correspondence: rfarias@mcw.edu
[1] Division of Child Neurology, Department of Neurology, Children's Hospital of Wisconsin, Medical College of Wisconsin, 8915 W Connell Ct, Milwaukee, WI 53226, USA
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constant choreoathetoid movements noted in the right upper extremity and buccal dyskinesias with salivation. Lorazepam was administered again in order to improve his agitation.

Table 1 summarizes the patient's diagnostic workup. Cerebrospinal fluid (CSF) revealed pleocytosis with markedly elevated protein, and thus, antibiotics and acyclovir were initiated for presumed meningoencephalitis. Magnetic resonance imaging of the brain and spine with gadolinium was unremarkable. cEEG revealed abundant, frontally predominant generalized rhythmic delta activity at 1-Hz with bursts of overriding beta frequencies. State changes were present, but no sleep architecture was documented (Figs. 1, 2). This pattern was noted

Table 1 Diagnostic summary

Admission laboratories	Infectious disease workup
Sodium 141 meq/L	*CSF*
Glucose 154 mg/dL	WBC 145/μL, RBC 1150/μL, protein 243 mg/dL, glucose 59 mg/dL
BUN 14 mg/dL	Meningitis and encephalitis NAAT panel negative
AST 51 U/L	West Nile Virus antibodies negative
ALT 57 U/L	Bacterial culture negative
Ammonia 6 μmol/L	Enterovirus/parechovirus PCR negative
White count 8.5 10*3/μL	Arbovirus antibody panel negative
Hemoglobin 15.5 g/dL	Lyme disease antibodies negative
Platelets 263	HSV PCR negative
D Dimer 1.93	VDRL non-reactive
Creatine kinase 1239	Autoimmune encephalopathy panel negative
Sedimentation rate 15 mm	*Serum*
C reactive protein 0.8 mg/dL	Autoimmune encephalopathy panel negative
Toxicology screen: +opioids (patient consumed cough syrup)	HSV PCR negative
	HIV p24 antigen: non-reactive, HIV 1/2 antibody reactive
	HIV RNA PCR: HIV RNA 242,000 copies/mL HIV RNA 5.38 log copies/mL
	Enterovirus and parechovirus negative
	Bacterial culture negative
	CMV negative
	RPR positive, *Treponema pallidum* agglutination positive

This table demonstrates diagnostic workup

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CSF* cerebrospinal fluid, *CMV* cytomegalovirus, *HIV* human immunodeficiency virus, *HSV* herpes simplex virus, *NAAT* nucleic acid amplification test, *PCR* polymerase chain reaction, *RBC* red blood count, *RPR* rapid plasma reagin, *VDRL* venereal disease research laboratory, *WBC* white blood count

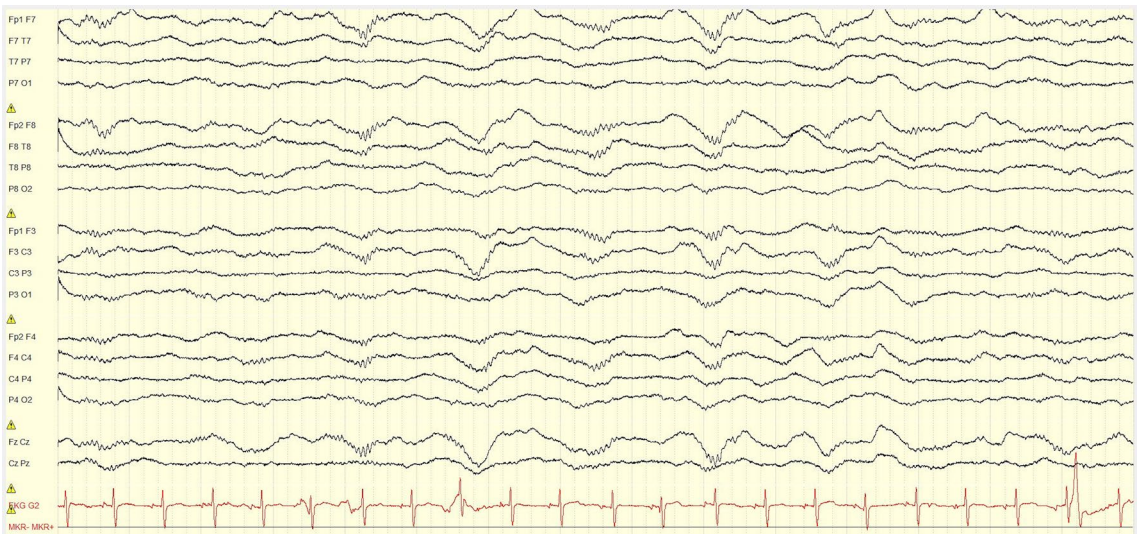

Fig. 1 The initial EEG tracing demonstrated unrelenting semi-rhythmic delta frequency activity of 1 Hz with superimposed frontally predominant bursts of rhythmic 12–14 Hz activity. High-pass filter 0.5 Hz; low-pass filter 70 Hz. Notch filter on

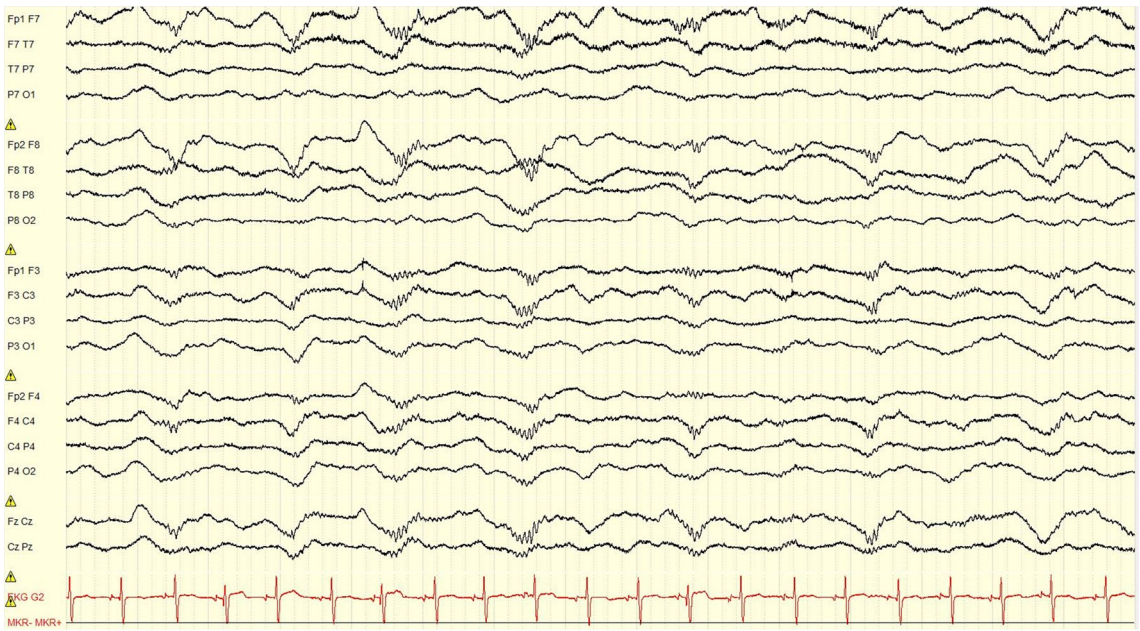

Fig. 2 A subsequent EEG 24 h after hospitalization demonstrates continued semi-rhythmic delta frequency activity of 1 Hz with superimposed frontally predominant bursts of rhythmic 12–14 Hz activity. High-pass filter 0.5 Hz; low-pass filter 70 Hz. Notch filter on

for the first 72 h of his hospitalization and transitioned to generalized slowing. The EEG findings coupled with the clinical presentation were concerning for NMDARE. Vital sign instability and choreoathetosis improved with initiation of dexmedetomidine infusion. Serum and CSF autoimmune encephalitis panels were sent. Intravenous immunoglobulin (IVIG) and methylprednisolone were initiated approximately 60 h post presentation.

A single 2-minute seizure recurred on day three after admission and valproate was initiated. Encephalopathy improved while on corticosteroids and IVIG, though insomnia, psychosis, and aggressive/hypersexual behavior emerged. On day six of admission, HIV PCR testing from admission returned positive and immune encephalitis panel on CSF and serum returned negative. No spinal fluid remained to perform HIV testing. Corticosteroids and IVIG were discontinued and he was started on antiretroviral therapy. Although encephalopathy improved throughout the remainder of his ICU stay, confusion, poor impulse control and aggressive behaviors persisted. Coinfections with *Chlamydia trachomatis* and systemic *T. pallidum* (venereal disease research laboratory in CSF was negative) were noted and he was appropriately treated. He returned to his pre-morbid state prior to discharge to home.

Discussion

We present a case of a teenage male with seizures, encephalopathy, and psychiatric disturbances following a prodromal febrile illness. Physical exam demonstrated vital sign instability suspicious for paroxysmal sympathetic hyperactivity (PSH), choreoathetosis, buccal dyskinesias, and corticospinal tract involvement with paraclinical studies demonstrating CSF pleocytosis with increased protein and EDB on cEEG. Antibodies against NMDAR were negative in CSF and serum. After a thorough workup, he was diagnosed with encephalitis in the setting of acute HIV seroconversion. We describe the similarities and differences of this case with NMDARE and add HIV seroconversion to the small (albeit growing) list of etiologies that have EDB as an EEG finding in encephalopathic patients.

This patient exhibited many signs and symptoms that were suggestive of autoimmune encephalitis. For instance, PSH was noted from the first day of hospitalization. It is estimated that some degree of autonomic instability occurs in over 90% of patients with NMDARE [10]. Frank PSH might also occur and is likely under represented in the literature [11]. However, it is somewhat unusual for PSH secondary to NMDARE to respond only after 24 h of dexmedetomidine without recurrence as we saw in our patient. Similarly, seizures in NMDARE occur in 80% of cases, but are more often either repetitive or associated with status epilepticus. More than one anti-seizure drug is usually required for seizure control [12]. Our patient, on the other hand had two single self-limited seizures that were well controlled on valproate. Our patient displayed intense psychiatric symptoms such

as mania, psychosis, paranoia, and insomnia which are commonly seen in patients with NMDARE [13]. However, it is difficult to discern whether these symptoms were exacerbated due to corticosteroids or ICU-induced delirium in combination with his pre-morbid intellectual disability.

While the patient's symptoms were highly suspicious for NMDARE, it was the presence of EDB on the patient's EEG that prompted clinicians to empirically initiate immunotherapy while waiting for confirmatory antibody testing. EDB has been reported in multiple pediatric and adult series of patients with NMDARE [14–18] and has been associated with a more severe course [7]. More recently, it has been described in other conditions such as Lafora disease [19], autoimmune glial fibrillary acidic protein astrocytopathy [20], methotrexate neurotoxicity [21] and febrile illness related epilepsy syndrome [22]. Similarly, in a large series of 182 patients, blinded investigators analyzed cEEG recordings in two cohorts: an ICU cohort and a mesial temporal lobe epilepsy cohort. EDB was found in only four patients, three of them in the ICU for various reasons and none with NMDARE. EDB in the ICU cohort was associated with worse prognosis [23]. The mechanism behind this pattern remains unclear but altered NMDAR-mediated currents might be responsible [7]. We postulate that NMDAR-mediated currents might be altered via various mechanisms and thus give rise to a similar EEG pattern, and while the presence of EDB should alert clinicians to NMDARE, other etiologies must be considered while managing a patient with suspected autoimmune encephalitis [24].

Our case has several limitations. It is difficult to discriminate the impact of benzodiazepines on the EEG pattern observed. However, this pattern persisted for 72 h after his arrival and when benzodiazepines were administered subsequently in his hospitalization, this pattern did not recur. Furthermore, similar to the original report of EDB in a cohort of patients with anti NMDARE (many of which had received benzodiazepines) [7], the beta activity tended to occur in bursts rather than in a generalized pattern. Additionally, HIV viral load was unable to be performed in spinal fluid, as the sample had been utilized for prior testing in its entirety. It remains possible that other encephalitides that were not screened for were responsible for the clinical presentation.

We determined that our patient's symptoms at presentation are consistent with HIV seroconversion with encephalitis. Seroconversion is the period during which HIV antibodies start rising to detectable levels. The symptoms are indistinguishable from "flu-like" illnesses [25]. The CSF findings in our patient are consistent with aseptic meningitis that is often associated with HIV seroconversion [26]. One to four percent of patients develop acute neurological disease during seroconversion [26]. The HIV-1 envelope glycoprotein 120 (Gp 120) has been implicated in its CNS neurotoxicity [27, 28]. The prominent mechanisms of neurotoxicity of Gp120 are its interaction with NMDAR [29], and both direct [30] and indirect [31] activation of NMDAR pathways have been demonstrated by researchers. NMDAR antagonists have also been shown to attenuate or prevent HIV-1 associated neuronal injury and cell death [29]. While EDB has been classically associated with NMDARE our observation of its association with HIV encephalopathy could likely be related to the NMDAR-mediated neurotoxicity of HIV-1. Despite our observations, a causal relationship cannot be extrapolated based on a single case report.

Conclusion

Utilization of cEEG monitoring for encephalopathic patients in the ICU is becoming increasingly common. Not only does this practice improves timely detection and treatment of non-convulsive seizures and status epilepticus but it also assists in detecting distinct EEG patterns that aid in prediction of outcome and/or point toward an etiology of neurological disease. Our case highlights, the need for comprehensive evaluation of the critically ill child with encephalopathy in order to reach the appropriate diagnosis, despite all signs and symptoms pointing toward NMDARE. While EDB is most commonly reported in patients with NMDARE, it is more frequently being recognized in other cohorts, many of which are being monitored with cEEG while in the ICU. Further studies are necessary to establish the incidence of this pattern in critically ill patients with encephalopathy and its significance.

Author details

[1] Division of Child Neurology, Department of Neurology, Children's Hospital of Wisconsin, Medical College of Wisconsin, 8915 W Connell Ct, Milwaukee, WI 53226, USA. [2] Division of Pediatric Critical Care Medicine, Department of Pediatrics, Children's Hospital of Wisconsin, Medical College of Wisconsin, 8915 W Connell Ct, Milwaukee, WI 53226, USA.

Author's Contributions

Heather VanDongen-Trimmer was involved in data collection, manuscript redaction and editing, original conceptualization of the manuscript. Binod Balakrishnan was involved in data collection, manuscript redaction and editing. Kumar Sannagowdara was involved in data collection, image identification, review and editing, manuscript redaction and editing. Raquel Farias-Moeller was involved in data collection, manuscript redaction and editing, original conceptualization of the manuscript, project supervision.

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Conflict of interest

The authors have no potential conflicts of interest to disclose.

Ethical approval/Informed consent
Ethical approval was obtained by our institutional review board prior to submission and the case is devoid of personal identifying information.

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