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CASE REPORT

Anti-NMDA receptor encephalitis with paroxysmal sympathetic hyperactivity: an under-recognized association?

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Introduction

While autonomic instability occurs as part of anti-N-methyl D-aspartate (anti-NMDA) receptor encephalitis, anti-NMDA receptor encephalitis is not a recognized cause of the clinical syndrome of paroxysmal sympathetic hyperactivity (PSH). We present a case of anti-NMDA receptor encephalitis in which PSH was a cardinal feature and discuss the mechanistic implications of such an association.

Case report

A 31-year-old woman had a generalized tonic–clonic seizure and then developed progressively worsening neuropsychiatric symptoms, including mania, hallucinations, echolalia, and suicidal ideation. She was previously healthy; she did not have any known medical or psychiatric disease. She was not on any medications prior to presentation. She was initially admitted to a psychiatric unit but was transferred to a medical ward after one week of psychiatric treatment, as her symptoms worsened despite anti-psychotic medications. Neurologic examination was notable for catatonia that progressed to coma. She was intubated and mechanically ventilated due to apnea. Brain magnetic resonance imaging (MRI) was normal. Electroencepahlography (EEG) revealed right hemispheric rhythmic slowing with episodic suppression, suggesting non-convulsive status epilepticus. The patient was then transferred to our hospital for further evaluation. Lumbar puncture was notable for lymphocytic pleocytosis (white blood cell count =115), negative viral polymerase chain reactions (PCR). Anti-NMDA receptor antibodies were detected in the serum and cerebrospinal fluid (CSF). An oophorectomy was performed and this revealed a benign adenoma. Patient was treated with high-dose cortiosteroids, plasma exchange, and finally rituximab. Over six weeks the patient's condition slowly improved and she was discharged to home awake, conversant and ambulating with assistance.

One week after symptom onset, the patient experienced intermittent episodes of sinus tachycardia, hypertension, tachypnea, diaphoresis and extensor posturing. During a typical episode, which could last for 20–120 min and occurred as often as three times per day, her heart rates were 100–125 beats/minute, blood pressures 160–180/80–100 mmHg, and respiratory rates 20–25 breaths/minute (Fig. 1). For comparison, the patient's basal vital signs are heart rates 80–90 beats/minute, blood pressures 100–120/60–80 mmHg, and respiratory rates 16–20 breaths/minute. During these episodes, there was no electrographic correlate on EEG. The episodes were both spontaneous and stimulus responsive (for example, during endotracheal suctioning). The episodes, consistent with PSH, were initially treated with dexmedetomidine, which was titrated to a maximum dose of 1.0 mcg/kg/hr for 7 days. The episodes were recognized as PSH and initially treated about six days into the patient's hospital course. She was already had already received a full course of corticosteroids and was receiving plasma exchange at this time. Gabapentin and

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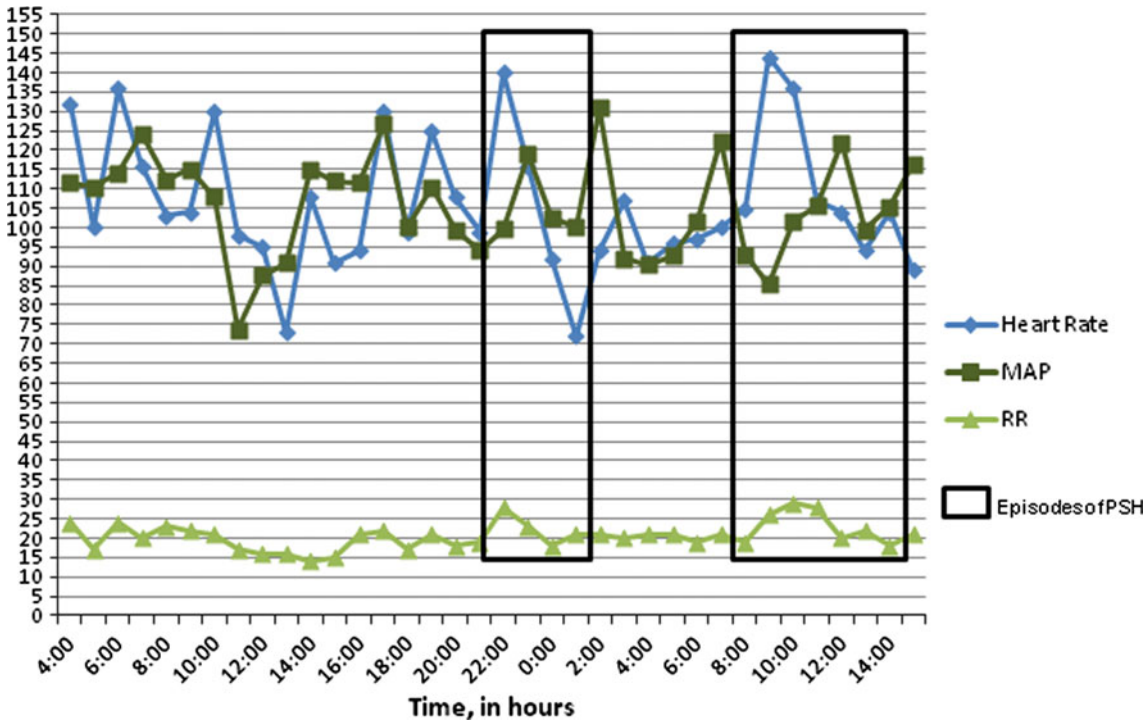

Fig. 1 Representative episodes of PSH

propranolol were also added for symptom control, but eventually weaned off as her symptoms abated approximately six weeks into the illness. The patient showed a characteristic step-wise reversal of neurological deficits as she recovered. At her nadir, she was comatose but started to follow commands after a few weeks. While she continued to have hallucinations, she also had lucid periods where she could communicate effectively with health providers and family. As the patient neurologically improved, her episodes of PSH became less frequent and the paroxysms were shorter in duration. Six weeks after initial presentation, the patient was weaned off of gabapentin and propranolol because she was no longer having vital sign abnormalities. Neurological exam was also significantly improved, the patient was conversational, oriented, and ambulatory.

Discussion

We present a case of anti-NMDA receptor encephalitis with typical clinical and serologic features [1]. Our patient demonstrated dramatic episodes of sympathetic hyperactivity, fitting the syndrome of PSH. While episodic autonomic instability is a frequent feature of anti-NMDA receptor encephalitis, this instability is not routinely recognized as PSH. For instance, 93 of 100 patients in Dalmau's 2008 case series "developed hypoventilation, autonomic imbalance, or abnormal movements." [2] We believe that the autonomic instability associated with anti-NMDA receptor encephalitis may often be PSH. Although hypoventilation requiring mechanical ventilation is often cited as an important feature, we hypothesize that, as in our case, episodic tachypnea may be superimposed over baseline hypoventilation. Recognition of PSH has both mechanistic and treatment implications.

PSH, also known as Paroxysmal Autonomic Instability with Dystonia (PAID), is a hyper-adrenergic clinical syndrome most frequently recognized in traumatic brain injury (TBI) [3], but other causes have been cited including intracranial hemorrhage and anoxic brain injury [4], though firm criteria have yet to be established in the literature. PSH presents with a constellation of tachycardia, hypertension, tachypnia, hyperpyrexia, often accompanied by diaphoresis and dystonic movements. We chose the term PSH to describe our patient's vital sign abnormalities because it accurately portrays the patient's clinical picture without implicating an etiology. While the nomenclature is controversial, the term "paroxysmal sympathetic hyperactivity" has gained favor in the literature as it encompasses cases where dystonia is not the prominent movement disorder [5]. Historically, bromocriptine, opioids and propranolol served as the mainstays of therapy [6]. More recently, symptom control with dexmetetomidate [7] and gabapentin [8] have been reported. PSH often goes unrecognized in patients outside of the setting of TBI, thus

specific PSH management strategies may be overlooked in other illnesses.

Imaging studies in TBI demonstrate widespread lesions, particularly in the white matter associated with diffuse axonal injury (DAI), without focality [3]. Rather than arising from a single lesion, PSH is likely caused by disrupting the sympathetic circuit, thus explaining the episodic nature of the condition, as well as its disparate causes. Baguley proposed a model encapsulating the sympathetic balance, the excitatory: inhibitory ratio model (EIR) [9]. In brief, the absence of descending inhibition results in exaggerated spinal reactivity, with sympathetic efflux triggered by non-nociceptive peripheral stimuli. Modulation likely occurs at several levels, but is probably integrated at the level of the hypothalamus, which is rich with bi-directional connections. Anti-NMDA receptor encephalitis may represent the functional companion to the structural lesion encountered in TBI. Specifically, by attacking the NMDA receptors, this encephalitis disrupts the sympathetic circuit, producing the clinical manifestations of autonomic instability. Two anesthetic agents, ketamine and phencyclidine, may induce receptor blockade similar to the NMDA antibody. Ketamine binds to the ion channel of the NMDA receptor thus it is mechanistically similar to NMDA-R antibodies. As observed in PSH, ketamine often produces hypertension and tachycardia [10]. Future work should focus on creating an experimental model of PSH en vivo capitalizing on these observations.

Conflict of interest Dr. Hinson is the recipient of 2012 American Brain Foundation Practice Research Training Fellowship. Dr. Takahashi has nothing to disclose. Dr. Altowaijri has nothing to disclose. Dr. Baguley has received honoraria from consultancy work for both Ipsen and Allergan, relating to the use of botulinum toxin. Dr. Bourdette has research grants from the National Institutes of Health, the Department of Veterans Affairs and National MS Society and he has received honoraria for speaking or consulting with Elan Pharmaceuticals, Biogen Idec and Teva Neurosciences.

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