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Case Report

Paroxysmal sympathetic hyperactivity following status epilepticus in a 22-year-old with Juvenile Neuronal Ceroid Lipofuscinosis: A case report

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ABSTRACT

The Neuronal Ceroid Lipofuscinosis (NCL) refers to a group of rare neurolipidosis disorders characterized by progressive blindness, deterioration of speech and motor function, cognitive decline, behavior problems, seizures, and premature death. We report a case of a 22-year-old man with CLN3 variant, homozygous NCL (aka Juvenile Neuronal Ceroid Lipofuscinosis) complicated by epilepsy who presented with episodes of recurrent seizure-like activity following status epilepticus, but now without electrographic correlate. Episodes were accompanied by tachycardia, diaphoresis, hypertension, and a fearful facial expression likely representing paroxysmal sympathetic hyperactivity (PSH), and improved with administration of propranolol. It is possible that status epilepticus provoked these episodes of PSH.

1. Introduction

Neuronal Ceroid Lipofuscinoses (NCL) are a group of rare genetic metabolic neurodegenerative disorders caused by a buildup of ceroid lipofuscin in the brain [1]. NCL affects 2–4 in 100,000 births [2]. There are over thirteen genes (CLN 1–14, except CLN 9) containing 430 genetic mutations underlying NCL. These genes encode proteins found in the secretory, endosomal, and lysosomal pathways, but exact mechanisms of all gene mutations remain unclear. In most cases, the inheritance pattern of NCL is autosomal recessive, except for CLN4 which is autosomal dominant and gives rise to the adult onset form [3]. There is limited data on the clinical progression of the disorder due to its rare prevalence and the shortened lifespan of affected patients.

There are four subsets of JNCL characterized by age of onset: infantile, late-infantile, juvenile, and adult. Common features between the four subsets are visual decline, psychomotor regression, ataxia, myoclonus, and refractory epilepsy [1]. The prognosis is better as the age of onset increases, with infantile onset having the worse prognosis and adult onset having the best prognosis [1]. Juvenile NCL (JNCL) is seen in the described patient and most often presents between 4 and 7 years with rapidly progressive vision loss due to retinopathy. Between 10 to 12 years, increased seizures, behavioral issues, cognitive decline, and, sometimes, parkinsonism are common in JNCL [1,4]. Death typically occurs by the third or fourth decade [4]. Given there are few people with JNCL who are in their third or fourth decade of life, little is known about the later manifestations of JNCL.

Paroxysmal sympathetic hyperactivity (PSH), a well-known complication of traumatic brain injuries due to dysregulation of sympathetic nervous system control [5], has been described in patients with JNCL at the time of infection or environmental triggers. In our patient, we observed PSH following status epilepticus, which has not previously been reported to our knowledge [6]. Although episodes may appear similar to seizures, clinical manifestations and continuous video electroencephalogram (cEEG) monitoring can differentiate the two entities and guide appropriate management.

2. Case description

A 22-year-old man with a history of CLN3 variant, homozygous NCL was transferred to our institution from an outside hospital for continuous EEG monitoring due to concern for nonconvulsive status epilepticus.

This patient was diagnosed with JNCL at age 5 after initially presenting with loss of color vision and central vision loss, which was followed over time by progressive intellectual impairment, seizures, dystonia, and spasticity. Now he is blind, severely intellectually impaired, and suffers from epilepsy, behavioral problems

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(aggression and irritability), hallucinations, dystonia, and spasticity. At baseline, he is aware of and can interact with his environment. He recognizes voices, follows simple commands, and communicates through one- to two-word phrases or hand motions. He ambulates with assistance and uses a wheelchair for long distances. His medication regimen at the time of presentation included clonazepam 0.125 mg tablet three times daily, divalproex sprinkle 7–125 mg capsules once daily, pyridoxine 25 mg tablet once daily, lacosimide 100 mg tablet twice daily, aripiprazole 1 mg/ml solution 9 mL twice daily, sertraline 100 mg once daily, and a rescue diazepam 10 mg gel suppository as needed. He previously had adverse reactions to levetiracetam and lorazepam. There had been no recent changes to his antiepileptic regimen or to other medications.

His typical seizure semiology is described as generalized tonic-clonic activity with 1 minute of tonic phase followed by 4 min of clonic phase. His seizures occur every 2–4 weeks. He rarely has clusters of seizures without returning to baseline. The last time a cluster occurred was 18 months prior to this presentation.

Two days prior to presentation to the outside hospital, the patient experienced a seizure and returned to baseline shortly after. The next day, he had 4 seizures, each 4 h apart, without return to baseline. His parents reported that the semiology of these seizures was consistent with his typical seizure semiology. He received multiple doses of clonazepam and midazolam and was brought to an outside hospital that night. No seizures were observed after arrival, but his mental status did not return to baseline. A noncontrast head CT showed no acute findings. Complete blood count, complete metabolic profile, and urinalysis showed no evidence of infection or metabolic derangement. EKG showed normal sinus rhythm. His daily total divalproex dose was increased from 875 mg to 1000 mg. He was transferred to our institution for continuous EEG monitoring due to concern for nonconvulsive status. He arrived at our institution approximately 60 h after the initial onset of seizure activity and approximately 18 h after the last observed seizure of his typical semiology. Six hours after admission to this hospital, the patient's parents observed clinical events that were new and distinct from his typical seizures. His mental status still had not returned to baseline at this point.

During 48 h of cEEG, over 20 push-button events of varying lengths were captured. The following symptoms and observations of the episodes are listed here in no particular order: (1) fearful facial expression and calling for his father, (2) non-sustained multi-directional nystagmus, (3) body rolled to right side and right arm became hypertonic, flexed, adducted, and internally rotated, lower extremities held extended, with intermittent right leg shaking (not stereotyped episode to episode), (4) rocking back and forth with a quick frequency and low amplitude, (5) brief tachycardia to 140 beats/min, 6) hypertensive to 150/90 mmHg, (7) tachypnea to at least 25 breaths per min, (8) flushed skin and diaphoretic on forehead, arms, and palms, (9) decreased awareness from baseline, and (10) no electrographic correlate present concurrently. When each episode ceased, his muscles relaxed, heart rate and blood pressure normalized, diaphoresis resolved, and the patient verbalized that he felt better. These episodes lasted from 10 s to 5 min and occurred as frequently as every 10 s during some clusters. No inciting triggers could be identified. The EEG showed mild diffuse slowing and mildly increased beta activity during wakefulness, as well as rare frontopolar predominant sharp waveforms during the first day of monitoring. On the second day, eye leads were added. During the awake state, the background again showed mild slowing with excess beta activity and left > right frontal activity appearing to correspond with the eye leads. During sleep, intermittent interictal discharges were observed, sometimes broad right or maximal at F8/T2/T4/T6, broad discharges from the left hemisphere, and some with a more generalized, frontal predominant field. No electrographic correlate was found for any of the events (Fig. 1).

Given the presentation of abrupt tachycardia, hypertension, diaphoresis, abnormal posturing, and the lack of electrographic correlate to these events, PSH was clinically suspected. Focal status was thought to be less likely given the recurrent presence of auto-

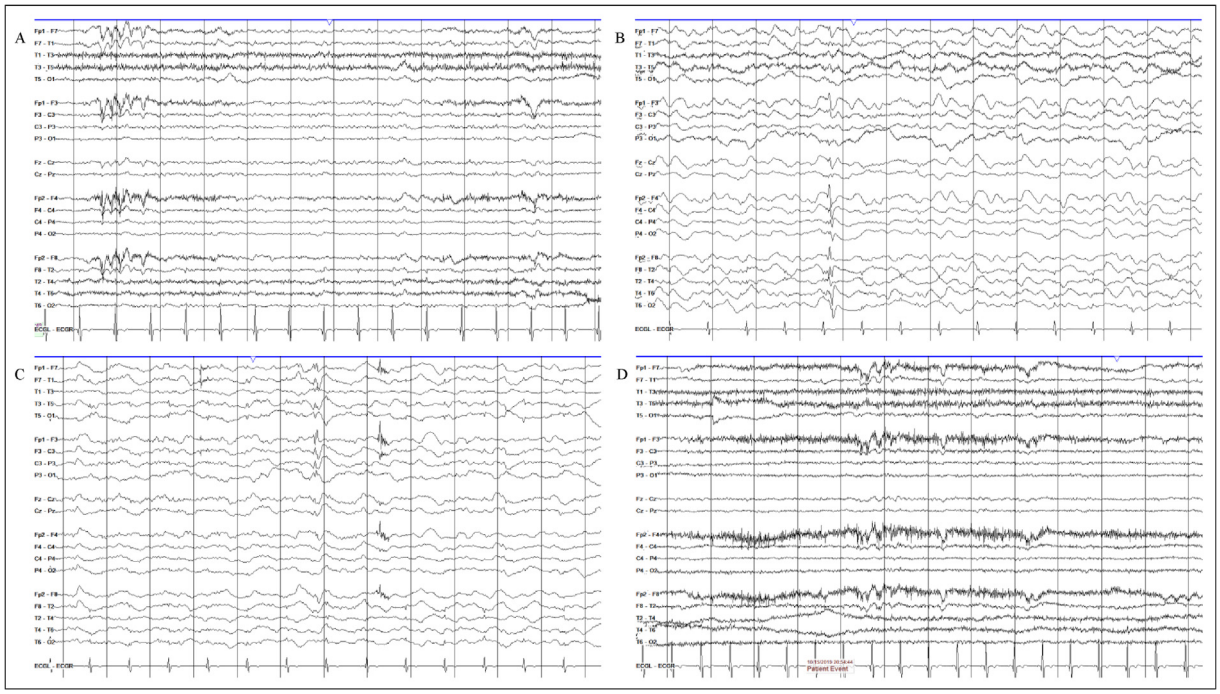

Fig. 1. EEG tracings during admission. A) Longitudinal bipolar montage demonstrating baseline awake EEG; B & C) Longitudinal bipolar montage EEG demonstrating representative, sporadic interictal discharges, seen predominantly during sleep; D) Longitudinal bipolar montage EEG recording at the time of a typical clinical event. There was no clear change in the EEG from baseline seen with events.

nomic features, the lack of clear stereotyped movements, and lack of response to benzodiazepines. Due to the high suspicion for PSH, propranolol was initiated at 10 mg by mouth every 6 h. The episodes decreased in frequency and severity immediately. He did not have any episodes in the first 5 h after taking propranolol. Approximately six hours following each dose, he had minor, but similar, episodes that could be intentionally shortened with deep breathing. This pattern continued and was observed consistently over the next few days. The correlation between propranolol initiation and resolution of the episodes supported the suspected diagnosis of PSH. Over the next few days, the episodes dissipated, and mental status returned to baseline. Propranolol was continued, and the patient was discharged to an acute neurologic rehabilitation hospital.

3. Discussion

The patient's episodes of increased muscle tone and hyperadrenergic state without evidence of seizure activity on cEEG likely represented PSH. Using the PSH Assessment Measure (PSH-AM) outlined in Meyfroidt et al., this patient scored 18, with any score ≥ 17 meaning PSH is the probable diagnosis (Fig. 2) [5]. The main features that differentiated this patient's episodes from those of typical PSH are multi-directional nystagmus and the rocking and shaking movements, which made this presentation more difficult to discern clinically from seizure (Table 1). Given that the episodes were not stereotyped, were not consistent with his typical seizure semiology, had no EEG correlate, did not respond to benzodiazepines, and immediately abated with the administration of propranolol, PSH was the suspected diagnosis. Supportive ancillary testing was not feasible for our patient but could be considered in some cases. Ictal SPECT could be used during an episode to exclude evidence of a seizure focus not seen on scalp EEG, though would require careful coordination of isotrope injection and imaging, as well as consistent patient cooperation. Autonomic testing could also be pursued on an outpatient basis.

There is limited information regarding the incidence of PSH in JNCL. Ostergaard (2018) reported five cases of patients with JNCL who presented with PSH in late adolescence [6]. Mild episodes were evoked by environmental stimuli, such as moving from bed to chair, brushing teeth, and loud noises. More severe episodes, which required ICU admission, were primarily associated with underlying infections as inciting factors. When the inciting factors of the PSH episodes were resolved, the episodes of PSH abated.

A: Clinical feature scale (CFS) score				
	0	**1**	**2**	**3**
Heart rate (beats per min)	<100	100-119	120-139	≥140*
Respiratory rate (breaths per min)	<18	18-23	24-29*	≥30
Systolic blood pressure (mm Hg)	<140	140-159*	160-179	≥180
Temperature (°C)	<37.0*	37.0-37.9	38.0-38.9	≥39.0
Sweating	Absent	Mild	Moderate*	Severe
Posturing during episodes	Absent	Mild	Moderate	Severe*

B: Diagnosis likelihood tool (DLT): one point per feature present
Antecedent acquired brain injury
Clinical features occur simultaneously*
Episodes are paroxysmal in nature*
Sympathetic over-reactivity to normally non-noxious stimuli*
Absence of parasympathetic features during episodes
Features persist for >3 consecutive days*
Features persist for >2 weeks post-brain injury
Two or more episodes daily*
Absence of other presumed causes of features*
Features persist despite treatment of alternative differential diagnosis
Medication administered to decrease sympathetic features*

C: Interpretation of scores	
CFS subtotal	Sum of CFS scores for each of the six features (0-3 points for individual features; maximum subtotal = 18)
CFS subtotal severity scores	0=nil; 1-6=mild; 7-12=moderate; ≥13=severe
DLT subtotal	Sum of points for each feature present (one point per feature; maximum subtotal=11)
PSH-AM	CFS subtotal + DLT subtotal
PSH-AM score	<8=PSH unlikely; 8-16=PSH possible; ≥17=PSH probable

Fig. 2. PSH Assessment Measure. This is the PSH-AM found in Meyfroidt et al. [5]. The patient described had a CFS subtotal of 11 and a DLT subtotal of 7, giving him an PSH-AM score of 18. This makes PSH a probable diagnosis. * Indicates the symptoms present in the patient described.

Table 1
Comparison of PSH and Focal Seizures. While there are some similarities in the presentation, the key differences are the sympathetic features like tachycardia, tachypnea, hypertension, and diaphoresis in PSH as compared to focal seizures. Also, response to treatment can differentiate the two with beta blockade resolving PSH and antiepileptic drugs resolving focal seizures.

	Paroxysmal sympathetic Hyperactivity	Focal Seizures
Definition	"Simultaneous, paroxysmal transient increases in sympathetic (elevated heart rate, blood pressure, respiratory rate, temperature, sweating) and motor (posturing) activity." [7]	Seizure activity initiated in a single area of the brain
Presentation	Tachycardia, tachypnea hypertension, diaphoresis, posturing	Aura, automatisms, lateralizing motor features, vocalizations, post-ictal confusion, hyperadrenergic state, tachycardia if mesial temporal lobe seizure
Stereotyped	No	Yes
Diagnostic Tool	PSH Assessment Measure (PSH-AM), autonomic testing	EEG
Treatment	Beta-blocker	Anti-epileptic drugs
Response to beta-blockade	Responsive	Not responsive

Further, the patients with JNCL that Ostergaard (2018) followed over fifteen years were found to have age-related significant decrease in parasympathetic activity leading to autonomic imbalance and sympathetic predominance by the late adolescent period [6]. About 80% of PSH cases are found in patients after a traumatic brain injury (TBI). The pathophysiology is felt to involve injury to the brainstem causing disruption of descending inhibitory pathways, resulting in spinal circuit excitation [5]. Lesions in the midbrain, pons, periventricular gray matter, corpus callosum, and deep gray nuclei due to brain injuries (anoxic brain injury, stroke, tumors, infections, unspecified) have an increased risk of resulting in PSH [8]. The etiology of PSH in JNCL is unknown, but it has been suggested that there is a loss of inhibitory control over excitatory autonomic centers [5]. Sympathetic outflow may also have reduced manifestations in a pediatric patient given the variation in insular structure connectivity at a younger age [9]. This reasoning could contribute to why episodes of PSH present later in adolescence with JNCL.

There is an ongoing effort to better understand how status epilepticus affects long term brain function. It is evident that prolonged convulsive status epilepticus is associated with high morbidity and mortality because irreversible neuronal activity may occur [10,11]. Neuronal damage occurs in 10 to 50 percent of people with status epilepticus lasting over 30 min, which can lead to neurologic deficits [12]. Given the patient's status epilepticus lasted for at least 12 h without returning to baseline, there is a high likelihood of neuronal injury, and possibly within the pathway mediating autonomic function. Given this patient's previous diagnosis of JNCL, it is also possible that having a neurodegenerative disease could increase the likelihood of neuronal injury during status epilepticus, causing neuronal deficits which potentiate or unmask the presentation of sympathetic excitation.

This report is unique because relatively few patients with JNCL survive into or beyond their early 20 s, and no identical presentation of PSH following status epilepticus has been reported. It is unknown whether this presumed PSH is due to progression of the disease independently or was a consequence of the antecedent status epilepticus. The patient's parents were able to concretely explain and demonstrate video of the differences between the new episodes and the patient's typical seizures. Furthermore, the patient's longstanding child neurologist confirmed that these episodes, as described, were new. Patients with JNCL and other neurodegenerative and neurodevelopmental disorders with associated epilepsy tend to have consistent seizure semiology. When semiology differs, it is important to explore the possibility of a new condition in the context of patient history.

While there are significant limitations to proposing the diagnosis of PSH following status epilepticus in this single instance, this case report aims to make physicians and caregivers aware of the variety of symptoms that can present as a result of an extended lifespan of patients with JNCL. Patients may have further complications from the progression of JNCL with age, which are still unknown given the low prevalence of patients in their third decade of life. It is difficult, yet important, to differentiate if complications arise from the pathophysiology of JNCL or from associated conditions, like status epilepticus [7].

4. Conclusion

This patient's unique presentation suggests that the pathophysiologic underpinnings of paroxysmal sympathetic hyperactivity following status epilepticus may share commonality with those seen following other types of brain injury. Awareness of various presentations of neurologic symptoms in JNCL typically seen in other neurologic disorders remains crucial for understanding later manifestations of JNCL and associated conditions.

5. Declarations of interest

None.

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