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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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. He was blind by age 7, and his seizures persisted. By age 12, he was severely intellectually impaired and suffered from seizures, behavioral issues, cognitive decline, and, sometimes, parkinsonism. He died by age 28 due to his underlying disease.

Paroxysmal sympathetic hyperactivity (PSH) is a well-known complication of traumatic brain injuries due to dysregulation of sympathetic nervous system control [5]. 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.
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, lacosamide 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. 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.](image-url)
onomic 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 isotope 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.

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.
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 pathophysologic 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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