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Drug-Resistant Epilepsy in Children with Juvenile Huntington's Disease: A Challenging Case and Brief Review

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ABSTRACT

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder with a progressive decline in cognitive, motor, and psychological function. Chorea tends to be the most common associated movement disorder, although other variants of several abnormal movements are also seen. Adult-onset HD is the most common subtype. Juvenile Huntington's disease (JHD) accounts for 5% – 10% of all HD cases and presents as a rapidly progressive disorder with a multitude of characteristics. We report on a 9-year-old male with JHD who presented with refractory epilepsy. His EEG findings, seizure type, and antiepileptic drug usage are discussed with a brief review of the currently available relevant literature. The currently reported case sheds light on anti-epileptic drugs that proved effective in our patient and the importance of screening for JHD when a child presents with seizures that are difficult to control.

Keywords: Huntington Disease, Epilepsy

INTRODUCTION

Huntington's disease (HD) is a rare genetic disorder that is inherited in an autosomal dominant pattern often from the patients' paternal side. It is caused by the expansion of a CAG trinucleotide repeat in the HTT gene.[1] This gene produces the Huntington protein, which is thought to be important for basic neuronal function. Patients with Juvenile Huntington's Disease (JHD) often have more than 60 trinucleotide repeats rather than the normally expected 10 – 35 repeats. JHD is typically diagnosed when its onset is before the age of 20 years old.[2] The clinical course is rapidly progressive, often with almost all patients only surviving 10 – 15 years after the appearance of

symptoms.[3] JHD is characterized by bradykinesia, rigidity, dystonia, tremors, myoclonus, slurred speech, swallowing problems, and epilepsy.[4] Seizures are almost entirely limited to JHD in contrast to adult-onset HD. Epilepsy seems to be more prevalent in children who have symptoms before the age of 10 years old.[5] Chorea is also generally absent to minimal in JHD compared with adult-onset HD.[5]

Although seizures appear to be one of the main symptoms of JHD, studies elaborating on details of semiology, clinical course, and diagnostic studies are few. Several years ago, a multicenter review by Cloud et al. discussed 34 cases of genetically confirmed JHD with reported seizures, but only 16 had accompanying EEG data.[6] Seizures also appear to be responsible for more than 50% of hospitalizations of children with JHD.[7] There have been more recently reported cases because of improvements in diagnostic technology and clinical care leading to the expansion of available knowledge of JHD and the features of accompanying epilepsy. We describe a patient with refractory epilepsy and his associated neuroimaging studies, EEG findings, and antiseizure medications.

CASE PRESENTATION

A 9-year-old male first presented to the neurology concussion clinic at the age of 4 years, a year after a motor vehicle accident. During this accident, he was not restrained in the car seat and sustained a concussion. His family was not certain if he lost consciousness during the accident. A brain magnetic resonance imaging (MRI) scan at that time showed a small cystic area with a fluid level and hemorrhages in between the superior wall of the right maxillary sinus and inferior wall of the right orbit, that were likely related to the trauma. However, the brain parenchyma structure was described as essentially normal. Several months after the accident, his family reported some nonspecific yet concerning symptoms, including being offbalance, frequent falling, remarkable changes in his mood, and overall easy fatigue and tiredness. He also had trouble with small hand muscles` functions, such as using a fork, knife, or spoon, and holding pens, pencils, and crayons. He was referred to physical and occupational therapy services accordingly. He showed some clinical response after a few months of therapy sessions, as he was able to run steadily, walk up, and down stairs, use utensils appropriately, speak in sentences, draw, and use pencils and crayons as before. A follow-up brain MRI demonstrated a resolving lesion along the roof of the right maxilla sinus that likely represents a resolving hematoma. Further updated brain MRI images revealed an abnormal T2/FLAIR hyper intensity of the bilateral caudate nuclei and putamina with volume loss, one of the radiological signatures of JHD (**Figs. 1 – A**&**1 – B**).

Regarding his medical history, he was born at 35 weeks via spontaneous vaginal delivery without any complications or time spent in the neonatal intensive care unit. His list of medical problems includes balance problems, developmental delay, eczema, epistaxis, headache, mild intermittent asthma, and later post-concussion syndrome. The patient father was reported to have dementia and progressive cognitive and motor decline; however, he did not have any formal diagnosis of a precise neurological condition. Further family history details were not available. Given the various concerns and family history, the patient underwent genetic testing. Molecular testing of exon 1 of the HIT gene showed 103 CAG repeats of full penetrance consistent with JHD.

He presented to our emergency department at the age of 9 years old because of numerous episodes of generalized onset tonic-clonic seizures and severe abdominal pain. Over a short period, he had increased seizure frequency from weekly to every other day to daily. The seizures were typically described as whole body stiffening, then all extremities rhythmic shaking, along with eye flickering that usually lasted for 1 – 2 minutes. He also had focal onset seizures described as raised bilateral upper extremity, eye deviation to the left, left head torsion without full version, bilateral tonic lower extremities, and rhythmic movements of the mouth. There was no apnea, color changes, or tongue biting.

Nevertheless, at times, he had urinary incontinence. He was started on antiseizure medications, including levetiracetam, oxcarbazepine, clobazam, and clonazepam as needed for spasms and prolonged seizures. His physical exam was evolving with expressive and receptive language delay (nonverbal), truncal hypo tonicity, spastic extremities with cogwheel rigidity, and worsening tremors in the upper extremities. His EEG showed diffuse slowing and epileptiform discharges consistent with mild diffuse encephalopathy and occasional focal slowing in the left posterior quadrant, indicating underlying focal neuronal dysfunction. His follow-up EEG showed rare and independent spike and wave discharges over the central and temporal regions suggesting cortical hyper

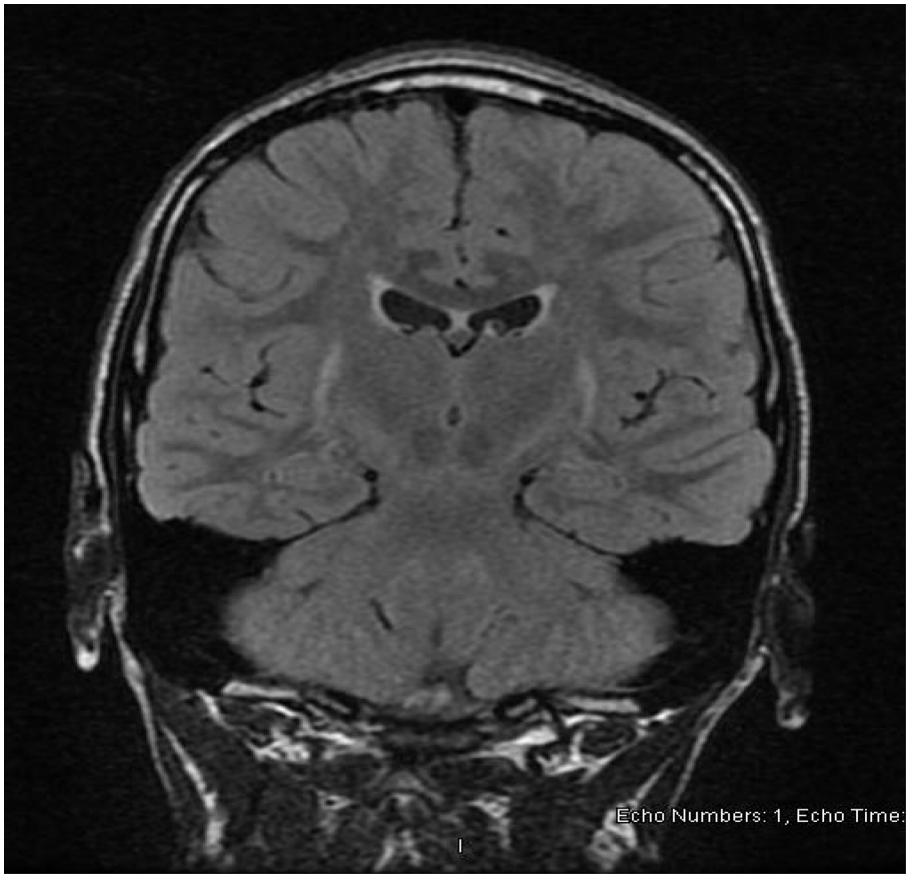

Figure 1-A: Coronal view T2/FLAIR MRI sequence demonstrating abnormal T2/FLAIR hyperintensities of the bilateral caudate nuclei and putamina.

excitability and an increased risk for focal onset seizures (**Fig. 2-A**). It also showed rare bursts of generalized sharp and slow-wave delta discharges with bifrontal predominance, which suggested an increased risk for generalized or focal onset seizure with rapid generalization (**Fig. 2 – B**). There was a generalized background slowing with a posterior dominant rhythm lower than expected for his age and a poorly formed and sustained sleep architecture, which suggested mild encephalopathy. A repeated brain MRI demonstrated the slight interval progression of ex vacuo dilatation of the frontal horns. Also, there was bifrontal periventricular hypo density that was related to the known atrophy of the caudate nuclei and putamina in line with JHD. With time, he also began having frequent myoclonic seizures on a daily basis. Therefore, oxcarbazepine was weaned subsequently.

Apart from struggling with epilepsy control, he has multiple other neurological issues, including severe spasticity with developing contractures, a minimal level of motor function, being wheelchair-bound, slowly progressive swallowing dysfunction, complete loss of vocalization, and continued loss of bowel and bladder control. He also continued to have a variety of almost constant abnormal movements, including generalized bradykinesia, upper extremities tremors, facial tic-like movement, and occasional dystonic movements. This constellation of various movements was only stopped during sleep. His family described some choreiform movements, but it was felt that these were minimal and rather infrequent.

He underwent a trial of tetrabenazine to relieve his continuous movements, but the response was minimal and complicated by a neuroleptic malignant syndrome that led to discontinuing the medication.

DISCUSSION

HD is a degenerative neurological disorder due to the expansion of a progressively abnormal CAG trinucleotide repeat that results in the functional decline across all domains and various movement disorders.[8] JHD is a severe subtype of HD with childhood-onset. It has more severe CAG expansion

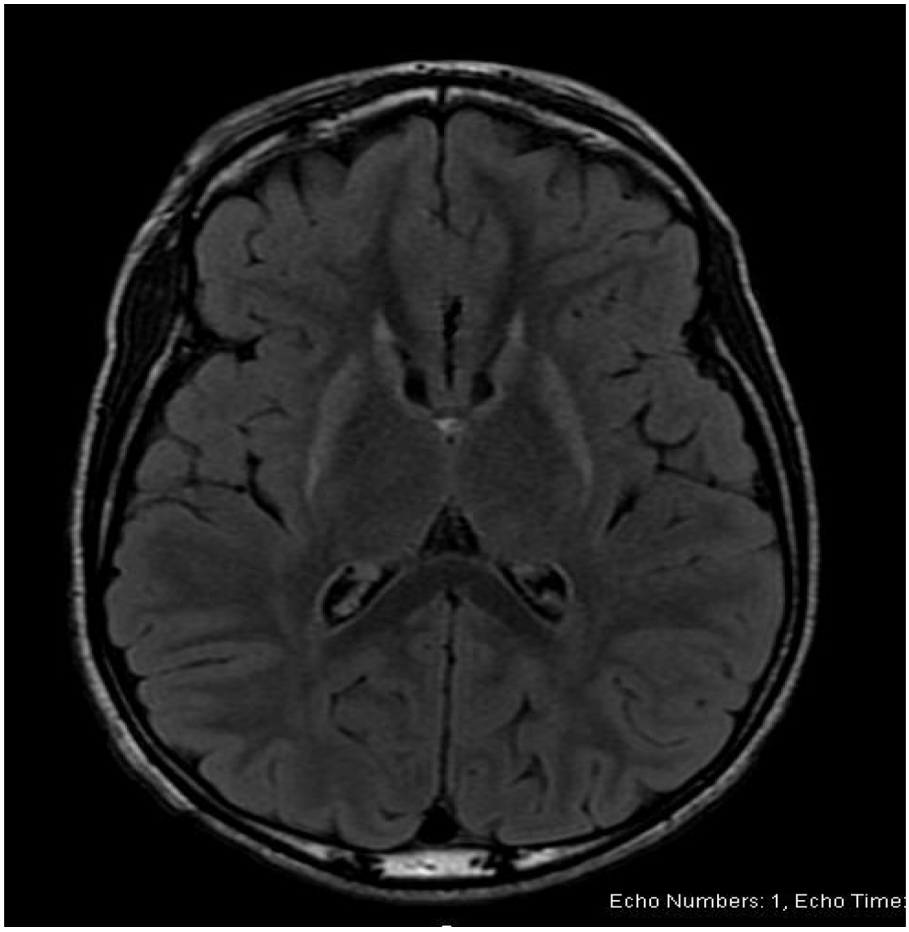

Figure 1-B: Axial view T2/FLAIR MRI sequence demonstrating volume loss of the caudate nuclei bilaterally that resulted in mild expansion of the frontal horns of the lateral ventricles bilaterally.

and more burdens of neuropsychiatric manifestations.[9] Typically, patients have more than 60 CAG repeats, and the vast majority of cases are paternally inherited. There is also growing and accumulating evidence that children with more than 80 CAG repeats may constitute a distinct subgroup of highly expanded genetic locus and have more severe outcomes.[10] Seizures seem to be a very prominent clinical feature in JHD in contrast to adult-onset HD.[11]

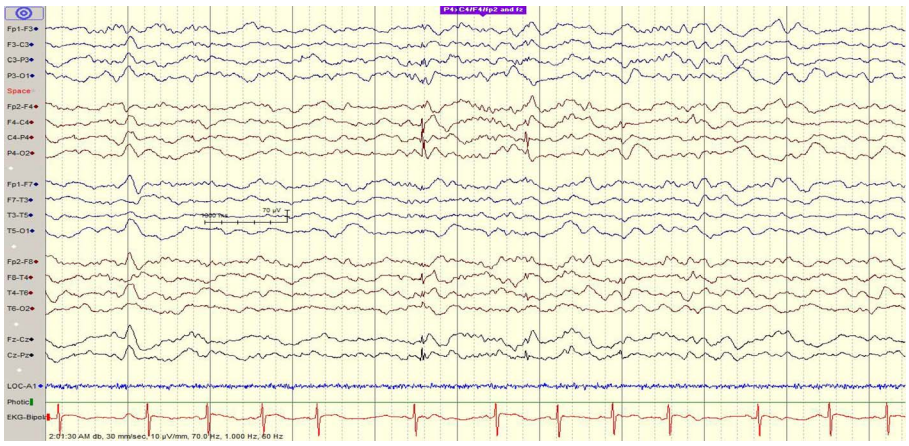

Figure 2-A: Interictal EEG showing bilateral independent epileptiform spike discharges from the right frontal, central, and temporal areas.

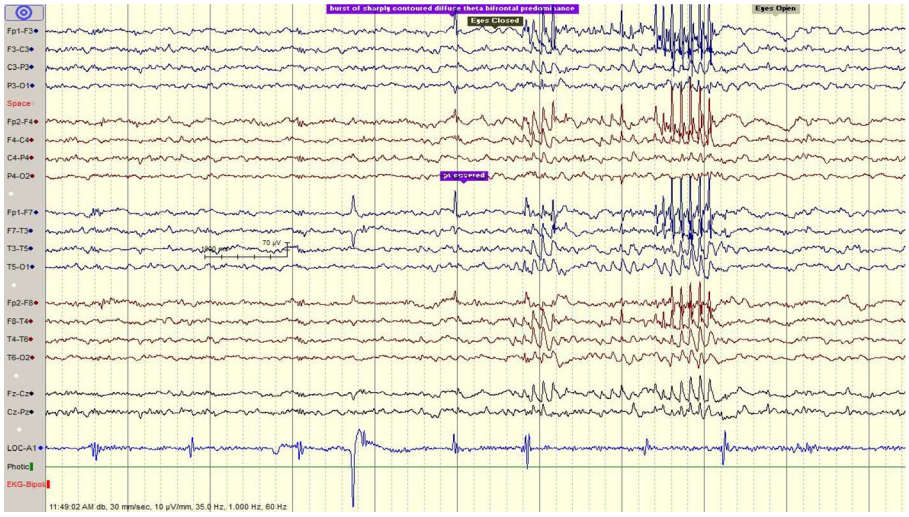

Figure 2-B: Interictal EEG showing runs of sharply contoured theta sharp waves and spikes in the bifrontal areas.

Here, we presented a 9-year-old male with JHD and early-onset refractory epilepsy. Although it is noted that many patients with JHD have epilepsy, the exact underlying neurophysiological mechanisms and etiological pathways remain unclear. Older theories from available neurophysiological studies suggested that early neuronal cortical death is probably a contributing factor.[12] Primary neuronal degeneration and changes in striatal synapses seem to be more noticeable in children with early and severe clinical seizures.[13] It was noted in the available literature that younger age at onset was related to more rapid disease progression and shorter patient survival, which could also explain the burden of our patient's epilepsy.[14] The age of seizure onset appears to be a major factor regarding the intractability and response to antiseizure medications.[15]

The pathophysiology of seizures in JHD remains unknown, especially concerning the age of presentation and severity. We are uncertain if the motor vehicle accident that he sustained at the age of three might have exacerbated the rapid progression of our patient's JHD symptoms. Some epidemiological studies have suggested that concussions or mild traumatic brain injury (TBI) might be associated with a twofold or greater increase in post-traumatic epilepsy. However, a study involving 330 patients determined that there was not an increase in the incidence of epilepsy, and concussions and TBI should not be considered significant risk factors for the first 5 – 10 years following the events.[16]

It is extremely challenging to locate precise epidemiological data about genetically proven JHD since only a handful of reported cases exist across the globe. In the largest published report by Cloud and his group, the prevalence of epilepsy was observed in 34% of patients in the JHD cohort. They concluded that the most common seizure semiology was generalized tonic seizures, followed by myoclonic, and absence seizures.[6] Our reported patient has a mix of generalized tonic-clonic seizures, and unaware focal seizure with secondary generalization, which is not a seizure semiology that has been reported before in JHD, to our knowledge.

Electroencephalogram (EEG) data in epileptic children with JHD are sparse as well. EEG characteristics in patients with adult-onset HD are mostly interictal epileptiform discharges. Landau reported that interictal polyspike wave discharges were the most common epileptiform finding in children with adolescent-onset JHD.[17] A couple of years later, Ullrich et al. reported that generalized polyspike and slow-wave complexes, spike, and slow-wave complexes, multifocal spikes, and focal spikes are the most commonly observed EEG changes.[18] In general, it seems that children with JHD tend to have more generalized spike-wave complexes with polyspikes being the most common observation.[17] Focal or multifocal EEG discharges are less noted. Our patient's EEG demonstrated focal surface negative sharp waves that were identified out of the left occipital (O1 electrode) region throughout the study, with some field-effect extending into the right occipital head region. However, they were otherwise relatively restricted to this focus. A subsequent EEG showed mild diffuse slowing and disorganization of the background and

occasional focal slowing in the left posterior quadrant. His longer monitoring EEG in the epilepsy unit was recently able to demonstrate rare and independent spike and wave discharges over the central (Fz/Cz>F7/FP2/F4/FP1/F3) and temporal (T6) regions, which suggest cortical hyperexcitability and an increased risk for focal onset seizures. This particular video EEG also captured rare bursts of generalized sharp and slow-wave delta discharges with bifrontal predominance, which suggest an increased risk for generalized onset seizures, or focal onset seizures with rapid generalization (**Figs. 2 – A & 2 – B**).

In adulthood-onset HD, several neuroimaging characteristics have been reported. In our patient, a brain MRI obtained at the age of 8 years old showed an abnormal T2/FLAIR hyper intensity of the bilateral caudate nuclei and putamina with volume loss of the caudate nuclei bilaterally. This volume loss resulted in the mild expansion of the frontal horns of the lateral ventricles bilaterally, which were thought to be consistent with the diagnosis of JHD (**Figs. 1 – A & 1 – B**). His brain MR Spectroscopy demonstrated normal metabolite patterns. Some reports described brain MRIs that showed hyper intensity involving the caudate nucleus and putamen on both sides[19] Other studies reported subcortical nonspecific T2 hyper intense lesions, particularly in patients with the rigid, more than the classical hyperkinetic form.[20] Cerebral volumetric loss has also been described in the basal ganglia, thalami, hippocampi, substantia nigra, and cerebellum with varying degrees of atrophy correlating with the disease stage.[21] Spectroscopy and brain positron emission tomography scans might provide a promising biomarker by enabling the early detection of abnormal striatal glucose metabolism.[22] Studies demonstrated that these neuroimaging changes occurred before the emergence of clinical symptoms.[23] Nevertheless, not much is known about typical MRI findings in JHD. One very recent cohort suggested that MRI findings probably extend beyond typical striatal structures as significant cerebellar enlargement was discovered in the JHD cohort, which may explain the observation of more hypokinetic symptoms in children with JHD.[24]

Considering the rarity of available data, the unavailability of consensus regarding seizure management in JHD is not surprising. The most commonly used antiseizure medications include sodium valproate, followed by phenytoin, and carbamazepine.[25] Other less used therapies include clonazepam, phenobarbital, ethosuxamide, gabapentin, zonisamide, and lamotrigine, among others.[5] Although seizures appear to be one of the major symptoms in JHD, most patients are being managed with single monotherapy agents. Intractable drug-resistant epilepsy is rather rare in the cohort of patients with genetically proven JHD. Our reported patient went through several antiseizure medications until the combination of oxcarbazepine, levetiracetam, and clobazam proved to be the most successful and has been well-tolerated.

CONCLUSIONS

JHD is a severe neurodegenerative brain disorder that presents serious diagnostic challenges and management limitations. Epilepsy is one of the major neurological manifestations in JHD, but intractable drug-resistant epilepsy is relatively rare. There are no scientifically rigorous systematic reviews of epilepsy characteristics, EEG features, imaging findings, and evidence-based management strategies. This reported case may provide insight into a unique patient with JHD and refractory epilepsy. Our patient demonstrated an early-onset clinical presentation, focal EEG findings, and medication-resistant epilepsy, which have not been extensively analyzed in this population. It will be interesting to continue to learn about how epilepsy in patients with JHD is being addressed with the vast array of new antiepileptic strategies being produced. Future reviews and prospective studies will hopefully help to determine which seizure management approach is best in this vulnerable group of rare patients to help them maintain the best possible quality of life. A major limitation of our reported case is that he had a history of TBI just before the emergence of his symptoms. This confounding incident made the process of cross-linking the clinical manifestations to the results of diagnostic studies more challenging.

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