Pearls & Oy-sters: Epilepsy is a key feature of pediatric-onset Huntington's disease

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Abstract: Pediatric-onset Huntington's disease (PoHD) presents differently from adult-onset disease. Children typically exhibit regression in school performance, psychiatric features such as inattention, and oral motor dysfunction. Unlike adult-onset HD, in which seizures occur at approximately the rate of the general public, at least half of children with HD develop epilepsy and seizures can be a presenting feature of PoHD. Here we present the case of a 10-year-old boy with a history of language delay, motor regression, oral motor dysfunction, and tremor who presented with a first lifetime seizure. Given a family history of Huntington's disease in his father, PoHD was considered, and a pathogenic allele with 88 repeats was confirmed in the child. As symptoms progressed, history alone could not differentiate abnormal movements from seizures. Continuous video electroencephalography helped to demonstrate epileptic myoclonic jerks and guide treatment.

Pearls:
- Learning delay, psychiatric co-morbidities such as inattention, oral motor dysfunction, and seizures are common presenting symptoms of pediatric-onset HD (PoHD).
- At least half of children with HD develop epilepsy, compared to ~1% in adult-onset HD.
- Continuous video EEG monitoring is a useful diagnostic tool for differentiating seizures, movement disorders, and sleep disturbances in HD.
- Anti-seizure medications can be chosen to address multiple symptoms, such as mood stabilization, movements, and sleep.

Oy-sters:
- PoHD diagnosis may be missed or delayed, since the presentation significantly differs from adult-onset HD.
- Whole exome sequencing does not detect trinucleotide repeat expansions, thus targeted testing is necessary to evaluate CAG repeats in the HTT gene.
- Chorea is less common in PoHD than adult-onset HD, and if present, is less prominent and occurs later in the disease course.

Case Report:
A 10-year-old boy presented to the emergency department with a first lifetime seizure. The event occurred in the early morning. His family described that after brushing his teeth, he started drooling, his eyes deviated upward, both arms began shaking, and he appeared to have difficulty breathing. The seizure resolved within 30 seconds, and he was sleepy for approximately 10 minutes afterwards. He had no recent illness, head trauma, prior history of seizure, or family history of seizure. His family noted a new intention tremor that had worsened over the past 9 months.

The child was born at term after an uncomplicated pregnancy. He sat unassisted at 8 months, walked at 12 months, and talked at 1.5 years of age. However, at 4 years old he was noted to have language delay. By 6 years of age he developed difficulty with previously learned tasks such as using utensils and doing buttons. His speech became difficult to understand and deteriorated to only single words. His behavior became withdrawn and inattentive. At this time, he underwent a neurodevelopmental evaluation at an outside center and was diagnosed with ADHD. Special education services were initiated. Magnetic resonance imaging (MRI) of the brain without contrast (Figure 1), routine electroencephalogram (EEG),
ophthalmologic examination, audiology evaluation, chromosomal microarray, and fragile X testing were unremarkable. Whole exome sequencing demonstrated a single variant of unknown significance in PCDHB2 c.976G>T, p.G326C, not inherited from his mother, and his father’s sample was not submitted. Mitochondrial DNA sequencing was also negative. Family history was notable for Huntington’s disease in his father who was diagnosed in his late 30s and required 24-hour nursing care by age 50. The child’s symptoms were not consistent with adult-onset HD, so his initial work-up did not include testing for HD.

At the time of presentation to the emergency department, our patient had returned to his baseline functional status. On examination, he was a thin boy with language delay. He was able to wave hello and follow simple commands, but he responded only in single words. Cranial nerve testing was normal, including extraocular movements. He was noted to have tic-like movements characterized by frequently rubbing his fingers together or touching the side of his face or shoulder. Due to the patient’s limited language, it was not possible to assess for suppressibility or urge. Reflexes were normal in all extremities. He had decreased axial tone and a positive scarf sign, which can be informative in children as well as neonates. Coordination testing demonstrated intention tremor on finger-to-nose testing, not present at rest. Gait was intact. Comprehensive metabolic panel, complete blood count, and urinalysis were unremarkable. Computed tomography of the head without contrast was normal.

He was referred to Pediatric Neurology Clinic for further work-up. Repeat routine EEG showed a medium voltage disorganized background with occasional 9-10 Hz posterior dominant rhythm. Spike-and-slow wave complexes were prominent in the parietal-occipital regions and occurred in between runs of photic stimulation (Figure 2A). MRI without contrast at 11 years old showed subtly increased T2 hyperintensity and associated volume loss involving the bilateral caudate and putamen, with associated prominence of the lateral ventricles (Figure 1). Generalized volume loss was evidenced by widened cerebral sulci.

Overall, his presentation was most consistent with a unifying diagnosis of pediatric-onset Huntington’s disease (PoHD). The child’s mother requested genetic testing, which demonstrated 19 CAG repeats in the HTT gene allele inherited from his mother and 88 CAG repeats, diagnostic of HD, anticipated from his father’s pathogenic allele with 44 repeats.

The boy was started on levetiracetam but continued to have generalized tonic-clonic seizures, and valproate was added. His behavior worsened including restlessness, aggression, sleep disturbance with frequent nighttime awakenings, and dysphagia. He was tried on risperidone and quetiapine, but these were discontinued due to paradoxical worsening of behavior and sleep. On examination at 13 years of age, he had slow saccades, asymmetric hyperreflexia, with clonus at the left ankle, cogwheel rigidity, bradykinesia, retropulsion, and camptocormia.

His family reported increased shaking on awakening, but the etiology (i.e., seizure versus movement disorder) could not be determined by history alone. Overnight continuous video EEG monitoring in the epilepsy monitoring unit (EMU) demonstrated myoclonic jerks with associated EEG correlate, worse on awakening (Figure 2B), and separately, bursts of poly-spikes and waves with no clinical correlate (Figure 2C). Clobazam was added nightly, which helped both sleep and myoclonic jerks. Over time, clobazam was felt to be contributing to his excessive daytime somnolence, and, therefore, the dose was reduced. Seizures and myoclonic jerks remained under good control. He is currently maintained on levetiracetam 75 mg/kg/day divided twice daily, valproate 30mg/kg/day divided twice daily, and clobazam 0.1mg/kg nightly. A gastrostomy tube was placed due to worsening dysphagia.
Discussion:

HD is caused by a trinucleotide CAG expansion in exon 1 of HTT on chromosome 4p16.3, which encodes the huntingtin protein.1 HD is inherited in an autosomal dominant manner, with anticipation that is more likely to occur when the pathogenic allele is paternally inherited, as in our patient. A normal allele has fewer than 27 repeats, while 40 or more repeats is fully penetrant and will lead to HD.2 Pediatric cases often have more than 60 repeats.3,4 Trinucleotide repeat expansions require targeted testing as they are not detected by whole exome sequencing. MRI often shows atrophy of the caudate and putamen but may be normal early in the disease course.4

In adults, HD classically manifests with early cognitive and/or functional decline with or without psychiatric disturbances, followed by motor symptoms, including chorea. In PoHD, chorea is a less common feature and presents later in the disease course. Cerebellar signs and parkinsonian features, such as rigidity, dystonia, and bradykinesia, are more prominent in PoHD.3,4 Other presenting symptoms characteristic of PoHD include declining school performance, abnormal behavior, oral motor dysfunction, or gait disturbance.3,4 As demonstrated in our patient, the differences between pediatric- and adult-onset of HD makes recognition of PoHD difficult for providers with limited experience with PoHD.

The rate of epilepsy in adult-onset HD is approximately that of the general public (~1%).5 In the pediatric population, however, initial symptoms often include seizures.6 Epilepsy occurs in approximately half of patients with PoHD and is associated with a longer CAG repeat length and younger age of onset.6,8 Much of the existing literature on seizure prevalence in PoHD dates to before the availability of genetic testing, and to date, there is no prospective analysis of epilepsy in PoHD.

Seizures in PoHD are important to consider as one of the most common reasons for hospitalization and causes of significant distress for the patient and caregivers.9,10 Seizures can be generalized tonic-clonic, myoclonic, absence, or mixed, meaning children can have more than one seizure type.7,8 However, if myoclonic seizures are an early presenting symptom, then other forms of progressive myoclonic encephalopathy should be included in the differential diagnosis.3,8,11 EEG abnormalities in PoHD may be generalized, focal, or multifocal.7,8,11 Common features include a disorganized background, spike/polyspike-and-wave complexes, and photo-paroxysmal responses. The EEG may evolve over time to diffuse slowing with abatement of epileptiform discharges.12

Several hypotheses regarding the contributing circuit-level changes leading to seizures in PoHD were recently reviewed.13 Neuronal loss may lead to an imbalance of excitatory and inhibitory synaptic function, as striatal GABAergic medium spiny neurons are especially vulnerable. Pyramidal neurons in motor and premotor cortex exhibit dysmorphic dendrites, loss of dendritic spines, depolarized resting membrane potentials, and higher firing rates. Decreased expression of the glutamate transporter GLT-1 on astrocytes may lead to increased excitation.

Valproate is the most used and likely most effective anti-seizure medication (ASM).7,8,11,12,14 More recently, the use of ASMs such as clobazam, clonazepam, zonisamide, lamotrigine, topiramate, and levetiracetam have been reported.4,7,11,14 Phenytoin and carbamazepine are now used less often due to their side effect profiles.7 Lamotrigine should be used with caution, as it can worsen myoclonus. ASMs should be chosen based on comorbidities both to help target features such as mood, sleep, or movement disorders, and to minimize adverse side effects and polypharmacy. As demonstrated in our patient, continuous video EEG monitoring can help clarify the contribution of seizures, movement...
disorder, and sleep disorder to a patient’s presentation. An EMU stay can also be used to monitor ASM tolerability and effects on mobility, balance, and sleep.

PoHD usually has a shorter duration and more rapid progression than adult-onset HD.\textsuperscript{4,7,15} Three phases have been proposed: (1) behavior challenges, learning difficulties, gait disturbance, oral motor problems; (2) cognitive deterioration, rigidity, speech disturbance, and seizures; (3) more frequent, refractory seizures and loss of ambulation.\textsuperscript{15} On average, adult life expectancy is about 15-20 years after symptom onset, whereas PoHD has an average life expectancy of 8-9 years from symptom onset.\textsuperscript{15}

Overall, epilepsy is underappreciated as a common feature of PoHD but is important for general neurologists, movement disorders specialists, epileptologists, and child neurologists to recognize.

**Figure 1**

**Brain MRI scan demonstrating progression of basal ganglia atrophy over time.** T2 FLAIR axial images at (A) 6 years of age compared with (B) 11 years of age show atrophy of the caudate (arrows) and putamen (arrowheads) at age 11 years. Coronal images at (C) 6 years of age and (D) 11 years of age demonstrate widening of the sulci and ex vacuo expansion of the ventricles at age 11 years.
**Figure 2**

**EEG changes over time.** (A) Initial EEG at 10.5 years of age demonstrating generalized poly-spike and slow wave bursts without clinical changes. Note that these bursts occur between runs of intermittent photic stimuli but are not induced by them. (B) EEG at age 13 demonstrating generalized poly-spikes and slow waves associated with myoclonic jerks, often action-induced, more prominent during wakefulness, but also occurring in sleep. (C) The same EEG at age 13 showing bursts of poly-spikes and slow waves during sleep with no ictal correlate.
References

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