A Native Haitian Woman with Unverricht-Lundborg Disease

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Abstract  
Unverricht-Lundborg disease (ULD) is an autosomal recessive progressive myoclonic epilepsy. The prevalence is highest in specific European countries and North Africa. Affected individuals have myoclonic and tonic-clonic seizures and a variable degree of ataxia and cognitive impairment. We report a native Haitian woman with ULD who was wheelchair bound due to nearly continuous myoclonic seizures exacerbated by activity and emotional distress. The seizures and their dramatic increase with volitional activity were recorded during video electroencephalography monitoring. Rational antiepileptic drug therapy controlled the seizures well enough for the patient to achieve a level of independence she had not experienced in over 25 years.

Introduction  
Unverricht-Lundborg disease (ULD), the “purest” progressive myoclonic epilepsy (PME) syndrome, is an autosomal recessive disorder due to mutations in the cystatin B gene (CSTB). The prevalence is highest in Scandinavia (especially Finland), followed by North Africa, Italy, and France [1, 2]. We describe a native Haitian woman with ULD who was severely disabled from her seizures for over 25 years due to incorrect diagnosis of her epilepsy.
syndrome and ineffective antiepileptic drug (AED) treatment. Initiation of an appropriate AED regimen produced an immediate and profound decrease in myoclonic seizures and a resulting independence she had not experienced since childhood.

Case Report

Clinical History

In 2010, a 41-year-old woman was referred to our center for diagnostic video electroencephalography (EEG) monitoring. She was an only child born in Haiti to nonconsanguineous native Haitian parents. She reported no history of epilepsy in her maternal lineage, and her father died before she was born. Cognitive and motor development were normal, and there was no history of meningitis, encephalitis, febrile seizure, or head trauma.

At age 13 years, without provocation, she began to experience myoclonic and generalized tonic-clonic seizures. Within a year, she was having at least 1 generalized tonic-clonic seizure nearly every day and essentially continuous, low-amplitude myoclonic seizures involving primarily facial muscles and all extremities. Both frequency and amplitude of the myoclonic seizures were increased by volitional activity and emotional distress. Walking became treacherous due to falls from activity-induced myoclonic seizures in the lower extremities, and she became wheelchair dependent. Similarly, eating and drinking were complicated by movement-induced increases in myoclonic seizures of the hands and fingers. Cognition was unaffected. Due to the frequency of her seizures, she was withdrawn from school, and shortly thereafter, she and her mother moved to Brooklyn, NY, USA, where she completed high school while wheelchair bound. She was treated initially with a combination of phenobarbital and carbamazepine, and at some point after moving to the USA, topiramate was substituted for phenobarbital. Upon presentation to our center, her AED regimen consisted of carbamazepine and topiramate, both at 400 mg per day in divided doses. None of these medication combinations had been particularly effective.

Examination, Neuroimaging, and Laboratory Studies

The patient’s general medical examination was normal. Neurological examination was notable for normal cognition and nearly continuous, spatially limited myoclonus in the perioral region as well as in the hands and fingers, creating an appearance similar to fasciculations. There was no ataxia, but independent ambulation was impossible due to the very frequent and large-amplitude activity-induced lower extremity myoclonic seizures.

Complete blood count and comprehensive metabolic panel were normal, as was a brain MRI scan. Serum testing for lysosomal storage diseases, performed in 2012, was negative. In 2016, the patient underwent genetic testing for mutations associated with epilepsy, which revealed a 56 dodecamer repeat in the CSTB gene, consistent with a genetic diagnosis of ULD [3].

Video EEG Monitoring

Upon admission for diagnostic video EEG monitoring (in 2010), all AEDs were discontinued. Interictal wake EEG was notable for continuous, diffuse, often sharply contoured theta slowing and frequent, up to 200 μV, generalized, 4- to 5-Hz spike-wave and polyspike-wave discharges, at times occurring in 1- to 1.5-s bursts. The discharges were more frequent in wakefulness (40–50 per 5 min) than in sleep (15–20 per 5 min), when there were also fragments of generalized discharges (Fig. 1a). There were extremely fre-
quent myoclonic seizures involving the limbs, head, oral region, or axial muscles, clearly exacerbated by both anxiety and volitional movement (online suppl. video 1, www.karger.com/doi/10.1159/000484136). The clinical myoclonus corresponded with a short (<1 s) burst of generalized spike and/or polyspike and wave discharges (Fig. 1b).

Treatment

Prior to discharge from the epilepsy monitoring unit, the patient received an intravenous loading dose of sodium valproate, which immediately resulted in a small but observable decrease in myoclonic seizure frequency. This was followed by an intravenous loading dose of levetiracetam, which produced an immediate and profound decrease in seizure frequency. The patient was incredulous as she observed and felt the regression of the seizures as the drug was infused.

During outpatient follow-up, lacosamide was added to her regimen with additional clinical benefit. For the first time in decades, she could walk unassisted, eat without spilling or dropping food, and speak an entire sentence without multiple pauses and hesitations due to perioral and facial myoclonus. During 7 years of follow-up, multiple attempts to decrease each of the 3 AEDs (sodium valproate 2,000 mg per day, levetiracetam 3,000 mg per day, and lacosamide 400 mg per day) were unsuccessful due to a rapid increase in seizure frequency and associated clinical disability. In addition, separate attempts to substitute clobazam and perampanel for sodium valproate were unsuccessful due to either lack of efficacy or intolerable side effects.

When the CSTB mutation was discovered, the patient underwent a trial of N-acetylcysteine, but she discontinued it on her own because, even at a low dose, she felt nauseous and unwell and had not noticed clinical benefit [4, 5].

Discussion

The PMEs are generalized genetic epilepsy syndromes typically characterized by myoclonic and tonic-clonic seizures, ataxia, and a variable degree of progressive cognitive impairment. They are categorized genetically and phenotypically into 5 major diseases. Although often debilitating, ULD is the clinically mildest PME, in part because the cognitive impairment is rarely severe and may be completely absent.

At clinical onset, ULD may be difficult to distinguish from some of the other PMEs as well as from juvenile myoclonic epilepsy. However, the fundus examination, rate of seizure progression, and presence or absence of ataxia, dementia, and cerebellar signs all provide valuable clinical diagnostic data. In patients with ULD, within several months to a year after onset, the myoclonic seizures become stimulus sensitive, extremely frequent, spatially diffuse, and often difficult to control with AEDs that are generally very effective in juvenile myoclonic epilepsy and other genetic generalized epilepsies, such as topiramate and valproic acid. The reflex myoclonic seizures may be so severe that the patient cannot walk without falling or eat without spilling or dropping their food and drink, as was true in this case. Although the seizures never remit, they may be substantially reduced with appropriate AEDs and in some cases with N-acetylcysteine [4, 5]. The diagnosis is confirmed when genetic testing reveals a mutation in CSTB gene, which encodes a cysteine protease inhibitor [3]. Typically, the mutation is an unstable dodecamer repeat expansion in the promoter region.
Conclusion

ULD should be considered in the differential diagnosis of any patient with a consistent clinical presentation, even if from a low-prevalence area. Patients suspected of having ULD or any of the other PMEs should undergo genetic testing for mutations associated with these syndromes in order to provide a definitive genetic diagnosis and information crucial for treatment, counseling, and prognosis. Aggressive treatment with effective AEDs, particularly levetiracetam, can significantly improve quality of life by increasing independence.

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Fig. 1. a Typical electroencephalography (EEG) during stage 2 non-REM sleep showing very frequent generalized and fragments of generalized epileptiform discharges. b EEG during wakefulness showing high-amplitude generalized epileptiform discharges associated with clinically apparent isolated myoclonic seizures.