Pearls & Oy-sters: When Genetic Generalized Epilepsy Becomes Progressive

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Pearls

- Early signs of Lafora disease can mimic a benign genetic generalized epilepsy of adolescence.
- Early genetic testing and confirmatory skin biopsy are key diagnostic components.
- While management options may be limited to antiseizure rather than curative therapies, there are opportunities to partner with the family and patient to optimize quality of life.

Oy-sters

- Progressive myoclonic epilepsy should be part of the differential in an adolescent patient with a refractory generalized epilepsy.
- Vision complaints and cognitive changes are red flag symptoms in an adolescent with new-onset generalized epilepsy.
- Unusual EEG features like slow posterior dominant rhythm (PDR) for age, occipital-predominant discharges, and photosensitivity should increase suspicion for a progressive myoclonic epilepsy.
- Ethical dilemmas often arise in discussions of a fatal, degenerative process in a teenage patient population. It is important to anticipate and address them early and repeatedly.

A 14-year-old girl presented for second opinion of refractory seizures and perceived visual inattention. She first presented to a neurologist 6 months prior for increasingly frequent episodes of dropping small objects like her cell phone. Given subjective bilateral hand weakness, she was evaluated with contrasted MRI brain and c-spine, EMG/nerve conduction studies of upper extremities, and a routine EEG. All studies were normal, except routine EEG, notable for an 8-Hz PDR with frequent generalized 4-Hz spike and wave discharges. She was diagnosed with juvenile absence epilepsy (JAE) and started on levetiracetam with brief subjective improvement, but persistent dropped objects and momentary impaired awareness. In school, the patient demonstrated increasing difficulty with reading fluency, described as "inability to focus on the page," and with comprehension, attributed to a learning-related attention deficit. Ophthalmologic evaluation demonstrated 20/20 visual acuity bilaterally, so vision changes were initially attributed to momentary impaired awareness. Lamotrigine was added for persistent absence seizures.

At the time of reevaluation, in addition to persistence of previous symptoms, the patient reported difficulty in other subject areas and pervasive mood changes. Physical examination was notable for a well-appearing teen able to speak in fluent, complete sentences with intact immediate and delayed recall, yet with impaired ability to perform hand constructions and perform simple math calculations. She had prominent positive and negative myoclonus at the wrists bilaterally on upper extremity extension. The remainder of her examination was normal. In contrast to 6 months earlier, routine EEG now demonstrated a poorly organized

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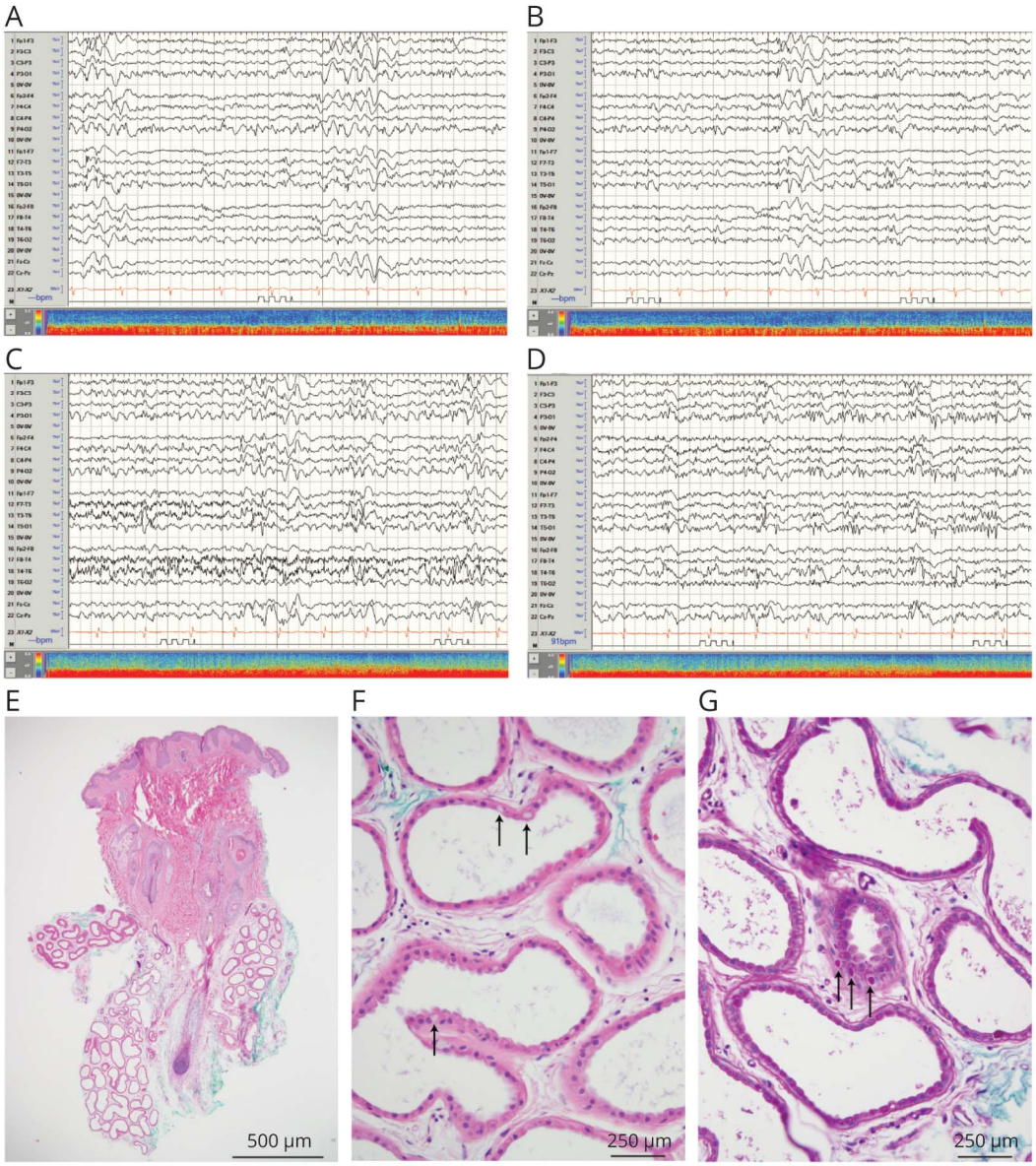
PDR of 5–6 Hz with frequent polymorphic, 4–5 Hz bioccipital, multispike, and slow wave. Photic stimulation produced generalized discharges at nearly all frequencies tested.

An epilepsy gene panel demonstrated 2 *EPM2A* variants: a recurrent pathogenic exon 2 deletion and a missense variant of uncertain significance (c.745 G > T, p.V249L). Parental testing revealed biparental inheritance. Skin biopsy of the axilla revealed diastase-resistant, periodic acid–Schiff positive intracytoplasmic inclusions in the secretory cells of apocrine glands, known as Lafora bodies (figure). This confirmed a diagnosis of Lafora disease.

Upon receiving results, the patient was cross-tapered from lamotrigine to valproic acid given relative contraindication for theoretical worsening of myoclonic seizures on lamotrigine, and levetiracetam was weaned due to lack of efficacy and mood dysphoria. Clonazepam was added to mitigate persistent myoclonic jerks. The patient's family self-initiated a modified Atkins diet for the dual potential benefits of improving seizure control and decelerating disease progression. Over the subsequent 8 months, the

Figure EEG and Skin Biopsy Confirming Lafora Body Disease Diagnosis



EEG recording (15 µV sensitivity, 0.1 TC) displayed as a longitudinal bipolar montage at time of diagnosis displays a posterior dominant rhythm (PDR) of 6 Hz while awake (A) and intermittent 3–4 Hz polyspike and wave discharges during wake and sleep (B) with admixed, occipital-predominant spikes. EEGs 6 months later are notable for more prominent slowing of the PDR to 5 Hz with more frequent occipital interictal epileptiform discharges during wake (C) and nearly continuous bilateral, posterior temporal-occipital discharges during sleep (D). Skin biopsy from the axilla at low magnification (E) contains eccrine and apocrine sweat glands. Under higher magnification, scattered perinuclear, intracytoplasmic inclusions are visible (arrows) in the secretory cells of apocrine sweat glands (F). These polyglucosan inclusions, known as Lafora bodies, are more readily apparent with periodic acid–Schiff stain (arrows, G).

patient has become progressively cognitively impaired, most notably with short- and long-term memory deficits, despite a relatively low seizure burden. Per parental wishes, she remains cognizant of her diagnosis of intractable epilepsy yet does not have insight into the name or progressive nature of her disease.

Discussion

Lafora disease is a lethal, neurodegenerative myoclonic epilepsy, with an estimated overall frequency of 4 per million individuals worldwide.[1] It typically presents in healthy older children and early teenagers (range 8–19 years, peak 14–16 years), similar to many genetic generalized epilepsies, such as JAE or juvenile myoclonic epilepsy (JME). While the early stages may be similar as multiple seizure types including myoclonic, tonic-clonic, and absence seizures are present in Lafora disease and JME, focal occipital seizures with transient blindness or visual hallucinations are relatively specific to Lafora disease.[2,3] Lack of response to 2 antiseizure medications would be unusual for JAE or JME, as would progressive cognitive and psychological impairment matched by EEG changes (slowing of the PDR, frequent occipital or generalized, irregular spike-wave discharges, loss of sleep features, and photosensitivity).[2] While these symptoms prompted consideration of a progressive myoclonic epilepsy,[3] additional degenerative processes must be considered including metabolic, mitochondrial, or rarely lysosomal disorders. Blood and CSF lactate levels, visual and somatosensory evoked potentials, dilated ophthalmologic examination, and magnetic resonance spectroscopy are additional evaluations that may yield different etiologic clues.

Clinically, Lafora disease progresses to increasingly refractory seizures including status epilepticus, cognitive decline at or after seizure onset, dysarthria, ataxia, and subsequently spasticity and dementia.[2] It is imperative to keep Lafora disease on the differential for genetic generalized epilepsy, as management and prognosis are very different. In Lafora disease, most patients die within 10 years of symptom onset, typically from aspiration pneumonia related to status epilepticus.[1]

To establish a diagnosis, genetic testing remains the gold standard, supported by ancillary skin biopsy. Lafora disease is an autosomal recessive disorder, caused by biallelic loss of function variants in *EMP2A* or *NHLRC1*, which respectively encode laforin and malin. Physiologically, laforin (a phosphatase) and malin (an E3 ubiquitin-protein ligase) regulate glycogen chain formation; if absent, poorly branched and hyperphosphorylated glucose polymers aggregate in neurons, skin, liver, and skeletal muscle as insoluble polyglucosans, visualized as pathognomonic Lafora bodies on skin biopsy. Falsely negative skin biopsies are potential pitfalls early in the disease course. A genotype–phenotype correlation of Lafora disease has not been established. In contrast, among patients with allelic homogeneity, there is clinical heterogeneity. Our patient fit the diagnosis of Lafora disease clinically, but a skin biopsy was completed given the uncertainty of a VUS and to facilitate entry into a natural history study and potential clinical trial. Brain MRI is usually unremarkable at onset, as in this patient, though mild cerebellar or cortical atrophy can be seen at later stages.[1]

Currently, treatment for Lafora disease is supportive, first focused on achieving seizure control with minimal side effects. Antiepileptic agents found to be most effective include valproic acid and benzodiazepines as first line, then levetiracetam, zonisamide, and topiramate as myoclonic seizures become refractory.[4] A recent open-label trial studied perampanel as an adjunct for 10 patients with Lafora disease; 4 patients had a significant reduction in seizures, almost 75% from baseline.[5] Many of these agents, as well as phenobarbital or primidone, are considered effective for myoclonic epilepsy of other etiologies. In Lafora disease, phenytoin, lamotrigine, carbamazepine, and oxcarbazepine are relatively contraindicated due to a potential exacerbation of seizure burden.

Given that neurodegeneration presumably arises from accumulation of Lafora bodies, lowering the rate of glycogen synthesis is also a therapeutic approach, for which metformin and the ketogenic diet have been studied, thus far with equivocal results. Metformin, through AMP-activated protein kinase, nonspecifically inhibits ATP-consuming pathways such as glycogen synthesis. A retrospective study of 12 patients with Lafora disease treated with adjunctive metformin for 18 months demonstrated only 3 patients with a clinical response (including 2 with transiently reduced seizure burden and global clinical improvement), though the patients studied were middle to late stage in their disease course, limiting conclusions about the potentially preventative effects of this therapy.[6] Our patient's family had self-initiated a modified Atkins diet, a less restrictive variation of the ketogenic diet. The ketogenic diet is a high-fat, low-carbohydrate diet that relies on fatty acids as a primary energy source rather than glucose to minimize glycogen formation and subsequently Lafora body formation. A study in 2006 evaluated 5 patients at various stages treated with the ketogenic diet; while the diet was tolerated, it did not appear to change disease progression in this limited cohort.[7] Quality of life should also be considered in switching to a restrictive diet with an as yet unproven benefit. Multiple emerging precision therapies offer hope for upcoming clinical trial recruitment including adeno-associated virus–mediated replacement of *EPM2A* or *NHLRC1*[3] to rescue haploinsufficiency, fusion of a cell-penetrating antibody to pancreatic α-amylase, which digests Lafora bodies (VAL-0417),[8] and an antisense oligonucleotide for PTG, a glycogen synthesis activator, to limit Lafora body production.[9]

Because treatments are currently limited and the prognosis is invariably a rapid decline within 10 years, early psychosocial support is a priority. For this patient, guidance from a hospital-wide ethics committee was sought both for routine care and research assent, as family preferences for nondisclosure were balanced with the obligations of the medical team for truth-telling to jointly maximize quality of life of the patient. Another issue to consider is genetic testing of

asymptomatic family members, as our patient is the oldest of 5 healthy siblings. Most professional organizations recommend deferring testing of asymptomatic minors[10,11]; however, guidelines also acknowledge certain situations when testing may allow for early and deliberate social, financial, and medical planning.[12,13] Interestingly, a majority of parents surveyed in other childhood-onset neurodegenerative disorders have advocated that the ultimate decision whether to pursue testing rest with the affected family rather than the medical team. Providers are encouraged to initiate ongoing, longitudinal conversations with families about their motivations to test and engage in joint decision-making with assistance from genetic counselors while contemplating these difficult decisions.

Conclusion

Lafora disease is an autosomal recessive, progressive myoclonic epilepsy with a fatal prognosis. The diagnosis must be considered early in genetic generalized epilepsies with a similar onset, but clinicians should be perceptive of its differentiating symptoms, including vision changes, cognitive decline, and medically refractory seizures. The field requires further research on pathology-directed treatment, as current management is symptom-based, yet there are promising clinical trials on the horizon. Lastly, the young adolescent patient population poses unique ethical dilemmas as clinicians and families navigate discussions on prognosis with the patient.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Monica Aldulescu, DO	Department of Pathology, Ann & Robert H. Lurie Children's Hospital of Chicago, IL	Acquisition of pathology images
Cynthia Stack, MD	Division of Pediatric Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago, IL	Acquisition and interpretation of EEG recordings
Tracy Gertler, MD, PhD	Division of Pediatric Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago, IL	Primary clinical neurologist, coauthored manuscript

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