

# Lafora Disease

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*Lafora disease (LD) is an autosomal recessive disorder characterized by seizures and progressive neurologic deterioration, and is usually fatal within 10 years of onset. LD is a member of the family of progressive myoclonic epilepsies, which are a heterogeneous group of disorders characterized by myoclonic epilepsy, developmental regression, and associated neurologic symptoms. The following is a report and discussion of a 20-year-old man with no relevant past medical history until the age of 16 years when he had his first generalized tonic-clonic seizure. At a recent medical evaluation, he reported having clusters of generalized tonic-clonic seizure activity 2 to 3 times per week, had recently developed status epilepticus, and was having progressive impairment of cognitive function. The unique clinical elements of LD, including later onset of disease, the excellent initial response to anticonvulsants, and the neurophysiologic clues to the diagnosis are discussed and detailed in relation to this man. Additional research is required to discover a third, unknown locus for LD and to further elucidate the features of the laforin and malin complex-associated pathway. No preventative or curative treatment is currently available for LD and treatment focuses on palliation. [Rev Neurol Dis. 2006;3(3):131-135]*

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**Key words:** Lafora disease • Progressive myoclonic epilepsies • Lafora bodies • Spike-wave discharges • EPM2A • NHLRC1

**L**afora disease (LD) is an autosomal recessive disorder characterized by seizures and progressive neurologic deterioration. It is usually fatal within 10 years of diagnosis, although relatively milder phenotypes have been reported. It is a member of the family of progressive myoclonic epilepsies (PMEs), which are a heterogeneous group of disorders characterized by myoclonic epilepsy, developmental regression, and associated neurologic symptoms. We present the case report of a recently diagnosed patient that emphasizes some of

the unique clinical elements of LD, including later onset of disease, excellent initial response to anticonvulsants, and neurophysiologic clues to the diagnosis.

### Case Report

The patient is a 20-year-old right-handed man with no relevant past medical history until age 16 years, when he sustained his first generalized tonic-clonic seizure. Initial diagnosis included neurocysticercosis due to a small calcified lesion discovered on magnetic resonance imaging, since the patient resided in an endemic area. The patient was treated with a 6-month course of steroids, during which time he was seizure-free. He continued to be seizure-free for approximately 1 year after discontinuation of steroid therapy with phenytoin. Recurrence of tonic-clonic seizures followed a single instance of alcohol ingestion. He was restarted on anti-epileptic drug (AED) therapy, which failed to prevent the seizures. Multiple anticonvulsant medication trials were then initiated, with initial response but limited effect. At the time of evaluation the patient had clusters of generalized tonic-clonic seizure activity 2 to 3 times per week, usually occurring while awake, with markedly fewer seizures at night. He also had recently developed status epilepticus. The patient reported sometimes having a "bad smell" prior to a seizure. Since the recurrence of seizures, his family noted a slowing in his cognitive functioning that they ascribe to his multiple AEDs (5 in total) as well as to the recurrent seizures. Prior to recurrence, the patient had completed high school and enrolled in an engineering program at his local university. He was fluent in English and Spanish. Currently, however, he is having significant word-finding difficulties in

both English and Spanish, and progressive difficulties in reading.

The patient was born in Guatemala, he had no relevant past medical history, and he denied any other significant past history, including the abuse of ethanol or illicit drugs. Family history was positive for a great aunt and a second cousin with a seizure disorder of unknown etiology. The parents are of Latin American origin without history of consanguinity.

On admission, the patient's general medical examination was normal. On neurologic examination, he

complexes seen during the waking state. There was a marked attenuation of these complexes during drowsiness and sleep. A diagnostic skin biopsy revealed characteristic Lafora polyglucosan bodies (Figure 2).

### Discussion

LD, first described by Gonzalo R. Lafora in 1911,<sup>1,2</sup> is an autosomal recessive disorder characterized by seizures, cognitive decline, and progressive neurologic deterioration, leading to death within 10 years of onset. LD is classified under the PMEs. Compared with other PMEs it

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*Cerebellar ataxia, progressive dementia with psychosis, and muscle wasting with respiratory failure leading to death develop as the disease progresses.*

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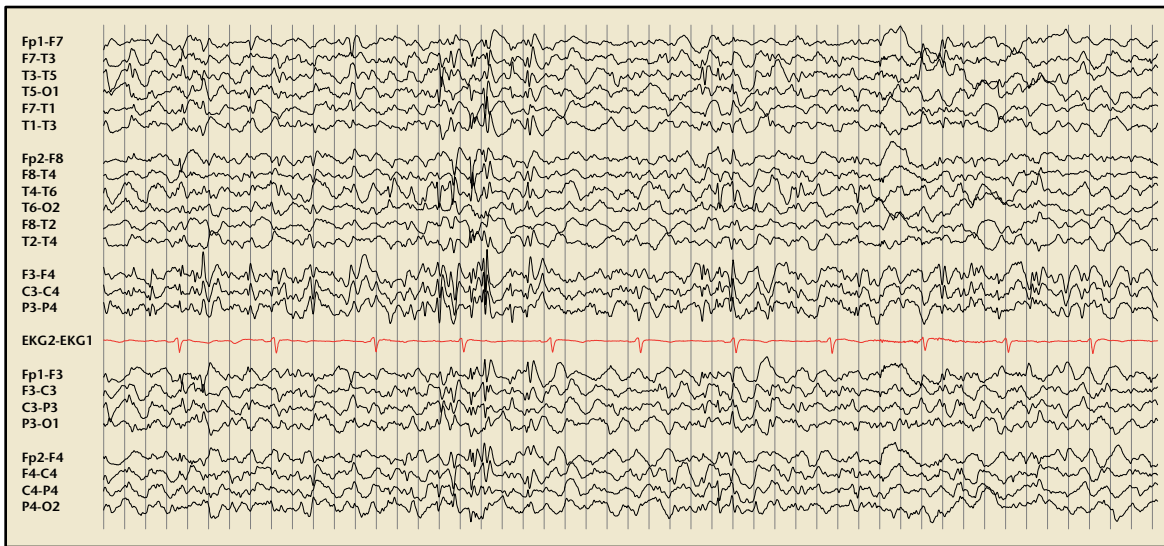
was oriented to name and place, but not time—he missed the month and day, but knew the year. Speech was slow with significant word-finding difficulties. He was unable to follow 3-step commands. Cranial nerves 2 to 12 were intact to testing, with normal strength, bulk, tone, and sensation in all extremities. Coordination examination was abnormal, with diminished finger-to-nose and rapid alternating-movement testing. Frequent myoclonic jerks were noted involving the hands and arms during the examination. There was no evidence of gross ataxia.

### Investigations

Video electroencephalogram (EEG) monitoring showed multiple eye-flickering events lasting several seconds accompanied by runs of 3 to 4 Hz polyspike discharges, predominant in the frontocentral regions bilaterally (Figure 1). Interictally, the EEG displayed moderate (5 to 6 Hz) background slowing with frequent multifocal bisynchronous and independent spike and spike-wave

has a later onset, usually occurring between the ages of 10 to 18 years.<sup>3</sup> LD may be benign initially, presenting as a primary generalized epilepsy, and being responsive to medications during the early phase. However, this is short-lived, with the appearance of myoclonus and refractory seizures within the first 2 to 4 years. Other seizure types include tonic-clonic, absence, complex partial seizures, and prominent myoclonus. Cerebellar ataxia, progressive dementia with psychosis, and muscle wasting with respiratory failure leading to death develop as the disease progresses. Visual hallucinations can be a prominent feature, often in association with occipital seizures in the early phase of the disease. With progression of the illness, status epilepticus and refractory myoclonus become prominent features.<sup>4,5</sup>

The electrophysiologic features of LD are dynamic, changing over the time course of the disease. Initially, the EEG consists of multifocal spike and wave discharges, sometimes occurring in complexes with an



**Figure 1.** Awake electroencephalogram. Prominent background slowing and multifocal spike-wave discharges are evident, with occasional 3 to 4 Hz bisynchronous spike-wave bursts.

approximate frequency of 3 Hz with a preserved background. Photosensitivity is present at this time, with epileptiform discharges elicited by low-frequency photic stimulation. Spike and wave discharges can attenuate during sleep, with preservation of sleep architecture (Figure 3). As the disease progresses, however, there is deterioration of the background and sleep architecture. Generalized epileptiform bursts are seen, with faster frequency spike-wave complexes when compared with the initial phases of the disease.<sup>6</sup> This EEG progression is characteristic of LD and, together with the attenuation of spike-wave discharges in sleep, should raise the possibility of PMEs in any given patient.

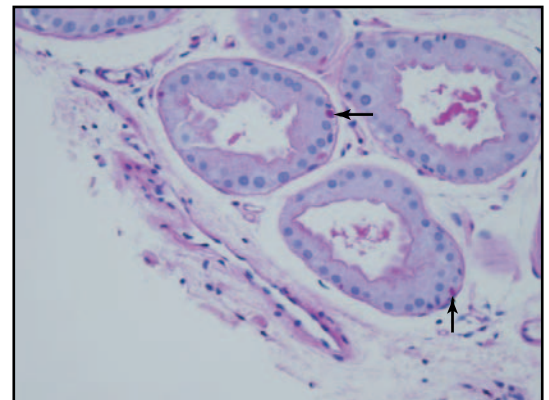
LD displays pathognomonic basophilic periodic acid-Schiff-positive (PAS+) intracellular polyglucosan bodies, known as Lafora bodies, located in the central nervous system, retina, liver, muscle, and sweat gland duct cells (Figure 2). Currently, 2 genes (EPM2A and NHLRC1) have been isolated that are responsible for the LD phenotype.<sup>7</sup> The EPM2A gene is found on the 6q24 chromosome and encodes a protein phosphatase

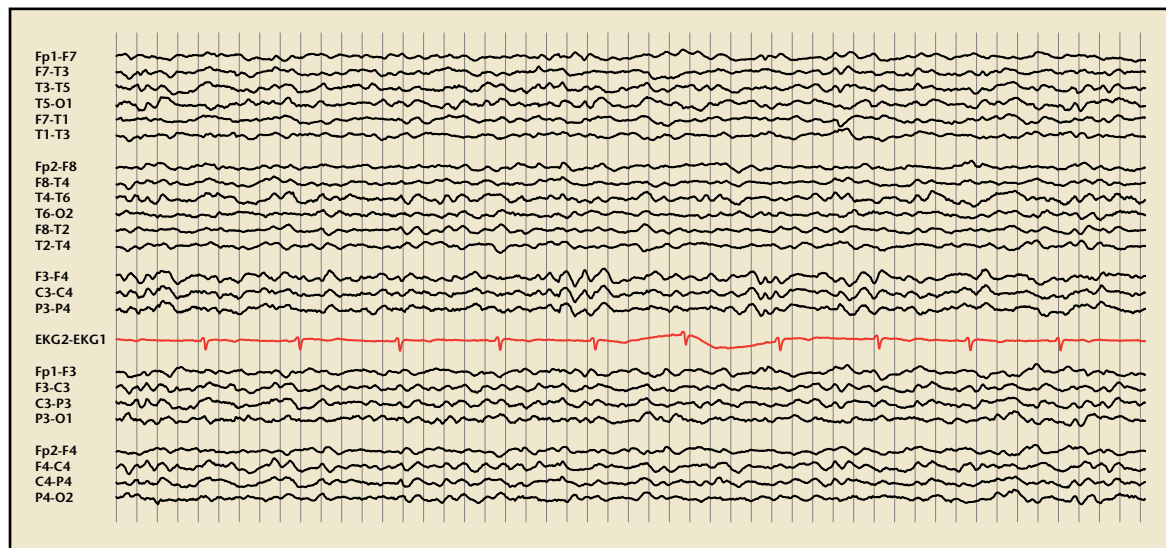
known as laforin.<sup>8</sup> Currently, 38 different mutations and polymorphisms have been described in the EPM2A gene, including missense, nonsense, insertion, and deletion mutations. There is a great deal of allelic heterogeneity with the LD phenotype, without the identification of a specific site mutation. This results in the prediction of only a small number of mutant alleles in specific populations. Most of these mutations to laforin are thought to be functionally “null,” with loss of phosphatase activity. For example, a nonsense mutation may result in an abnormally shortened RNA tran-

script, thereby truncating the protein, whereas a missense mutation may affect the structure or function of laforin, producing a “null” effect.<sup>9,10</sup> These missense mutations can occur in several regions of the EPM2A gene, with the same effect on the protein, possibly by affecting proper post-translational folding. Missense mutations can also affect the interaction of laforin with R5 and malin, which are proteins that interact with laforin in vivo.

Mutations of the NHLRC1 gene result in an LD phenotype that has a less severe course and longer lifespan than that of the EPM2A mutation.

**Figure 2.** Eccrine gland biopsy at 40x. Characteristic Lafora polyglucosan bodies can be visualized as periodic acid-Schiff-positive intracellular inclusions (arrows).





**Figure 3.** Sleep electroencephalogram. There is marked attenuation of the spike-wave complexes, with occasional poorly formed spindle activity noted.

NHLRC1 is located on the 6p22 chromosome and encodes malin, an ubiquitin ligase that is involved in the ubiquitin-mediated proteolysis cascade. Malin regulates the cellular concentration of laforin through ubiquitin-mediated degradation.<sup>11</sup> Missense mutations of NHLRC1 disrupt the ubiquitin ligase activity of malin, interfering with the above degradation pathway.

Approximately 10% of LD families screened for EPM2A and NHLRC1 showed no sequence abnormalities, suggesting a third, unknown locus for LD. Chan and colleagues<sup>12</sup> reported the genotyping of a consanguineous LD family with multiple affected members, which showed no involvement of either the EPM2A or NHLRC1 locus.

The pathologic hallmark of LD is the Lafora polyglucosan body, which is an intracellular aggregate composed mainly of glucose and protein (Figure 2). Lafora bodies stain positive for anti-ubiquitin and anti-advanced glycation end-product antibodies. This suggests that the Lafora body represents a by-product of a defective biochemical pathway

related to glycogen metabolism, with mutations in laforin interfering with steps in glycogen synthesis. Higher concentrations of Lafora bodies are found in organs with the highest glucose metabolism, including the brain, heart, and liver.<sup>13,14</sup> Higher amounts of laforin are normally found in these areas as well. In the mouse model, disruption of the EPM2A gene resulted in the forma-

sively to the glycoprotein accumulation products found in Lafora bodies, as cellular degeneration occurs even in their absence. It is the disruption of the pathway associated with the laforin-malin complex that seems to lead to cellular degeneration and death, thereby producing the LD phenotype. Additional research is required to further elucidate the features of this pathway, and to dis-

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*Currently, there is no preventative or curative treatment for LD.*

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tion of Lafora bodies, neurodegenerative changes, ataxia, and myoclonic epilepsy. However, the majority of degenerating neurons did not contain Lafora bodies, suggesting that the neurodegeneration in LD is a global phenomenon and not linked only to the presence of accumulation products.<sup>15</sup>

The interaction between malin and laforin seems to regulate a common biochemical pathway that is integral to the normal functioning of neurons. It does not seem that the pathology of LD is related exclu-

cover the third mutation responsible for LD.

No preventative or curative treatment is currently available for LD. Treatment focuses on palliation, with valproate, phenobarbital, and benzodiazepines the traditional mainstays of therapy, as these seem to be the most effective in treating the concomitant myoclonus. Recent clinical experience suggests that newer anticonvulsants such as levetiracetam, piracetam, and zonisamide are effective therapies for the myoclonus and seizures. ■

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## Main Points

- Lafora disease (LD) is an autosomal recessive disorder that is usually fatal within 10 years of onset and is characterized by seizures, cognitive decline, and progressive neurologic deterioration.
- Studies of LD have demonstrated that electroencephalograms initially consist of multifocal spike and wave discharges, often occurring in complexes with an approximate frequency of 3 Hz with a preserved background. As the disease progresses, however, generalized epileptiform bursts are seen, with faster frequency spike-wave complexes and background deterioration.
- Although the EPM2A and NHLRC1 genes have been isolated as responsible for the LD phenotype, studies also suggest a third, unknown locus for LD.
- The pathologic hallmark of LD is the Lafora polyglucosan body, an intracellular aggregate composed mainly of glucose and protein; however, studies suggest that the neurodegeneration in LD is a phenomenon not linked only to the presence of glycoprotein accumulation products.
- The disruption of the pathway associated with the laforin-malin complex seems to lead to cellular degeneration and death, thereby producing the LD phenotype.
- No preventative or curative treatment is currently available for LD and treatment focuses on palliative care.