RESEARCH PAPER

Genetically Confirmed Lafora Disease Presenting as Progressive Myoclonic Epilepsy in an Adolescent Female: A Case Report

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Abstract

Background: Lafora disease is a rare autosomal recessive progressive myoclonic epilepsy caused by pathogenic variants in the EPM2A or NHLRC1 genes. It typically presents during adolescence with progressive myoclonus, generalized seizures, cognitive decline, and rapid neurological deterioration. Early diagnosis remains challenging because initial clinical manifestations often overlap with other epileptic syndromes.

Case Presentation: A 17-year-old girl presented with a two-month history of involuntary jerky movements involving all four limbs, gait imbalance, impaired attention, and progressive memory decline. She had experienced recurrent episodes of loss of consciousness over the preceding two years and had discontinued antiepileptic therapy three months before presentation. Neurological examination demonstrated cognitive impairment (MMSE 18/30; MoCA 11/30), generalized myoclonic jerks, and cerebellar ataxia. Electroencephalography revealed generalized periodic epileptiform discharges with electrographic seizures, whereas magnetic resonance imaging of the brain was unremarkable. Whole exome sequencing identified a homozygous likely pathogenic EPM2A variant (c.2T>G), confirming Lafora disease. The patient was initially treated with multiple antiseizure medications and intravenous immunoglobulin. Four months later, she developed refractory status epilepticus requiring intensive care, mechanical ventilation, intravenous methylprednisolone, and escalation of antiseizure therapy. Although seizure control improved, persistent myoclonus and progressive cognitive impairment remained.

Conclusion: This case highlights the importance of considering Lafora disease in adolescents presenting with progressive myoclonic epilepsy and cognitive decline despite normal neuroimaging. Electroencephalography combined with early genetic testing is crucial for establishing the diagnosis, guiding management, facilitating genetic counselling, and avoiding delays in recognizing this rapidly progressive neurodegenerative disorder.

Keywords: Lafora disease; Progressive myoclonic epilepsy; EPM2A; Whole exome sequencing; Status epilepticus; Genetic diagnosis

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Introduction

Lafora disease (LD) is a rare, fatal, autosomal recessive neurodegenerative disorder belonging to the group of progressive myoclonic epilepsies (PMEs). The disease is primarily caused by pathogenic variants in the EPM2A or NHLRC1 genes, which encode the proteins laforin and malin, respectively. These proteins regulate glycogen metabolism, and their dysfunction results in the accumulation of insoluble polyglucosan inclusions known as Lafora bodies within neurons and several extra-neural tissues. Progressive neuronal damage caused by these abnormal glycogen deposits leads to worsening epilepsy, cognitive impairment, cerebellar dysfunction, and premature mortality. (1,2)

The disease typically manifests during late childhood or adolescence, most commonly between 10 and 18 years of age, in previously healthy individuals. Initial symptoms usually include generalized tonic-clonic seizures, myoclonic jerks, visual seizures, or focal seizures, followed by rapidly progressive cognitive decline, behavioral disturbances, cerebellar ataxia, dysarthria, and increasing neurological disability. As the disease progresses, seizures become drug resistant, and many patients eventually develop recurrent episodes of status epilepticus requiring intensive care support. Despite advances in epilepsy management, the prognosis remains poor, with progressive neurological deterioration over the subsequent years. (1,3,4)

The diagnosis of Lafora disease is often delayed because its early manifestations overlap with several

other causes of progressive myoclonic epilepsy, including Unverricht-Lundborg disease, neuronal ceroid lipofuscinosis, mitochondrial disorders, and other inherited epileptic syndromes. Electroencephalography commonly demonstrates generalized spike-wave or polyspike-wave discharges with progressive background slowing, whereas magnetic resonance imaging may remain normal during the early stages of the disease. Consequently, neuroimaging alone is insufficient for establishing the diagnosis. Recent advances in molecular diagnostics, particularly whole exome sequencing, have significantly improved the accuracy and timeliness of diagnosis by enabling definitive identification of pathogenic variants in EPM2A or NHLRC1. (5,6,7)

Currently, no disease-modifying therapy is available for Lafora disease, and treatment remains largely supportive. Management primarily focuses on controlling seizures using combinations of antiseizure medications while avoiding drugs that may aggravate myoclonus. Additional supportive measures, including rehabilitation, nutritional support, psychological care, and genetic counselling, play important roles in improving quality of life for affected patients and their families. Early genetic confirmation is also valuable for family screening and reproductive counselling in view of the autosomal recessive inheritance pattern. (2,8)

We report the case of a 17-year-old adolescent female presenting with progressive myoclonic epilepsy, cognitive decline, cerebellar ataxia, and recurrent refractory seizures. The diagnosis was confirmed by whole exome sequencing demonstrating a homozygous likely pathogenic EPM2A variant (c.2T>G). This case highlights the diagnostic value of integrating clinical evaluation, electroencephalographic findings, and molecular genetic testing in adolescents with progressive myoclonic epilepsy, particularly when conventional neuroimaging remains unremarkable. The report also emphasizes the therapeutic challenges associated with this rare and relentlessly progressive neurological disorder.

Case Presentation

A 17-year-old female presented to the Neurology Outpatient Department on 20 January 2025 with a two-month history of progressively worsening involuntary jerky movements involving all four limbs, impaired attention, memory decline, and gait imbalance. According to her parents, she had developed increasing difficulty in concentrating during classroom activities and had experienced a noticeable decline in academic performance despite previously achieving normal scholastic milestones until the tenth standard. There was no history of fever, head trauma, toxin exposure, visual disturbances, or developmental delay.

The patient had a significant past history of recurrent episodes of sudden loss of consciousness beginning approximately two years before presentation. She had been diagnosed with epilepsy and was started on antiseizure medications; however, treatment adherence was poor, and she had discontinued medication three months before the current admission. There was no history of chronic systemic illness, previous neurosurgical intervention, or metabolic disorder. She was born to non-consanguineous parents, had an uneventful perinatal history, and had one younger sibling who was healthy. No similar neurological illness was reported among first- or second-degree relatives, suggesting the absence of an apparent family history despite the autosomal recessive nature of the disease.

On admission, the patient was conscious, cooperative, and oriented to time and person. Her vital parameters were stable, with a blood pressure of 110/60 mmHg, pulse rate of 78 beats/min, oxygen saturation of 100% on room air, and she was afebrile. Neurological examination revealed significant impairment of higher mental functions. Cognitive assessment demonstrated an MMSE score of 18/30 and a Montreal Cognitive Assessment (MoCA) score of 11/30, indicating moderate cognitive dysfunction. Cranial nerve examination was unremarkable. Motor examination showed generalized myoclonic jerks involving all four limbs with muscle power graded **4/5** bilaterally. Sensory examination and both superficial and deep tendon reflexes were normal. Cerebellar examination demonstrated truncal and gait ataxia, impaired upper limb coordination on finger–nose testing, and a positive tandem gait test, while nystagmus was absent. These findings suggested progressive myoclonic epilepsy associated with cerebellar dysfunction and cognitive decline.

Routine laboratory investigations, including complete blood count, liver and renal function tests, serum electrolytes, hepatitis B surface antigen, anti-hepatitis C antibody, serum calcium, magnesium, and phosphorus levels, were within normal limits. Cerebrospinal fluid examination revealed normal cell counts, protein, glucose, and IgG index, and autoimmune as well as measles antibody testing was negative, thereby excluding inflammatory or infectious etiologies. Brain magnetic resonance imaging showed no structural abnormalities. Electroencephalography, however, demonstrated generalized periodic epileptiform discharges with brief runs of electrographic seizures, supporting the diagnosis of progressive myoclonic epilepsy despite normal neuroimaging.

Prior to the diagnosis, the patient was treated with intravenous immunoglobulin (120 g) together with combination antiseizure therapy comprising levetiracetam (1 g twice daily), sodium valproate (200 mg twice daily), clobazam (10 mg once daily), and clonazepam (0.25 mg twice daily). She demonstrated partial improvement in seizure control and was discharged with advice for regular neurological follow-up.

Considering the progressive neurological deterioration with refractory seizures, whole exome sequencing (ORION panel) was performed. Genetic analysis identified a homozygous likely pathogenic variant in the EPM2A gene (NM_005670.4), exon 1, c.2T>G (p.Met1?), consistent with Lafora disease (Myoclonic Epilepsy of Lafora type 1) inherited in an autosomal recessive pattern. Mitochondrial gene analysis did not reveal any pathogenic variants. The genetic findings established the definitive diagnosis of Lafora disease and explained the patient's clinical phenotype of progressive myoclonic epilepsy with cognitive impairment.

Approximately four months later, on 19 May 2025, the patient was brought to the emergency department with 13–15 generalized seizure episodes over a 10-hour period without regaining consciousness between events, consistent with convulsive status epilepticus. On arrival, she required endotracheal intubation and mechanical ventilation. Neurological examination revealed a Glasgow Coma Scale score of E4V1M1, reactive bilateral pupils, tachycardia (110 beats/min), and bilateral fine crepitations on respiratory examination. Emergency management included intravenous midazolam, levetiracetam and lacosamide. Repeat electroencephalography demonstrated persistent generalized epileptiform discharges with intermittent spikes and slow-wave complexes, indicating ongoing ictogenic activity. Serum ammonia was elevated, whereas repeat MRI of the brain remained normal.

The patient subsequently received intravenous methylprednisolone (1 g/day for five days) along with optimized multidrug antiseizure therapy consisting of levetiracetam, lacosamide, sodium valproate, phenobarbital, clobazam, and perampanel. She also received empirical antibiotic therapy with piperacillin–tazobactam for one week during intensive care management. Gradual clinical improvement allowed successful weaning from mechanical ventilation and discontinuation of continuous midazolam infusion. Nevertheless, persistent myoclonus and progressive cognitive impairment continued to affect her functional status, necessitating long-term neurological follow-up and multidisciplinary supportive care.

Discussion

Lafora disease is a rare autosomal recessive progressive myoclonic epilepsy characterized by refractory seizures, myoclonus, rapidly progressive cognitive decline, and neurological deterioration. Mutations in the EPM2A and NHLRC1 genes impair glycogen metabolism, resulting in the accumulation of poorly branched polyglucosan inclusions (Lafora bodies) within neurons and other tissues. The disease generally manifests during adolescence and follows an aggressive clinical course with progressive disability and early mortality. Despite advances in molecular diagnostics, Lafora disease remains underrecognized because its early manifestations frequently overlap with other forms of progressive myoclonic epilepsy. Consequently, timely diagnosis requires a high index of clinical suspicion together with electroencephalographic and genetic evaluation. (2,4)

The present patient demonstrated the classical age of onset and clinical phenotype of Lafora disease. She developed recurrent seizures during adolescence followed by progressive myoclonus, gait ataxia, impaired attention, and cognitive decline. Similar clinical characteristics have been consistently reported in genetically confirmed Lafora disease cohorts, where generalized tonic–clonic seizures or myoclonus often represent the earliest manifestations before progressive neurological deterioration becomes evident. Cognitive impairment observed in our patient, reflected by markedly reduced MMSE and MoCA scores, is also a hallmark of disease progression and reflects diffuse cortical involvement resulting from intracellular Lafora body accumulation. (1,3,5)

Electroencephalography played a pivotal role in raising diagnostic suspicion in our patient. The initial EEG demonstrated generalized periodic epileptiform discharges with electrographic seizures, while repeat EEG during clinical deterioration showed persistent generalized epileptiform activity consistent with ongoing ictogenesis. Previous studies have shown that EEG abnormalities in Lafora disease evolve with disease progression, initially demonstrating generalized spike-wave or polyspike-wave discharges and subsequently progressing to diffuse background slowing with frequent epileptiform activity as neurological dysfunction advances. Therefore, serial EEG remains an important investigation for diagnosis as well as assessment of disease progression. (6,7)

An important feature of this case was the absence of structural abnormalities on brain MRI despite significant neurological impairment. Neuroimaging may remain normal during the early stages of Lafora disease, whereas cerebral and cerebellar atrophy generally develop later in the disease course.

Consequently, a normal MRI should not exclude the diagnosis in adolescents presenting with progressive myoclonic epilepsy. Similar observations have been reported in several recent case reports where definitive diagnosis depended primarily on electrophysiological findings and molecular genetic testing rather than neuroimaging. (5,8)

The definitive diagnosis in the present case was established through whole exome sequencing, which identified a homozygous likely pathogenic EPM2A variant (c.2T>G). Molecular confirmation has become the diagnostic gold standard because clinical features alone cannot reliably distinguish Lafora disease from other inherited progressive myoclonic epilepsies, including Unverricht–Lundborg disease, neuronal ceroid lipofuscinosis, mitochondrial disorders, and dentatorubral–pallidoluysian atrophy. Early genetic diagnosis facilitates accurate counseling regarding prognosis, enables family screening, and avoids unnecessary investigations or prolonged diagnostic uncertainty. (1,2,9)

Although no curative therapy currently exists, prompt initiation of multidrug antiseizure therapy remains the cornerstone of management. Our patient initially received levetiracetam, sodium valproate, clobazam, clonazepam, and intravenous immunoglobulin, achieving partial seizure control. However, despite treatment she subsequently developed refractory status epilepticus requiring intensive care, mechanical ventilation, continuous midazolam infusion, corticosteroids, and escalation of antiseizure medications including lacosamide, phenobarbital, and perampanel. This clinical course reflects the progressive and drug-resistant nature of Lafora disease reported in the literature, where seizure control becomes increasingly difficult despite aggressive medical management. (10,11,12)

Although intravenous immunoglobulin and corticosteroids are not routinely recommended treatments for genetically confirmed Lafora disease, they were administered empirically during different stages of the patient's illness because an immune-mediated encephalopathy remained a diagnostic consideration at the time of acute neurological deterioration. Intravenous immunoglobulin (120 g) was given during the initial admission because of the rapid progression of myoclonus, cognitive decline, and seizures, the absence of an apparent family history, and the possibility of an autoimmune or immune-mediated encephalopathy while further investigations, including genetic testing, were underway. Subsequently, intravenous methylprednisolone (1 g/day for five days) was administered during the episode of refractory status epilepticus as adjunctive empirical therapy because seizures persisted despite escalation and optimization of multiple antiseizure medications. These therapies were therefore used as time-limited empirical interventions rather than as standard disease-specific treatments for Lafora disease.

Persistent myoclonus and progressive cognitive decline continued despite stabilization of acute seizures, emphasizing that current therapies primarily provide symptomatic relief rather than altering disease progression. Experimental therapeutic strategies targeting abnormal glycogen synthesis and gene-based interventions are currently under investigation; however, these approaches remain largely experimental. Until disease-modifying therapies become clinically available, management should focus on multidisciplinary supportive care, rehabilitation, nutritional support, psychosocial counseling, and optimization of antiseizure therapy to improve quality of life. (13,14,15)

The present report contributes to the limited literature on genetically confirmed Lafora disease from the Indian subcontinent. It demonstrates the diagnostic value of integrating detailed clinical assessment, electroencephalography, and whole exome sequencing in adolescents presenting with progressive myoclonic epilepsy. Early recognition of this rare disorder is essential for appropriate management, genetic counseling, and avoiding delays in diagnosis, particularly in patients with normal neuroimaging but rapidly progressive neurological deterioration.

Conclusion

Lafora disease is a rare but rapidly progressive neurodegenerative disorder that should be considered in adolescents presenting with progressive myoclonic epilepsy, cognitive decline, and cerebellar dysfunction, particularly when routine laboratory investigations and neuroimaging are inconclusive. This case demonstrates the pivotal role of electroencephalography in identifying ongoing epileptiform activity and highlights the diagnostic importance of whole exome sequencing for confirming an underlying *EPM2A* mutation. Although aggressive multidrug antiseizure therapy and intensive supportive care achieved temporary seizure stabilization, the patient continued to experience persistent myoclonus and progressive cognitive deterioration, reflecting the relentless course of the disease. Early recognition, prompt genetic diagnosis, multidisciplinary management, and appropriate genetic counselling are essential for optimizing patient care and facilitating family screening in this rare inherited epilepsy syndrome.

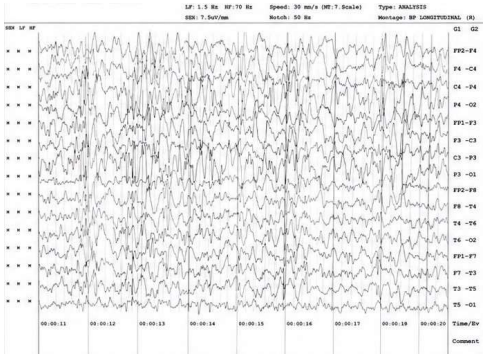

Figure 1. Initial EEG showing generalized periodic epileptiform discharges with electrographic seizure activity consistent with progressive myoclonic epilepsy.

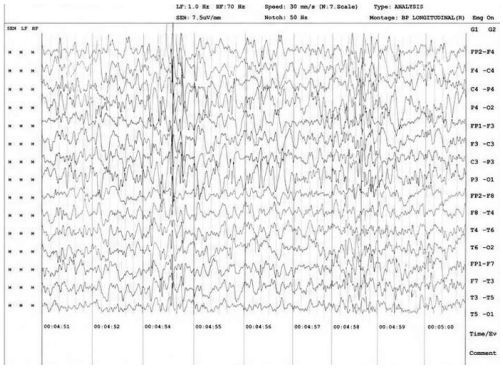

Figure 2. Representative EEG demonstrating persistent generalized epileptiform discharges and generalized spike-and-slow-wave activity consistent with progressive myoclonic epilepsy.

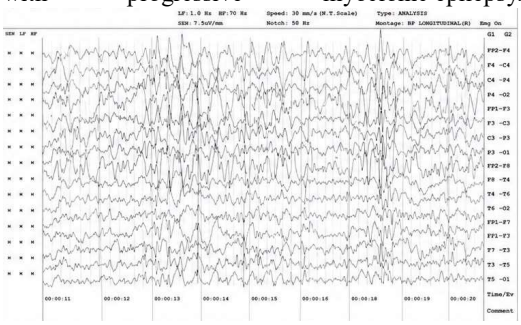

Figure 3. Initial EEG showing diffuse generalized epileptiform discharges consistent with progressive myoclonic epilepsy.

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