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CASE REPORT Open Access

Case report of Lafora disease: a rare genetic disorder manifesting as progressive myoclonic epilepsy

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Abstract

Background Lafora disease (LD) is a rare, autosomal recessive progressive myoclonic epilepsy caused by mutations in EPM2A or EPM2B. It is characterized by abnormal glycogen metabolism leading to poly-glucosan deposits, known as Lafora bodies, in various tissues. LD typically manifests during adolescence with progressive neurological decline, including myoclonic seizures, cognitive impairment, and ataxia. Early diagnosis is critical for symptom management, yet the disease remains challenging to treat due to its refractory nature.

Case presentation We report the case of a 15-year-old male who initially presented with tonic-clonic and myoclonic seizures, bilateral lower limb paralysis, and hand tremors. Despite normal initial imaging findings, subsequent clinical progression raised suspicion for progressive myoclonic epilepsy. Genetic testing identified a homozygous pathogenic variant in EPM2A, confirming the diagnosis of LD. electroencephalogram (EEG) findings evolved over time, showing generalized spikes, poly-spikes, and spike-wave complexes on a slow background, consistent with advanced LD. The patient's seizures proved refractory to standard anti-epileptic drugs, necessitating the addition of phenobarbital, metformin, and zonisamide, which eventually achieved partial seizure control. Family genetic screening identified heterozygous carriers without clinical symptoms, emphasizing the need for genetic counseling.

Conclusions This case highlights the diagnostic challenges of LD, particularly in its early stages when clinical and imaging findings may be nonspecific. The report underscores the importance of genetic testing in confirming the diagnosis and tailoring management strategies. Despite limited treatment options, individualized multi-drug regimens may help achieve partial symptom control. Early recognition and comprehensive management, including family counseling, are essential in improving quality of life for patients and their families.

Keywords Lafora diseas, Progressive myoclonic epilepsy, EPM2A mutation, Refractory epilepsy, Neurological decline

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Background

Lafora disease (LD, OMIM# 254780), also known as progressive myoclonic epilepsy-2 (EPM2), is a rare, fatal autosomal recessive disorder and a glycogen storage disease typically starting during adolescence in otherwise neurologically normal individuals caused by recessive mutations in either the Epilepsy progressive myoclonus 2 A (EPM2A) or EPM2B genes [1, 2]. LD is a rare orphan disease. Based on the comprehensive analysis of existing studies regarding LD mutations, we project an overall frequency of approximately four occurrences per million individuals worldwide. Over 250 individuals and families have been recorded with LD. Mutations in EPM2A account for 42%, while 58% are due to mutations in EPM2B [3].

Polyglucosans, or Lafora bodies (LB) are typically found in the brain, periportal hepatocytes of the liver, skeletal and cardiac myocytes, and in the eccrine duct and apocrine myoepithelial cells of sweat glands [4–8]. It is clinically characterized by insidious of progressive neurological features including seizures, action myoclonus, visual hallucination, ataxia and dementia [3]. Neuropsychiatric symptoms, including behavioral alterations, depression, and apathy, are often seen [3, 9]. During the initial stage, patients develop rare generalized tonic-clonic and visual seizures, along with myoclonus typically appearing within 2 to 12 months. In the intermediate stage, which typically starts two years after the onset of epilepsy, seizures and myoclonus worsen, and patients experience progressive dementia and symptoms related to the cerebellum. Finally, the late stage, which starts about 7 years after the first symptoms appear, is marked by severe declines in motor and cognitive abilities. These include gait ataxia that makes the person unable to move, daily myoclonus, drug-resistant epilepsy with seizure clusters or status epilepticus, and a number of other health problems [10].

The characteristic electroencephalogram (EEG) findings in human patients with early LD include generalized spikes/poly-spikes or spike-wave complexes on a slow background activity, during both wakefulness and sleep [11, 12]. As the disease progresses, the epileptiform activity increases, along with the frequency of the spike-wave complexes and the number of short-duration polys-pikes. These findings, in the proper clinical context, are highly suggestive of LD [13]. We report a 15 years old patient with LD due to EPM2A gene presenting with epilepsy progressive myoclonic 2 A.

Case presentation

A 15-year-old man presented to Amir Al momenin Hospital in Semnan, Iran with seizures, myoclonus, and tonic colonic seizures. He developed normally, completing secondary school. From the age of 14 years, he had experienced tonic-clonic and myoclonic seizures, but EEG and Magnetic Resonance Imaging (MRI) findings at that time were unremarkable (Fig. 1). The patient had no history of seizures until now. However, a history of seizures exists in the patient's brother and cousin, occurring once and not recurring. The patient's brother and cousin are 19 and 22 years old, respectively. Both reported experiencing a single episode of generalized tonic-clonic seizures, with no recurrence since then. Given that their clinical presentation was inconsistent with Lafora disease, genetic testing was not requested for these individuals.

The brain and EEG were normal. Under treatment with sodium valproate, seizures were controlled. Eight months later, the patient experienced tonic-clonic seizures with myoclonic jerks, bilateral lower limb paralysis, developmental disorder, and hand tremors. Laboratory results showed in Table 2.

EEG findings

EEG revealed seizure waves, suggesting generalized epilepsy with encephalopathy. Researchers proposed the possibility of progressive myoclonic epilepsy. The background of EEG consists of bilateral, symmetric, and synchronous 6 Hz frequency theta waves. We observed abundant bursts of generalized spike and wave as well as poly-spike and wave (Fig. 2). Early LD EEG displays generalized spikes, poly-spikes, or spike-wave complexes against a slow background activity. In progressive LD, the EEG shows more epileptiform activity, more spike-wave complexes, and a lot of short-duration poly-spikes. EEG figures show patterns typical of Lafora disease, which include slow background activity with theta frequency, generalized spikes and polyspikes, and spike-wave complexes.

These features point to a generalized, progressive myoclonic epilepsy, consistent with the clinical diagnosis of Lafora disease. The EEG findings correlate with the patient's symptoms of myoclonus, tonic-clonic seizures, and progressive neurological decline.

Genetic findings

The genetic analysis of this case led to the diagnosis of Lafora disease in the patient and the discovery of a homozygous EPM2A pathogenic variant (c.794 A > G; p.H265R). The sequencing-based detection of this missense mutation is validated by Sanger sequencing, revealing that the redundancy finally leads to loss of laforin function, leading to accumulation of Lafora bodies, which is a notable feature of the disease. The family members are heterozygous carriers of the variant and remain asymptomatic, consistent with the autosomal recessive inheritance pattern of the disease. Genetic confirmation of the common mutation highlights the

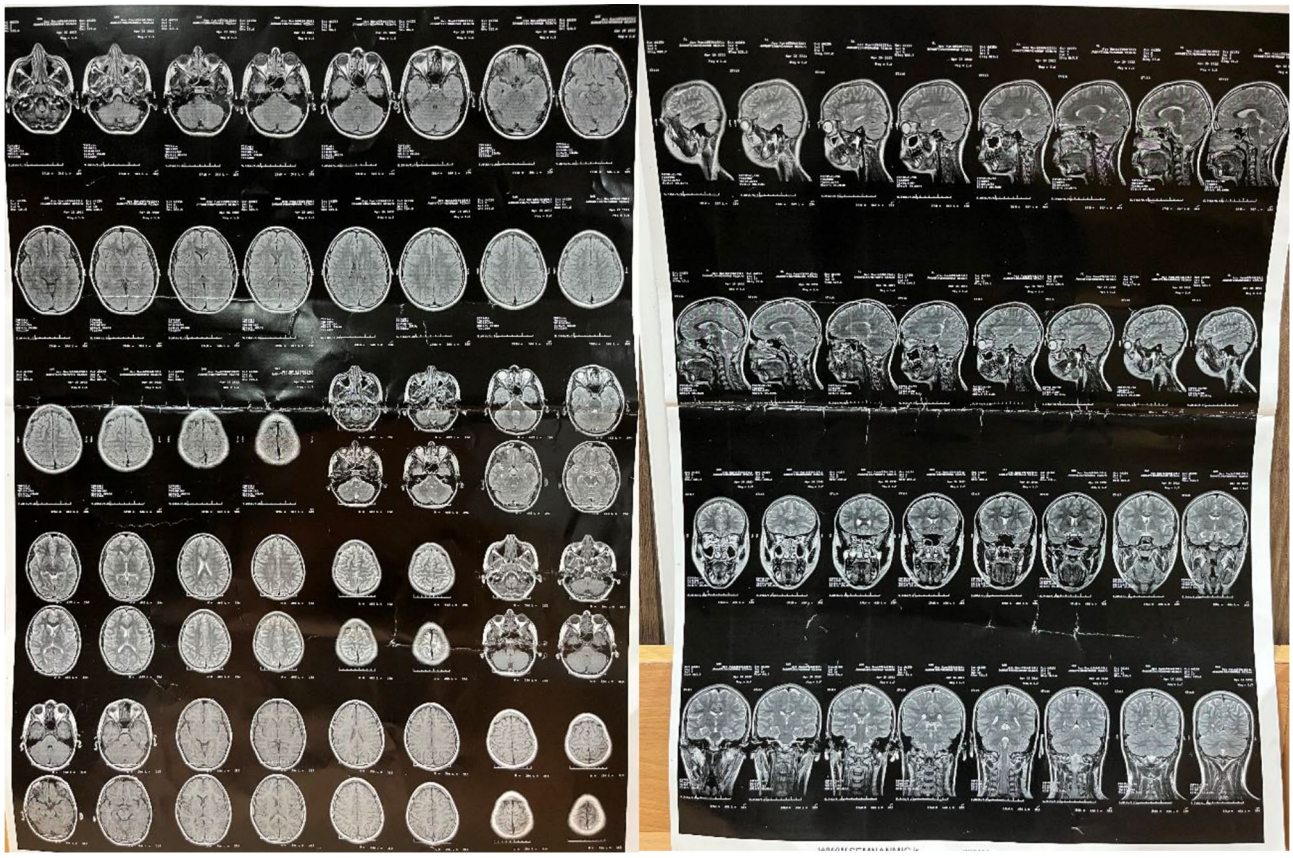

Fig. 1 Brain MRI of our patient affected with Lafora disease

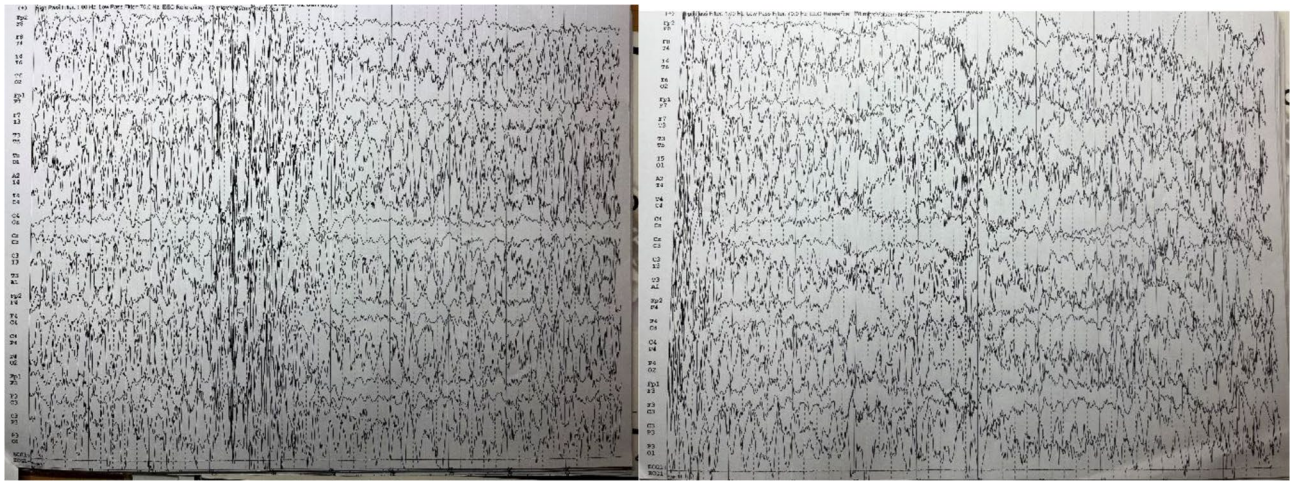

Fig. 2 Early recording's picture exhibits general spikes/poly-spikes and spike-wave complexes layered over a slow 6 Hz theta background. While the picture emphasizes further advancement with more short-duration poly-spikes and more frequent spike-wave complexes, the middle image shows an elevated frequency of these discharges. In these pictures, "seizure waves" more especially, the distinctive epileptiform discharges noted fit the changing pattern found in Lafora illness

importance of genetic counseling and also deepens our understanding of the molecular heterogeneity of Lafora disease. The c.794 A > G; p.H265R variant is a missense mutation located in exon 4 of the EPM2A gene, resulting in a substitution of histidine with arginine at amino acid position 265 (p.H265R). This alteration impairs the function of the laforin protein, a critical regulator of glycogen metabolism. Disruption of laforin activity leads to the accumulation of Lafora bodies abnormal glycogen aggregates that are a pathological hallmark of Lafora disease.

This finding provides key insight into the molecular mechanism underlying the patient's condition.

The American College of Medical Genetics and Genomics (ACMG) rule pp4 and pp1 (co segregation) makes this variant likely pathologic. Also, Sanger sequencing was normal.

ACMG classification guidelines include PP1 and PP4 as supporting and moderate evidence criteria, respectively, for assessing variant pathogenicity (13). PP1 is applied when a disease mutation segregates with the disease in several affected family members. It demands statistical or observational evidence that the variant is tracking with the phenotype through generations [14, 15]. PP4 is used when the clinical phenotype of the patient is very specific to the disease linked to the gene. This consists of unique clinical attributes or biomarker patterns [14].

These differences show how PP1 and PP4 work together in the process of classifying pathogens. PP1 strengthens genetic evidence by using information about families, while PP4 strengthens pathogenicity information by looking at the phenotype of a single patient.

In other family members, the aforementioned mutation is present in a heterozygous state, and siblings who do not have Lafora disease. Three months later, with intensified seizures and neurological symptoms, genetic and metabolic testing was performed:

Ammonium: 80, Levetiracetam: 5.2, Valproate Na: 80.6 and other showed in Table 1.

Despite escalating symptoms and unresponsiveness to anti-seizure medications, the patient, after additional hospitalization and the addition of phenobarbital (120 mg/day, divided into two or three doses), metformin, and zonisamide (Starting dosage is 100 mg/day, increasing by 100 mg every two weeks), achieved seizure control and was discharged.

The patient, experiencing a worsening of the aforementioned symptoms and showing no response to anticonvulsants, was readmitted. In addition to the previous medications, phenobarbital, metformin, and zonisamide were added. Following seizure control, the patient was discharged.

Table 1 Laboratory tests

Test	First tests	Eight months later	11 months later
Wbc	5.6	8	8
Hb	14	13.5	15.4
Plt	327	390	297
ESR	12	20	N
CRP	2	14	N
AST	33	23	24
ALT	34	12	21
Alk	516	N	N

Discussion and conclusions

LD is a severe form of Progressive Myoclonic Epilepsy that usually arises in late childhood or adolescence, resulting from biallelic pathogenic mutations in EPM2A or NHLRC1 [16, 17]. The initial signs of LD typically manifest during late childhood or adolescence, with the age range spanning from 8 to 19 years and peaking between 14 and 16 years [16]. Frequently, LD presents symptoms like migraines, declining academic performance, and noticeable seizures. Initially, individuals with LD may display typical behavior, although some may experience learning challenges. As the condition advances, tonic-clonic seizures occur, followed by sudden, widespread muscle spasms in the limbs and face. Temporary visual disruptions and hallucinatory episodes may also occur. A significant decrease in cognitive function and memory usually becomes apparent 2–6 years after the disease onset [18, 19].

In the early phases, brain MRIs may not reveal any irregularities, but as LD progresses, some patients may exhibit extensive brain degeneration. However, others may still display typical MRI results EEG abnormalities often precede noticeable clinical symptoms. Initially, EEG patterns may appear nearly normal or demonstrate diminished background rhythms, along with sporadic or generalized sudden epileptic events. As the illness progresses, there is a significant reduction in background activity, followed by recurrent epileptic seizures [3].

Differential diagnosis of other progressive myoclonic epilepsies (PME)

LD is characterized by the presence of Lafora bodies (polyglucosan deposits) in the brain, liver, muscles, and sweat glands, detectable by biopsy, along with specific genetic changes [20]. Unverricht-Lundborg Disease (ULD) progresses at a slower rate and does not exhibit these inclusions, with genetic testing for CSTB mutations providing clear results [21, 22]. Neuronal Ceroid Lipofuscinosis (NCL) typically presents as loss of vision, especially in juvenile variants such as Batten disease, and is diagnosed using EEG, MRI, and genetic analysis for several NCL genes [22]. Sialidosis may show a cherry-red spot in the eye (type I) and skeletal abnormalities (type II), with diagnosis supported by enzyme testing and genetic analysis for NEU1 mutations [23]. Myoclonus Epilepsy with Ragged-Red Fibers (MERRF), a mitochondrial disorder, is defined by muscular weakness and the presence of ragged-red fibers on muscle biopsy, with genetic testing identifying mitochondrial DNA variants such as m.8344 A > G [23, 24] (Table 2).

The diagnostic approach starts with clinical suspicion founded on age of onset and symptoms. MRI may be normal early but indicate brain degeneration later for LD; EEG commonly reveals either initial normal or reduced

Table 2 Differential diagnosis of other PME

Condition	Onset Age	Key Features	Diagnostic Clues	References
LD	8–19 years	Tonic-clonic seizures Myoclonus Cognitive decline Lafora bodies	Genetic testing for EPM2A/NHLRC1 mutations Biopsy for LB	[16, 17]
ULD	6–16 years	Myoclonic seizures Ataxia No Lafora bodies Slower progression than LD	Genetic testing for CSTB gene mutations	[21, 22]
NCL	Variable (infancy to adulthood)	Vision loss (in some types) Seizures Cognitive decline Characteristic inclusion bodies	EEG showing specific patterns MRI showing atrophy Genetic testing for various NCL genes	[22]
Sialidosis	Variable (childhood to adolescence)	Myoclonus Seizures Ataxia Cherry-red spot in the eye (type I) Skeletal abnormalities (type II)	Ophthalmic exam for cherry-red spot Enzyme activity testing Genetic testing for neuraminidase genes	[23]
(MERRF)	Variable	Myoclonus Seizures Muscle weakness< Neurological symptoms (ataxia, hearing loss, etc.)	Muscle biopsy showing mitochondrial abnormalities Genetic testing for mitochondrial DNA mutations	[23, 24]

background rhythms and later widespread epi-leptic episodes [25]. The progression of the case, first normal testing then EEG abnormalities.

The standard treatment for LD aims to alleviate symptoms, particularly seizures and myoclonus, and support quality of life. AEDs such as valproic acid, levetiracetam, clonazepam, phenobarbital, and zonisamide are used to control seizure frequency and severity [20]. As recent studies have indicated, perampanel offers specific advantages in various cases [26].

Metformin's role is notable, with evidence suggesting better outcomes when started early, but gastrointestinal side effects may limit dosing in some patients. High-throughput screening for glycogen synthase inhibitors and repurposing existing drugs. Metformin, a biguanide with neuroprotective effects, has shown promise in slowing LD progression. It received orphan designation from the EMA in 2016 and FDA in 2017. Studies on 12 patients treated with metformin for 18 months (mean dose 1167 mg/day) suggest potential benefits, especially in early stages, with slower disease progression observed [27]. Also, the ketogenic diet has been suggested to reduce abnormal glycogen accumulation, with preclinical evidence in mouse models [28].

In our case, a patient with refractory epilepsy initially failed to respond to standard AEDs, necessitating hospitalization and treatment escalation. Despite the addition of phenobarbital, metformin, and zonisamide, seizure control was achieved, leading to discharge. However, the patient experienced symptom worsening and non-response to anticonvulsants, prompting readmission. Additional medication adjustments were made, including reintroduction of phenobarbital, metformin, and zonisamide, resulting in seizure control and subsequent discharge. Lafora Disease is a rare, progressive neurological disorder with significant morbidity and mortality. Prompt recognition of its clinical manifestations and genetic basis is crucial for accurate diagnosis and appropriate management. This case emphasizes the importance of genetic testing in suspected cases of LD and the challenges in managing refractory epilepsy associated with the disease.

Abbreviations

LD Lafora Disease
LB Lafora bodies
EEG Electroencephalogram
MRI Magnetic Resonance Imaging

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Author contributions

RM: manuscript writing and literature search. SMH and SS: reviewed and substantively revised the paper. FV: patient and family follow-up examination, analysis and interpretation of data. All authors have read and approved the manuscript.

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Data availability

The data underlying the results presented in the study are available from National Center for Biotech-nology Information: SCV005907295.1 (https://www.ncbi.nlm.nih.gov/clinvar/variation/1047431/).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Written informed consent was obtained from the participants and/or their parents/legal guardians for publication of the case report.

Competing interests
The authors declare no competing interests.

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