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Family Members Carry the Disease-Causing Gene in a Patient with a Novel Whole-Code Gene Mutation in LD: A Case Report

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Abstract

Purpose: EPM2A has been shown to be the causative gene in patients with Lafora Disease (LD), a rare autosomal recessive disorder. LD most often develops in adolescence and is characterized by myoclonic epileptic seizures. It usually presents with intractable seizures, rapidly progressive dementia and vegetative state, and even death within 10 years. LD used to be particularly common in Mediterranean countries, but has been increasingly reported in the literature in Asian countries year by year. Here, we report a case of a patient with LD carrying the EPM2A gene, which presents as a novel whole code deletion mutation, while the causative gene was detected in all of his family members.

Methods: The patient's past and family histories were carefully questioned and routine ancillary tests such as routine blood, biochemical, cranial MR, video EEG, etc. were performed.

Result: The patient had a past history of epilepsy and currently presented with intractable epilepsy and progressive cognitive decline, while the patient's sister also had a history of epilepsy, and the effect of traditional antiepileptic medication was not apparent in them. Through genetic testing, the patient's family members were found to carry the LD gene, and the diagnosis of LD was confirmed.

Conclusion: In patients with a previous history of epilepsy and a family member with a similar disorder, it is essential that we take genetic testing measures. Early diagnoses can provide more accurate treatment for LD patients while reducing psychological stress in the family. We hope that by reporting a new case of LD patient with a mutation in a gene fragment, we can provide a reference for similar cases encountered in the future.

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Abbreviations

LD: Lafora Disease; V-EEG: Video Electroencephalogram; EDB: Extreme Delta Brush; PME: Progressive Myoclonic Epilepsy; T2WI: T2-Weighted Imaging; T1WI: T1-Weighted Imaging; AEDs: Antiepileptic Drugs; GS: Glycogen Synthase; PP1: Protein Phosphatase 1

Background

Lafora Disease (LD) is a rare autosomal recessive disorder with severe progressive myoclonic epilepsy. The disease usually occurs in late childhood or early adolescence. Death usually occurs within 10 years of symptomatic seizures due to persistent status epilepticus or other complications.

LD is caused by a loss-of-function mutation in EPM2A or NHLRC1, encoding laforin and malin, respectively [1]. In the absence of laforin or malin function, poorly branched and hyperphosphorylated glycogen accumulates in the Lafora body, ultimately leading to neurodegeneration and neurological disease [2].

The diagnosis of LD is usually based on past and family history, abnormal EEG, detection of Lafora vesicles on skin biopsy, and genetic testing is the gold standard for the diagnosis of LD. Treatment is mainly based on traditional antiepileptic drugs, while treatments based on downregulation of brain glycogen synthesis and disease gene replacement are under investigation. We report a typical case of a patient with LD (genetically tested for a new mutation in a gene fragment), while the family

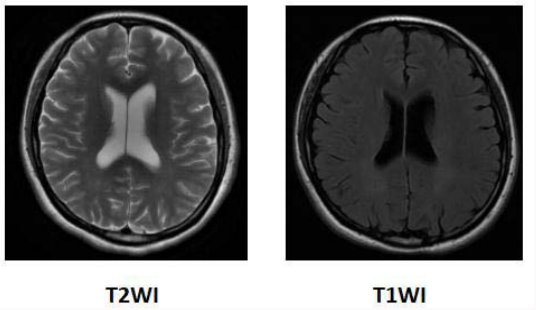

Figure 1: Both lateral ventricles were slightly enlarged on T2WI and T1WI, and no abnormalities were observed in the hippocampus.

members of this patient were tested to carry the causative gene.

Case Presentation

The patient, a 22-year-old female, was hospitalized with "recurrent loss of consciousness and seizures of the limbs for 9 h." History of epilepsy for 1 year, has been on oral levetiracetam 1 g BID antiepileptic treatment. The patient's sister in the family also suffers from epilepsy and is currently on antiepileptic medication for treatment. Physical examination: T: 38.5°C, P: 114 times/min, R: 20 times/min, BP: 103/74 mmHg. scattered rash all over the body, soft neck, no resistance, no cardiopulmonary auscultation, flat abdomen, no pressure pain, rebound pain, liver and spleen not reached under the ribs, no swelling of both lower limbs. Neurological system: Confusion, unresponsiveness, memory, orientation, and calculating power were diminished, bilateral eye movements were free, and there was no nystagmus. Limb muscle strength examination was uncooperative, muscle tone was enhanced, bilateral knee tendon reflexes were symmetrical, bilateral Babinski's sign was negative, Booker's sign was negative, and the autonomic nervous system was normal.

Head MRI showed mild dilatation of the lateral ventricles on both sides (Figure 1). Video Electroencephalogram (V-EEG) showed a large number of high spinous slow waves in each channel (Figure 2).

In response to the patient's medical and family history, we considered LD as a high possibility and therefore performed genetic testing on the patient and his family members. While waiting for the results, the patient again developed loss of consciousness, twitching of the limbs, salivation at the corners of the mouth, and upturning of the eyes, which lasted for several minutes and then resolved on its own. The patient was eventually diagnosed with LD after the EPM2A mutation was detected, showing a new mutated fragment of the gene, and the causative gene was carried in all of the patient's family members (Figure 3).

The diagnosis was undoubtedly a huge blow to the family, but it was also a psychological relief for the patient's parents. The clear diagnosis gave them the belief in treatment. Because there was no special treatment available at our hospital, the patient left the hospital automatically after the relative relief of her symptoms.

Discussion and Conclusion

LD is a type of Progressive Myoclonic Epilepsy (PME), a disorder characterized by myoclonus, seizures, and progressive neurological decline [3]. Because of its rarity, it has historically been more common in European countries such as Spain, Italy and France, but the number of cases in Asian countries such as China, India and the Middle East has been increasing over the past few decades [4]. LD is considered to be a glycogen metabolism disorder characterized by the accumulation of Lafora bodies (deformed glycogen molecules) in multiple organs [5], but the exact mechanism is still being studied.

LD usually begins with seizures and includes myoclonus, occipital lobe, generalized tonic-clonic, absence and atonic seizures. Myoclonic tics are the earliest manifestations, which are more pronounced under motor or light stimulation, making patients dependent on wheelchairs in the short-term [6]. This is followed by behavioral changes (mainly motor apraxia and ataxia), dysarthria (and even complete mutism) and mental decline, developing into a vegetative state within 5 years and dying within 10 years due to status epilepticus or aspiration pneumonia [7,8].

The age of onset of LD is usually 14 to 16 years, but 5 to 20 years has also been reported in the literature [3]. In contrast, our patient began to present with epileptic symptoms at the age of 21, with subsequent gradual onset of paroxysmal loss of consciousness, limb convulsions, and cognitive impairment, consistent with the above clinical presentation (The current patient status is shown in the Appendix). And the same myoclonus-based epilepsy was found

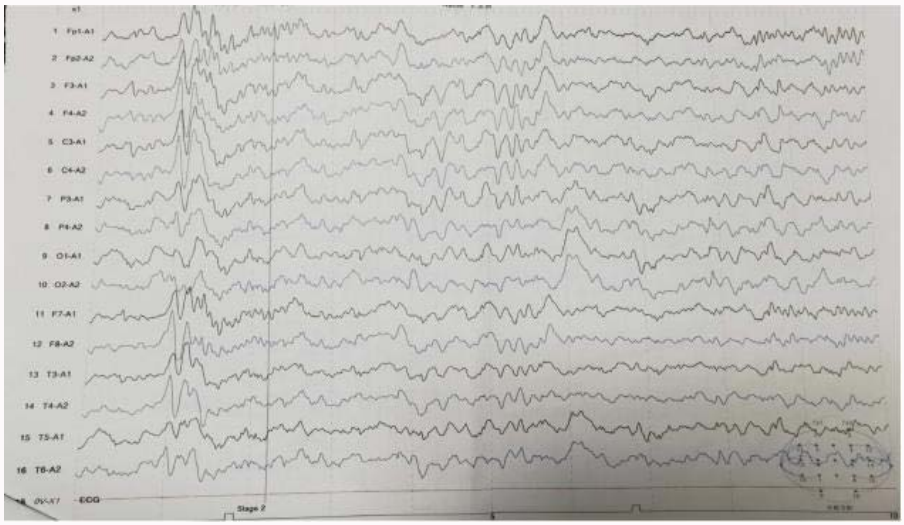

Figure 2: V-EEG exhibits massive, paroxysmal, high-to-high-amplitude spinous slow waves known as "Extreme Delta Brush (EDB)" activity.

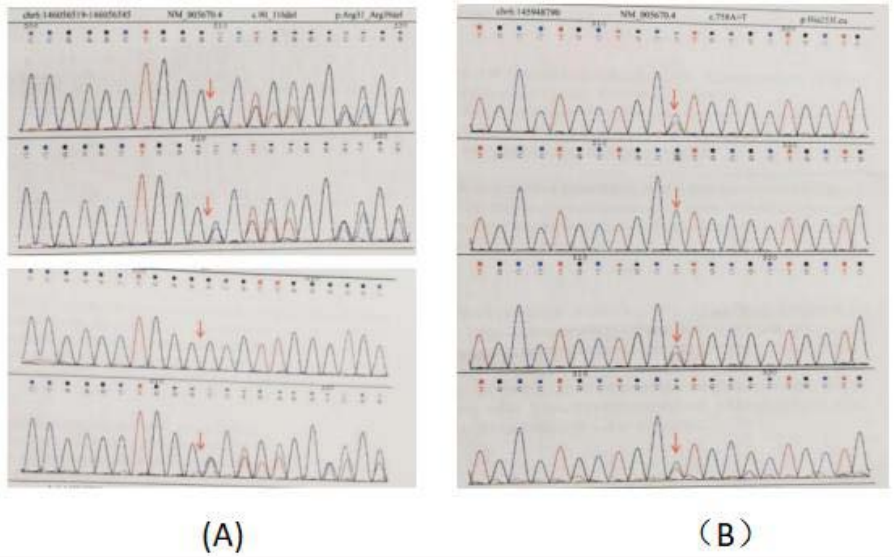

Figure 3: Sanger analysis showed that: (A) EPM2A gene heterozygous mutation was observed in both the patient and his father and sister on c. 90_116del and p.Arg39del; (B) On c.758A>T and P.IS253-Leu, the patient had heterozygous mutations under this gene fragment with his mother and sister, and the father was normal.

in this patient's 14-year-old sister, who started at the age of 11, the youngest patient with LD found within China.

The initial steps in clinical diagnosis are from clinical findings and EEG background slowing, paroxysmal bursts of irregular generalized epileptiform discharges (typical "EDB" activity) [9], and skin biopsy showing Lafora bodies, but ultimately confirmed by genetic testing [10]. Early diagnosis of disease is important because adequate understanding of the disease is one of the greatest contributing factors, and genetic testing should be considered early in refractory epilepsy [11].

Our patient had epileptic symptoms along with an EEG showing abnormal waveforms, so he was initially treated with conventional antiepileptic drugs, but the treatment was not satisfactory. However, the patient's medical history and family history made us suspicious, and the discussion led to a high probability of LD, so further examination of the patient was performed. Eosinophilic material was seen in the epithelial cells of the sweat glands on the skin biopsy of the patient's lower extremities, but the possibility of false positives could not be excluded. Because of the high level of expertise required by both the physician obtaining the skin biopsy specimen and the physician interpreting the histopathology, Lafora often presents with false positives, and because of its rarity, most pathologists are exposed to too few cases to be guided by experience. Also, axillary glands are stained with PAS, and documentation is required to distinguish Lafora vesicles from normal secretory gland contents [1].

We eventually diagnosed LD by genetic testing. Genetic testing is the gold standard of diagnosis. Two genes, EPM2A and NHLRC1 or EPM2B, encode proteins laforin and malin, respectively [5]. It has been reported that in about 250 families, 42% can be attributed to the EPM2A gene and the rest to the EPM2B gene. However, some patients had negative genetic tests for both genes [12], leading to the hypothesis that mutations located in non-coding regulatory regions or other genes could cause the disease, which was later confirmed by the PRDM8 gene [13]. There are about 157 different mutations in EPM2A. Some are misaligned, some non-sense, some exon and some entire gene deletion [1].

We report a novel whole-code deletion mutation (c.90_116del: p.Arg39del) with a deletion of nucleotides 90 to 116 in the coding region, resulting in a deletion of amino acids 31 to 39. And there is also a (c.758A>T:p His253Leu) heterozygous missense mutation, due to the mutation of nucleotide 758 from adenine to thymine in the coding region, resulting in the mutation of amino acid 253 from histidyl acid to leucovorin. To date, this is the first case of LD reported in China. The patient's parents were not consanguineously married, so whether other members of the clan also carry the disease-causing gene requires further follow-up.

Currently, AEDs are the only treatment available to control to some extent the severity and frequency of seizures and myoclonus in LD patients. Treatment options for LD also include viral delivery of functional laforin or malin, intracellular degradation of Lafora bodies by glucan degrading enzymes such as α-amylase, and by targeting Glycogen Synthase (GS) to down-regulate glycogen synthesis or Protein Phosphatase 1 (PP1) subunit R5 at gene, RNA or protein levels [14]. Both our patient and her sister have been on levetiracetam antiepileptic therapy since the onset of epileptic symptoms, but this patient had a poorer outcome compared to her sister, with progressive exacerbation and concomitant cognitive impairment, so we wonder if this is related to age at the time of medication use, which requires a lot of data statistics. While the genetics of Lafora body disease is developing, the identification of different genetic loci will help to understand the pathogenesis of the disease and design precise treatments accordingly, likely before many other severe epilepsies become treatable [15].

In conclusion, we report a new whole-code deletion mutation (c.90_116del: p.Arg39del) in the EPM2A gene. LD, although rare, has been recognized in an increasing number of countries. When faced with a patient with a history of epilepsy and family history, combined with objective test results, we have to be highly suspicious of the possibility of LD. The diagnosis is clarified by genetic testing. Because early diagnoses can provide more precise treatment for LD patients

and at the same time reduce the psychological stress of the patient's family. Finally, we hope that this case report will allow medical professionals to have further understanding and exploration of LD.

Authors' Contribution

LZ was responsible for conception and design, acquisition of data and interpretation of data, drafting the manuscript and revising it critically for important intellectual content; YZ was responsible for conception and design, acquisition of data and interpretation of data, drafting the manuscript and revising it critically for important intellectual content; ZZ was responsible for conception and design, interpretation of data, drafting the manuscript and revising it critically for important intellectual content; XF was responsible for acquisition of data, interpretation of data and revising the manuscript critically for important intellectual content; FZ was responsible for interpretation of data and revising the manuscript critically for important intellectual content. All authors have read and approved the manuscript.

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