Clinical Medicine Research
2022; 11(5): 126-129
http://www.sciencepublishinggroup.com/j/cmr
doi: 10.11648/j.cmr.20221105.12
ISSN: 2326-9049 (Print); ISSN: 2326-9057 (Online)

Progressive Myoclonic Epilepsy: Lafora Disease - Clinical and Genetic Findings

Mohammad Abul Kalam Azad[1, *], Mohammad Nazmul Hassan Chowdhury[1], Mohammad Abdullah Al Hasan[1], Mohammad Masum Emran[1], Panchanon Das[2], Maher Akther[3]

[1]Department of Neurology, Comilla Medical College, Cumilla, Bangladesh

[2]Department of Neurology, Chittagong Medical College, Chittagong, Bangladesh

[3]Department of Paediatrics, Comilla Medical College, Cumilla, Bangladesh

Email address:

dr.azad34th@yahoo.com (Mohammad Abul Kalam Azad)

[*]Corresponding author

To cite this article:

Mohammad Abul Kalam Azad, Mohammad Nazmul Hassan Chowdhury, Mohammad Abdullah Al Hasan, Mohammad Masum Emran, Panchanon Das, Maher Akther. Progressive Myoclonic Epilepsy: Lafora Disease - Clinical and Genetic Findings. *Clinical Medicine Research*. Vol. 11, No. 5, 2022, pp. 126-129. doi: 10.11648/j.cmr.20221105.12

Received: July 24, 2022; **Accepted**: August 29, 2022; **Published**: September 16, 2022

Abstract: *Introduction:* Progressive myoclonic epilepsies are group of genetic diseases with grave prognosis, consist of Lafora disease, Unverricht-Lundborg disease, the neuronal ceroid lipofuscinoses, type I sialidosis, action myoclonus-renal failure syndrome, Myoclonus epilepsy and Ragged-Red Fibers (MERRF) and type III Gaucher disease. Lafora disease (LD) is an autosomal recessive severe form of progressive myoclonic epilepsy typically start in adolescence with severe myoclonus, other focal and generalised seizures, refractory status epilepticus, ataxia, dementia and neuropsychiatric symptoms. It has a rapid malignant course with death in 4-8 years due to respiratory failure. Two common genetic form are known, 42% are caused by *EPM2A* and 58% *EPM2B* mutations. Recently mutations in an additional gene, *PRDM8* which is responsible for early onset phenotype has been reported. Aim*:* To diagnose and determine the common Bangladeshi mutations in Lafora disease. *Case report:* Our case consists with a nineteen years old boy, born from a first degree consanguineous marriage with a younger brother suffering from similar illness. He showed severe progressive myoclonic epilepsy, ataxia and dementia. EEG showed generalised slowing with polyspike-wave complexes and MRI revealed mild cerebral atrophy. Genetic study confirmed the diagnosis of Lafora disease. *Conclusion:* This case is a Progressive Myoclonic Epilepsy of Lafora disease (LD) type with missense mutations in *EPM2A* gene. There are also mutations found in *G6PD*, *GYS2* and *GAA* genes.

Keywords: Progressive Myoclonic Epilepsy (PME), Ataxia, Dementia, Lafora Disease, EPM2A Mutations, G6PD Deficiency

1. Introduction

Progressive myoclonic epilepsies are group of genetic diseases with grave prognosis, consist of Lafora disease, Unverricht-Lundborg disease, the neuronal ceroid lipofuscinoses, type I sialidosis, action myoclonus- renal failure syndrome, Myoclonus epilepsy and Ragged-Red Fibers (MERRF) and type III Gaucher disease. [1].

Lafora disease (LD) is an autosomal recessive severe form of progressive myoclonic epilepsy. It was described for the first time by white in 1988 [2]. It is particularly frequent in Mediterranean countries.

LD classically start in adolescence with action and stimulus-sensitive myoclonus, visual seizures, cerebellar ataxia, neuropsychiatric symptoms, progressive dementia, refractory status epilepticus and respiratory failure which lead to deaths within a decade [3].

In this article we report a case of nineteen year old young male who present with visual seizure, myoclonus and ataxia. This will helps in diagnosis and determining common

Bangladeshi mutations in LD.

2. Case Report

The case consists with a nineteen years old boy, born from a first degree consanguineous marriage with a younger brother suffering from similar symptoms. He was relatively healthy 3 years before referral to our hospital. He was born by normal vaginal delivery at full term with no complications. He had normal development during childhood and adolescence. At the age sixteen years he developed recurrent episodes of transient blindness, frequent myoclonic jerks and progressive cognitive deterioration.

On neurological examination he had scanning speech, cerebellar ataxia, severe dementia without any sensory deficit. Laboratory investigations including complete blood cell count, liver function test and urinalysis were normal. EEG Showed generalised slowing with polyspike-wave complexes and MRI showed mild cerebral atrophy.

Peripheral blood sample was collected in EDTA. At first genome wide microarray test was conducted to identify small to large scale chromosomal abnormalities (deletions/duplication/translocation and rearrangement). This microarray uses 642,824 probes speed across the genome to detect genetic abnormalities. The whole exome sequencing was conducted from this sample using NovaSeq6000 sequencing platform that uses Illumina SBS technology. Rare polymorphism may lead to false negative or positive results. Our clinical interpretation of variant closely follows American College of Medical Genetics (ACMG) guideline.

Table 1. *Primary Finding's of genetic study.*

Primary Finding's				
Gene	**Chr.**	**Transcript ID**	**Zygosity**	**Classifications as per ACMG guideline**
EPM2A	6	NM_005670 Exon 3	Missense Homozygous	Pathogenic LD
G6PD	X	NM_001042351 Exon 6	Missense Hemizygous	Pathogenic G6PD Deficiency

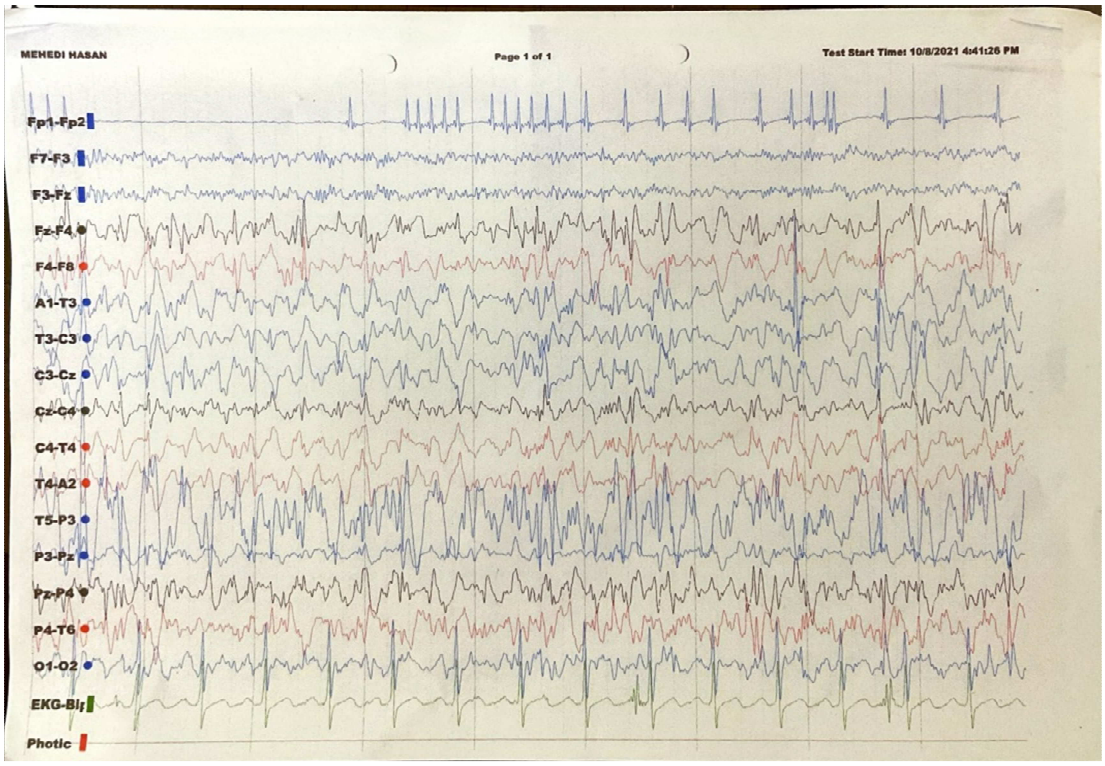

Figure 1. *EEG Showing polyspikes.*

Table 2. *Incidental Finding's of genetic study.*

Incidental Finding's				
Gene	**Chr.**	**Transcript ID**	**Zygosity**	**Classifications as per ACMG guideline**
GYS2	12	NM_021957 Exon 14	Missense Heterozygous	Pathogenic Carrier Glycogen storage disease 0
GAA	17	NM_001079803 Exon 15	Missense Heterozygous	Pathogenic Carrier Glycogen storage diseases II

3. Discussion

PMEs are about ten inherited neurodegenerative disorders characterised by progressively worsening myoclonic epilepsy and variable neurological dysfunction (ataxia, dementia)[4]. LD is one of the main teenage-onset PMEs. Age of presentation characteristics symptoms including occipital

seizures, progressive and fatal course, together with the EEG features, are suggest LD. Skin histopathology or genetic testing is require for definitive diagnosis [5]. A distinctive pathology characterizes LD. Cells of various types exhibit dense accumulations of malformed and insoluble glycogen molecules, known as polyglucosans, which differ from normal glycogen due to the fact that they lack the symmetric branching that allows glycogen to be soluble. These polyglucosan accumulations are called Lafora bodies (LBs) and are profuse in all brain regions and in the majority of neurons, specifically in their cell bodies and dendrites. Neuronal LBs localize in perikarya and dendrites but in axons, possibly explaining the cortical hyperexcitability seen in LD. LD is caused by mutations in the *EPM2A* or *EPM2B (NHLRCI)* genes, encoding the laforin dual specificity phosphatase and the ubiquitin E3 ligase, respectively, both involved in a complex and yet very incompletely understood pathway regulating glycogen metabolism [6]. Of these 42% are caused by mutations in *EPM2A* and 58% by *EPM2B* mutations. The ratio of *EPM2A* to *EPM2B* cases varies with population, with some regions having more *EPM2A* cases than *EPM2B*, and vice versa, and this is remarkably, not solely due to founder mutations [7, 8]. The most common *EPM2A* mutations is the R241X mutations, which accounts for approximately 17 percent of *EPM2A* mediated LD. Large deletions make up 10-15 percent of *EPM2A* mutations, with the remainder ranging from those causing approximately eight percent of *EPM2A*-mediated cases of LD (i.e R171H) to orphan mutations spread across the gene. For *EPM2B*, the two most common mutations are the missense mutations P69A and the frameshift mutation G158fs16 which affect~15 and~8 percent of *EPM2B*-mediated LD, respectively. As with *EPM2A*, the remaining EPM2B mutations span the gene and are rare, though some mutations (i.e C26S and D146N) are more frequently observed. Because deletions can be overlooked using conventional sequencing techniques, it is critical to consider deletions/duplication analysis in any suspected LD patients in whom initial sequencing of *EPM2A* and *EPM2B* reveals no change. Recently an additional gene, *PRDM8,* the mutation of which causes a variant of early childhood-onset phenotype in a single family, has been reported [9]. Now a days genetic testing is helping to treat the epileptic patients. LD can be confirmed by genome sequencing when histopathology give confusing result [10]. DNA testing also can identify nonsense mutations in Lafora Disease [11]. Certain mutations appears to be specific to particular ethnic groups and/or geographical locations. For example, LD affects French and Canadians from a geographically isolated area of eastern Quebec with an unusually high frequency, which is likely to be due to the ancestral *EPM2B* mutations. One study has been published on LD in Oman, in which all cases in 5 separate, unrelated families resulted from a single ancestral mutational event in *EPM2B*. Interestingly, the *EPM2A* R241X mutations commonly found in individuals of Spanish descent resulted from both recurrent events and founder effects. At least 5 unique haplotypes are associated with this mutation, indicating that a minimum of 5 separate mutational events have led to the prevalence of the R241X mutation. Accordingly, *EPM2A*-mediated LD is more common than *EPM2B*-mediated in Spain. The second most common mutations in *EPM2B*, the missense P69A mutation, appears to have occurred from multiple mutational events similar to the *EPM2A* R241X mutation [12]. Gentamicin can be used to correct nonsense mutations in mice [13]. More studies in mice and humans are needed to test this theory.

Our case showed missense homozygous mutations in EPM2A gene. There are also mutations found in *G6PD, GYS2* and *GAA* genes.

With regards to AEDs, there are no specific antimyoclonic agents active against LD, to relieve seizures and myoclonus, and the effects is felt throughout the course of the disease. Unfortunately, their effect is partial and they have no major influence on the progression of the cognitive and behavioural symptoms. Patients typically receive an AED, usually valproic acid, after the first generalized tonic-clonic seizure (GTCS). This is usually effective in suppressing, for some time, most GTCS, the symptoms associated with photic sensitivity, and some of the myoclonus. There are two unusual effects, which should lead to an early diagnosis of LD; first the EEG shows rapidly increasing, permanent interictal changes, including focal occipital spikes, despite the apparent clinical remission; second, the patients develop negative myoclonus, which becomes prominent before the more characteristic myoclonus jerks. Other AEDs are used during this stage: lamotrigine (LTG) is not very advisable in the context of a myoclonic epilepsy, but may help transiently; phenobarbital (PB) and primidone (PRM) are effective, but are often used at high doses and their cognitive effects are added to those of the condition; and levetiracetam (LEV) is increasingly used early for adolescent with IGE, hence in LD cases, even before confirmation of the diagnosis, Other helpful drugs include topiramate (TPM) and Zonisamide (ZNS), which both have marked antimyoclonic effects in some patients. Additional relief can be obtained, often transiently, with ethosuximide, felbamte, methasuxamide, and benzodiazepines (BZD). The latter (usually clobazam, clonazepam, and diazepam) should be used with care since there is a marked initial effect followed by quick tolerance. Finally, there have been 2 recent single case reports of dramatic beneficial effects of perampanel [14, 15].

In spite of receiving maximum dose of valproic acid, levetiracetum, perampanel and clonazepam, our patient is continuing to have 2 to 3 seizures per day.

4. Conclusion

Progressive severe myoclonic epilepsy, occipital seizures, cognitive deterioration and family history should guide clinician to achieve genetic study for Lafora disease. This study will help to evaluate the distribution of mutations of LD patients in our country. To find out the importance of

association between *EPM2A* mutations and other mutations needs further studies.

Conflict of Interests

All the authors do not have any possible conflicts of interest.

Acknowledgements

We thank Mr. Nuruzzaman Hossain for his tremendous help during manuscript preparation.

References

[1] Berkovic SF, Andermann F, Carpenter S, Wolfe LS. Progressive myoclonus epilepsies: specific causes and diagnosis. N. Engl. J. Med. 1986; 315: 296-305. [PubMed: 3088452] doi: 10-1056/NEJM.198607313150506.

[2] White JW Jr, Gomez MR. Diagnosis of Lafora disease by skin biopsy. J cutan Pathol. 1988; 15: 171-5. doi: https://doi.org/10.1111/j.1600- 0560.1988.tb00538.x

[3] Minassian BA. Lafora's disease: towards a clinical, pathologic, and molecular synthesis. Paediatr. Neurol. 2001; 25: 21-29. [PubMed: 11483392] doi: 10.1016/s0887.

[4] Striano P, Zara F, Turnbull J, et al. Typical progression of myoclonic epilepsy of the Lafora type, a case report. Nat. Clin. Pract. Neurol. 2008; 4: 106–111. [PubMed: 18256682] doi: 10.1038/ncpneuro0706.

[5] Karimipour D, Lowe L, Blaivas M, Sachs D, Johnson TM. Lafora disease: Diagnosis by skin biopsy. J Am Acad Dermatol. 1999; 41 (5): 790–792. doi: 10.1016/s0190-9622 (99)70026-5.

[6] Chan EM, Bulman DE, Paterson AD, et al. Genetic mapping of a new Lafora progressive myoclonus epilepsy locus (EPM2B) on 6p22. J. Med. Genet. 2003a; 40: 671–675. [PubMed: 12960212] doi: 10.1684/epd.2016-0842.

[7] Gomez-Garre P, Sanz Y, Rodriguez De Cordoba SR, Serratosa JM. Mutational spectrum of the EPM2A gene in progressive myoclonus epilepsy of Lafora: high degree of allelic heterogeneity and prevalence of deletions. Eur. J. Hum. Genet. 2000; 8: 954. [PubMed: 11175283] doi: 10.1038/sj.ejhg.5200571.

[8] Franceschetti S, Gambardella A, Canafoglia L, et al. Clinical and genetic findings in 26 Italian patients with Lafora disease. Epilepsia. 2006; 47: 640–643. [PubMed: 16529633] doi: 10.1111/j.1528-1167.2006.00479.x.

[9] Turnbull J, Girard JM, Lohi H, et al. Early-onset Lafora body disease. Brain. 2012; 135: 2684–2698. [PubMed: 22961547] doi: 1093/brain/aws205.

[10] Andrade DM, Ackerley CA, Minett TS, Teive HA, Bohlega S, Schere SW, et al. Skin biopsy in Lafora disease Genotype-phenotype correlations and diagnostic pitfalls. Neurology 2003; 61: 1611-4. doi: https://doi.org/10.1212/01.WNL.0000096017.19978.CB

[11] Ianzano L, Zhang J, Chan EM, Zhao XC, Lohi H, Scherer SW, et al. Lafora progressive myoclonus epilepsy mutation database-*EPM2A* and NHLRC1 (*EPM2B)* genes. Hum Mutat 2005; 26: 397. doi: 10.1002/humu.10306.

[12] Gomez-Abad C, Gomez-Garre P, Gutierrez-Delicado E, et al. Lafora disease due to EPM2B mutations: a clinical and genetic study. Neurology. 2005; 64: 982–986. [PubMed: 15781812] doi: 10.1212/01.wnl.0000154519.10805.f7.

[13] Delgado—Escueta AV, Bourgeois BF. Debate: Does genetic information in humans helps us to treat patients. CON—genetic information does not help at all. Epilepsia 2008; 49: 3-24 doi: 10.1111/j.1528-1167.2008.01922.x.

[14] Dirani M, Nasreddine W, Abdulla F, Beydoun A. Seizure control and improvement of neurological dysfunction in Lafora disease with perampanel. Epilepsy Behav. Case Rep. 2014; 29 (2): 164–166. doi: 10.1016%2Fj.ebcr.2014.09.003.

[15] Schorlemmer K, Bauer S, Belke M, et al. Sustained seizures remission in progressive myoclonic epilepsy (Lafora disease). Epilepsy Behav. Case Rep. 2013; 1: 118–121.[PubMed: 25667843] doi: 10.1016/j.ebcr.2013.07.00.