

# Lafora Disease Presented with Multiple Seizure

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## Abstract

*Among different types of Progressive Myoclonic Epilepsy (PME), Lafora disease is an autosomal recessive disorder, with age of onset 6-19 years. It is quickly progressive, and death occurs within 10 years. It is a glycogen metabolism disorder characterized by the presence of inclusion bodies, known as Lafora bodies within the cytoplasm of the skin, liver, breast and muscle. Lafora disease presents as a neurodegenerative disorder with difficult to control seizures mostly like progressive myoclonic epilepsy. But the disease may also present with multiple types of seizures like generalized tonic clonic, focal with secondary generalization, myoclonic, absence etc. Patient may also present with psychomotor regression with ataxia, dysarthria, dementia, visual hallucination etc. Electroencephalogram (EEG) shows generalized spike/polyspikes and waves with photosensitivity and background slowing. Diagnosis is*

*further confirmed by presence of inclusion bodies (Lafora body) with typical histological findings on skin biopsy and genetic testing. Here we present a case of Lafora disease that presented with progressive myoclonic epilepsy and generalized tonic clonic seizure. We took proper history, did meticulous clinical examination and investigated her at our institute. We confirmed the patient having Lafora disease with typical histological findings that is presence of Lafora body on skin biopsy taken from axilla. Then treatment was given to the patient accordingly and proper counseling was done about the disease and its prognosis.*

**Keywords:** Lafora disease, progressive myoclonic epilepsy, neurodegenerative disorder, multiple type seizure

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## Introduction:

Lafora disease is characterized clinically by the triad of seizures, progressive myoclonus, and dementia.<sup>1</sup> There are different types of Progressive Myoclonic Epilepsy (PME) with different underlying genetic mutation.<sup>2</sup> Such as, EPM1 (epilepsy, progressive myoclonus 1) or myoclonic epilepsy of Unverricht and Lundborg, and EPM2A (epilepsy, progressive myoclonus 2) or

myoclonic epilepsy of Lafora disease. Other causes of PME include ragged red fiber, sialidosis type I, Neuronal ceroid lipofuscinosis (Batten disease), cerebral storage disease (juvenile neuropathy, Gaucher's disease), dentatorubral pallidoluysian atrophy and juvenile neuroaxonal dystrophy.

Mutations in EPM2A cause Lafora disease which is rare worldwide. It has a worldwide prevalence close to four cases per million<sup>3</sup> with a higher incidence among children and adolescents of positive history. Both sexes are equally affected. The onset of clinical manifestation usually starts in the range of 8-19 years of age and peaks around 15 years of age.<sup>4</sup> It is frequent in Mediterranean countries (Spain, Italy, France), Northern Africa, Middle East, and Southern India where high rate of consanguinity is present.<sup>5,6</sup>

They are associated with multiple types of seizures like progressive myoclonus, focal muscle twitching, absence like attacks and generalized tonic-clonic, visual and hearing problems, motor functional regression, slow dementia. Affected individual may present with problems of gastrointestinal tract, urinary bladder, thyroid function and weight gain, depending on type of PME or underlying cause.<sup>7</sup> Learning difficulty may be observed in few cases as early as five years of age. Death is traditionally thought to occur within ten years

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of onset, mainly related to status epilepticus, aspiration pneumonia or other complications common in chronic neurodegenerative diseases.<sup>8,9</sup>

It is progressive, fatal myoclonic epilepsy transmitted in an autosomal recessive pattern due to mutation of the EPM2A gene encoding laforin or NHLRC1/EPM2B gene encoding manin.<sup>10</sup> The absence of either protein results in poorly branched, hyper phosphorylated glycogen, which precipitates, aggregates, and accumulates into Lafora bodies which accumulate in different tissues like brain, muscle, liver, and skin.

Diagnosis is usually based on clinical and EEG findings, detection of laforin in the cells, and confirmed by genetic test. Clinically the diagnosis of Lafora disease should be suspected in a previously healthy older child or adolescent presented with multiple seizure types.

EEG abnormalities often precede clinical symptoms. Initially the EEG shows slowing of background activity, loss of alpha rhythm on eye closure and sleep features, photosensitivity (EEG discharges on photic stimulation) is common. Epileptogenic discharges over the occipital region arising from slowed posterior dominant rhythm in the proper clinical context, is highly suggestive of the disease.

Skin biopsy is pathognomic with the detection of intracytoplasmic periodic acid-Schiff-positive inclusions, known as Lafora bodies (LBs). A convenient and the least invasive method of establishing the diagnosis of Lafora's disease,<sup>11,12</sup> however, might give false negative result.<sup>13</sup>

Molecular genetic testing by sequencing and deletion/duplication analysis of EPM2A and NHLRC1 represents the gold standard for confirming the diagnosis.

#### Case Presentation

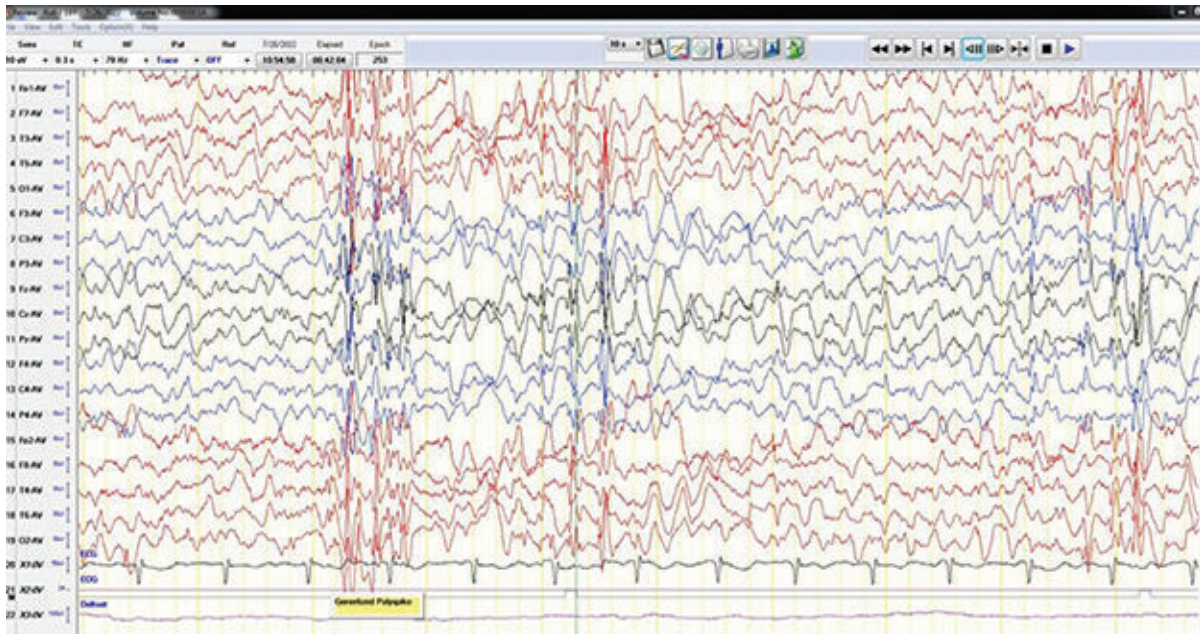
A 16-year-old female, student, hailing from Sylhet Sadar, was admitted at NINS on 23<sup>rd</sup> July 2022 with the complaints of seizure disorder for last 9 years. There was generalized shaking of whole body with loss of consciousness for 1-2 minutes, associated with eye blinking. Sudden jerky movement of limbs for 10-15 seconds were noted, which was present more in the morning but also throughout the day. There was no premonitory sign. Seizure was associated with incontinence of urine. These attacks started at her age

of 7 years. First it occurred in 3-4 months interval for the first 3 years, then it occurred 2-3 weeks interval, then weekly for 3 years, but now multiple times in a week. The patient was given anti-epileptic drugs like sodium valproate, levetiracetam, and clonazepam with minimal seizure control. Later the seizure was uncontrolled with medication.

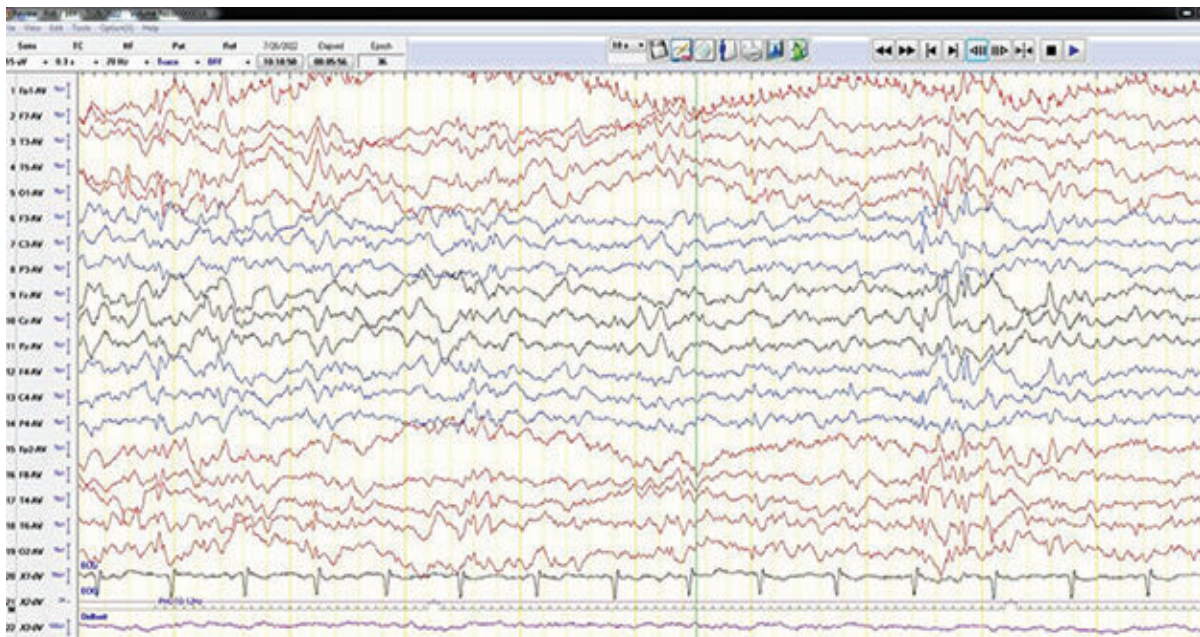
The patient is the first issue of four children of the consanguineous parents. One of her brothers developed same type of seizure at the age of 12 years. He presented with myoclonic jerk which was also progressive. Her parents were first cousins. She was born full term by elective Caesarean section after an uneventful pregnancy period. She had no birth injury. She was vaccinated as per EPI schedule. Her milestones of development were appropriate to age. The family noticed a decline in her cognitive function, such as difficulty in doing schoolwork and decline in memory. She also had unsteady gait.

On clinical examination, she was well alert, conscious, and cooperative. All vital parameters were within normal limits. Myoclonic jerks were noted. KF ring was absent. There was no organomegaly or lymphadenopathy. Examination of the central nervous system revealed that higher psychic function was altered in the form of decreased cognitive function with poor response. Speech was dysarthric. Cranial nerves were intact including fundoscopy. Muscle power was four over five in both upper and lower limbs. All modalities of sensation were normal. There was bilateral intention tremor and ataxia during walking.

Complete blood count with ESR was unremarkable. RBS was 4.8 mmol/L. Serum creatinine was 0.55 mg/dl, SGPT 19 IU/L, SGOT 27 IU/L, serum sodium 139 mEq/L, potassium 3.9 mEq/L. Serum calcium was 2.25 mEq/L. Ultrasonography of whole abdomen was normal. Serum ceruloplasmin was 26 mg/dl. 24-hour urinary copper was 167.93 microgram. KF ring was absent. EEG of brain showed abnormal EEG due to the presence of frequent generalized spike/ polyspikes and waves as well as multifocal spikes on a disorganized background, which was highly suggestive of progressive myoclonic epilepsy. CSF study revealed cell count 2/mm<sup>3</sup>, 100% lymphocyte, glucose 45 mg/dl, protein 23 mg/dl. Anti-measles antibody was negative.



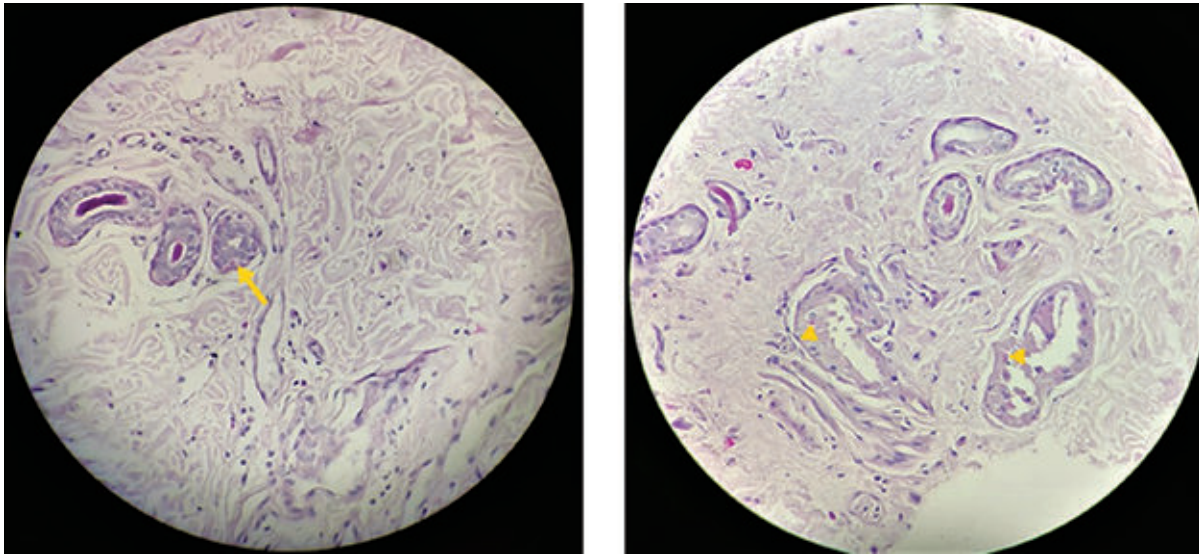
**Fig-1:** Abnormal EEG due to the presence of frequent generalized spike/ polyspikes and waves as well as multifocal spikes on a disorganized background.



**Fig-2:** Abnormal EEG due to the presence of frequent generalized spike/ polyspikes and waves as well as multifocal spikes on a disorganized background.

Histopathology report of the axillary skin showed that the epidermis was corrugated and hyperkeratotic, and

the sweat ducts revealed a few PAS positive homogenous globular bodies in the cytoplasm. Lafora bodies were present.



**Fig.-3:** Histopathology report of the axillary skin showed a few PAS positive homogenous globular bodies in the cytoplasm of sweat ducts.

Genetic test is gold standard in confirming the diagnosis of Lafora disease. But due to resource constrain and unavailability of genetic test in Bangladesh we could not do it for this patient.

#### Discussion:

Lafora disease was first described by a Spanish neuropathologist Gonzalo Rodríguez Lafora in 1911 in an adolescent patient suffering from progressive myoclonic epilepsy.<sup>1,4</sup> As Lafora disease presents as a neurodegenerative disorder, the patient suffers from confusion, speech difficulties, depression, decline in intellectual function, impaired judgement, and impaired memory. If areas of the cerebellum are affected, it is common to see difficulty with speech, coordination, and balance in Lafora patients. "Intracellular amyloid bodies" are seen in the brain and spinal cord of the patient. A characteristic Lafora body is periodic acid-Schiff (PAS)-positive diastase-resistant inclusions commonly seen in the gray matter of the brain. These bodies are free-lying and located mainly in the large pyramidal cells of the third and fifth layers of the cerebral cortex and mainly in the perikaryon.<sup>14,15</sup>

Lafora bodies can be seen in the myoepithelial cells of the secretory acini of the apocrine sweat glands and the eccrine and apocrine sweat duct cells.<sup>16</sup> Skin biopsy from the axilla is preferable and often diagnostic because of the higher number of the sweat glands whose PAS-

positive inclusion bodies can be more easily detected.<sup>17</sup> And in our patient, we also detected a few PAS positive homogenous globular bodies in the cytoplasm of sweat ducts.

In Oman, a 15-year-old girl was presented with Lafora disease where onset of symptoms was from 13 years of age,<sup>18</sup> which is similar to our patient. Progressive cognitive decline was present in this patient like other studies.<sup>18,19</sup> PME is a common presentation of Lafora disease which was also present in our patient, that is similar to other studies done in other parts of the world.<sup>18,20</sup> Progressive myoclonic epilepsy may also present as subacute sclerosing pan-encephalitis (SSPE). But from history, examination, EEG report and CSF study, SSPE was excluded here.

As reported in other parts of the world,<sup>18-21</sup> our patient also showed typical clinical, electrophysiological and histopathological findings consistent with Lafora disease.

So Lafora disease should be considered in the differential diagnosis of patients with progressive myoclonic epilepsy especially with early cognitive decline in appropriate geographic setting with a high frequency of consanguineous marriage and positive family history.

#### References

1. Turnbull J, Tiberia E, Striano P, Genton P, Carpenter S, Ackerley CA, et al. Lafora disease. *Epileptic Disord.* 2016; 18: 38-62. DOI: 10.1684/epd.2016.0842

2. Minassian BA, Lee JR, Herbrick JA, Huizenga J, Soder S, Mungall AJ, et al. Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. *Nat Genet.* 1998; 20: 171-4.
3. Orsini A, Valetto A, Bertini V, Esposito M, Carli N, Minassian BA, et al. The best evidence for progressive myoclonic epilepsy: a pathway to precision therapy. *Seizure.* 2019; 71: 247-57. DOI: 10.1016/j.seizure.2019.08.012
4. Karimipour D, Lowe L, Blaivas M, Sachs D, Johnson TM. Lafora disease: diagnosis by skin biopsy. *J Am Acad Dermatol.* 1999; 41: 790-2. DOI: 10.1016/s0190-9622(99)70026-5
5. Minassian BA. Lafora's disease: towards a clinical, pathologic, and molecular synthesis. *Pediatr Neurol.* 2001; 25: 21-9.
6. Striano P, Zara F, Turnbull J, Girard JM, Ackerley CA, Cervasio M, et al. Typical progression of myoclonic epilepsy of the Lafora type, a case report. *Nat Clin Pract Neurol.* 2008; 4: 106-11. DOI: 10.1038/ncpneuro0706
7. Berkovic SF, Andermann F, Carpenter S, Wolfe LS. Progressive myoclonus epilepsies: Specific causes and diagnosis. *N Engl J Med.* 1986; 315: 296-305.
8. Nitschke F, Ahonen SJ, Nitschke S, Mitra S, Minassian BA. Lafora disease - from pathogenesis to treatment strategies. *Nat Rev Neurol.* 2018; 14: 606-17. DOI: 10.1038/s41582-018-0057-0
9. Desdentado L, Espert R, Sanz P, et al. Lafora disease: a review of the literature. *Rev Neurol.* 2019; 68(2): 66-74.
10. Ferlazzo E, Canafoglia L, Michelucci R, Gambardella A, Gennaro E, Pasini E, et al. Mild Lafora disease: clinical, neurophysiologic, and genetic findings. *Epilepsia.* 2014; 55: 129-33. DOI: 10.1111/epi.12806
11. Carpenter S, Karpati G. Sweat gland duct cells in Lafora disease: diagnosis by skin biopsy. *Neurology.* 1981; 31: 1564-8.
12. Newton GA, Sanchez RL, Swedo J, Smith EB. Lafora disease: The role of skin biopsy. *Arch Dermatol.* 1987; 123: 1667-9.
13. Andrade DM, Ackerley CA, Minett TS, Teive HA, Bohlega S, Scherer SW, et al. Skin biopsy in Lafora disease: genotype-phenotype correlations and diagnostic pitfalls. *Neurology.* 2003; 61: 1611-4.
14. Flink R, Pedersen B, Guekht AB, Malmgren K, Machelucci R, Neville B, et al. Guidelines for the use of EEG methodology in the diagnosis of epilepsy. International League Against Epilepsy: Commission report. Commission on European Affairs: Subcommission on European guidelines. *Acta Neurol Scand.* 2002, 106: 1-7. DOI: 10.1034/j.1600-0404.2002.01361.x
15. Cendes F, Theodore WH, Brinkmann BH, Sulc V, Cascino GD. Neuroimaging of epilepsy. *Handb Clin Neurol.* 2016, 136: 985-1014. DOI: 10.1016/B978-0-444-53486-6.00051-X
16. Kälviäinen R. Progressive myoclonus epilepsies. *Semin Neurol.* 2015; 35: 293-9. DOI: 10.1055/s0035-1552620
17. Rubio G, Guijo CG, Mallada JJ, Cabello A, Merino AG. Diagnosis by axilla skin biopsy in an early case of Lafora's disease. *J Neurol Neurosurg Psychiatry.* 1992; 55: 1084-5. DOI: 10.1136/jnnp.55.11.1084
18. Al Mufargi Y, Qureshi A, Al Asmi A. Lafora Disease: Report of a Rare Entity. *Cureus.* 2020; 12(1): e6793. DOI: 10.7759/cureus.6793
19. Banu SH, Koli MZ. Progressive Myoclonic Epilepsy: Review Article with A Case Report of Lafora Disease. *Bangladesh J Child Health.* 2018; 42(2): 138-47.
20. Pondrelli F, Muccioli L, Licchetta L, et al. Natural history of Lafora disease: a prognostic systematic review and individual participant data meta-analysis. *Orphanet J Rare Dis.* 2021; 16: 362. DOI: 10.1186/s13023-021-01989-w
21. Harirchian MH, Shandiz EE, Turnbull J, Minassian BA, Shahsiah R. Lafora disease: a case report, pathologic and genetic study. *Indian J Pathol Microbiol.* 2011; 54: 374-5. DOI: 10.4103/0377-4929.81645