Progressive Myoclonic Epilepsy: Review Article with A Case Report of Lafora Disease

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Abstract
Progressive myoclonic epilepsy (PME) is an autosomal recessive, apparently a rare complex epilepsy syndrome. Among different types of PME, lafora body disease is more quickly progressive usually fatal within 2nd and 3rd decade. They are characterized by childhood or adolescent onset difficult to control multiple type seizures including myoclonous, generalized tonic clonic, absences, psychomotor regression with ataxia, dementia, dysarthria, visual hallucinations, and other general features. Early suspicion is important that leads to the rational diagnostic workout. The electro-clinical criteria would help a lot to exclude the benign epilepsy syndrome such as juvenile myoclonic epilepsy (JME) and suspect PME at the early stage of the complex epilepsy syndrome. Diagnosis is further clarified and confirmed by finding lafora body in skin and genetic study. Genetic mutation found in more than 87% cases in EPM2A gene or the EPM2B also known as NHLRC1 gene and are inherited in an autosomal recessive manner. EMP2A gene is located on chromosome 6q24. They are reported from Mediterranean basin, central Asia, India, Pakistan, northern Africa and Middle East where consanguineous marriage is common. We report a diagnosed case for the first time in Bangladesh. With the detail clinical history, rational use of the available investigation tools and clinical suspicion, diagnosis of the disorder at its early stage is possible. The rapid progress in genetic therapy would be a great hope in near future.

Key words: Progressive myoclonic epilepsy, EPM1, EPM2A, EPM2B, polytherapy,
neuropathy, Gaucher’s disease), dentatorubral pallidoluysian atrophy and juvenile neuroaxonal dystrophy.

EPM1, or Unverricht-Lundborg disease (ULD) is autosomal recessive, commonest among the PME syndrome, due to mutation in the Cystene B gene (CSTBG)\(^2,3,4\). Usually presents at 10-12 year of age with generalized tonic-clonic seizures or myoclonic jerks and absence attacks\(^5,6\). Seizures triggered by flickering sun light, trivial noise, may be violent with jerky falls causing injury\(^6\). Ataxia, deafness, cognitive regression and emotional instability is common. Siblings of the affected individuals having one recessive gene; generally do not show the signs of ULD, however mild symptoms are reported\(^7\).

EPM2A or Lafora disease (LD) is severe form of progressive myoclonus epilepsy (PME), first described in 1911. It is frequent in Mediterranean countries (Spain, Italy, France), Northern Africa, Middle East, and Southern India where high rate of consanguinity is present\(^8,9\).

Symptoms appear during childhood or adolescence (8-19year) with headaches, regressing school performance, spontaneous and induced myoclonus, generalized tonic-clonic seizures and/or fragmentary, symmetrical or generalized myoclonous, absence, and drop attacks. The myoclonous typically occurs at rest and increases with emotion, action or photic stimulation\(^8,9,10\). Visual symptoms are at times the characteristic manifestations as transient blackout, or visual hallucinations\(^8,11\).

Dysarthria and ataxia appear at early period, spasticity at the later stage of the disorder. Other features of progressive neurological degeneration are cognitive and/or behavioral deterioration, in a previously healthy child.

The main pathology of LD is accumulation of lafora bodies (carbohydrate storage products) that underlie the epileptic phenomena. Lafora bodies (LBs) are composed of abnormally formed, insoluble glycogen molecule\(^12,13\). They are found in skin, brain, liver, cardiac and skeletal muscle. In the central nervous system very large numbers of LBs in high number of dendrites may play a role in the epileptic diathesis\(^14\).

LD type of PME are inherited in an autosomal recessive manner, caused by mutations in either EPM2A or EPM2B gene (also known as NHLRC1 gene)\(^15-22\), a third LD locus is suggested from some biopsy proven LD families\(^23\).

**Diagnosis** is usually based on clinical and EEG findings, detection of laforine in the cells, and confirmed by genetic test. Clinically the diagnosis of LD should be suspected in a previously healthy older child or adolescent who present with fragmentary, symmetric, or generalized myoclonus and/or GT-C seizures, Visual hallucination (Occipital szs). Progressive cognitive and/or behavioral deterioration, dysarthria, ataxia, and at later stages spasticity and dementia,

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. Paroxysmal activity either focal (usually occipital), generalized or both, typically not accentuated by sleep. Epileptogenic discharges over the occipital region arising from slowed posterior dominant rhythm in the proper clinical context, is highly suggestive of the disease. Slowing of background activity with frequent bursts of diffuse epileptic discharges becomes evident within a few years\(^24-26\).

Skin biopsy is pathognomonic 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\(^27-29\), however, might give false negative result\(^30\).

Molecular genetic testing by sequencing and deletion/duplication analysis of EPM2A and NHLRC1 represents the gold standard for confirming the diagnosis. Skin biopsy remains a useful diagnostic tool in individuals with clinical diagnosis of LD in whom no pathogenic variant can be identified\(^30\).

Myoclonic movement disorders may be the presenting feature in a number of neurological diseases including seizure disorders, brain injuries, hereditary brain disorders, viral infections, and brain tumors.

Tourette syndrome is a movement disorder characterized by abrupt involuntary muscle movements called “ticks” and uncontrollable vocal sounds starting in childhood at 2 to 16 years of age\(^31\).

Huntington’s Disease is an inherited, autosomal dominant, neurodegenerative disease caused by
trinucleotide repeat mutation in the HTT gene. Childhood onset, **Juvenile Huntington disease (HD)**, is less common, present with ticks, emotional disturbances and loss of intellectual abilities. In advanced cases Wilson’s disease might be one of the differential diagnosis.

A multidisciplinary team involving the family members should be the treatment approach. Seizure control using antiepileptic drug (AED) is the corner stone. Certain AEDs should be avoided for their adverse effect i.e., phenytoin, carbamazepine, and lamotrigine may make the myoclonus worse. Seizure and psychomotor re-evaluation, behavior and sleep-wake pattern should be monitored at a regular interval.

School and social support is important for the patients’ wellbeing, achieved by cooperation and participation. The treating neurologist should inform the family about the current and updated treatment for such cases.

Genetic counseling is recommended for affected individuals and their families. Other treatment is symptomatic and supportive.

**Case report:**

A 14-year-old girl was brought to the neurology department, Dr. MR Khan Shishu Hospital in November 2017 with the complaint of increasing seizures that start with, eye blinking, right turn of face and neck, facial muscle spasm, drooling followed by generalized shaking and loss of consciousness for 1-2 minute. Discrete limb jerking for 10-15 seconds were noted in wake and in sleep state. These attacks 1st noticed at 12 year of age, initially occurred at 1-3 months interval, recently increasing to several attacks every week.

She had been a good student till class-V, was a fast reader and could compose poem by herself. The first symptom noticed at 10-year-age with staring, neck turning to right, stopped hand function while non-responsive for 50 seconds, 0-1/week, unprovoked or provoked by flickering light. During 11-13-year of age, slow motor functional regression, incoordination, frequent fall with slow developing ataxia, postural problem and tremor were noted. By the age 14-years she became dependent for her daily activities (dressing, washing, and feeding). She complaint of seeing flash lights at 13-year of age. Increasing visual problem was noticed since topiramate was introduced. She had remarkable weight gain at 13-year of age, diagnosed with hypothyroidism, and is on thyroxin since then.

The patient is second of three children of the consanguineous parent (1st cousin), was born full term by elective cesarean section after an uneventful pregnancy period. Her milestones of development were age appropriate. There was no family history of neurological disorder.

She looked apathetic with unstable posture (appendicular ataxia), had dysdiadochokinesia. On conversation she tried her best to communicate in language with marked scanning dysarthria. Her handwriting skill had regressed to almost like a 6-year old child.

Slow regression of her cognitive function was noted two years ago (dementia), however, she could recite a poem which she wrote a few years ago. She sang a full Tagor’s song with appropriate lyrics during examination. Her blood pressure recorded 130/90 mm of Hg, BMI was 29 kg/m² (high for height 1.55 meter, weight 70 Kg).

The somato-sensory evoked potential (SSEP) study revealed normal conduction in somatosensory pathways, rostral to the lumber cord. Peripheral conductions were also normal in sensory axons. There was no evidence of giant scalp potentials. Mild disturbance was found in central visual pathways on visual evoked potential test (VEP), however, the large VEP potential were suggestive of possibility of progressive myoclonic epilepsy. EEG at 10-year age revealed spike-wave discharges over the posterior region, generalized bursts of discharges were noted on photic stimulation.

Subsequent EEG records revealed focal and generalized transient bursts of moderate high amplitude spike-, polyspike-wave complexes. The slow background activities were non-reactive to eye closure and photic stimulation. No sleep rhythmic pattern was observed.

Prominent cortical sulci with mildly dilated lateral ventricles and hippocampal volume loss was noted on MRI. Lipid profile was within normal limit.
at 11-year age, later altered at 12-year of age with raised total cholesterol (173mg/dl) and triglyceride (140mg/dl) levels, SGPT (59 IU/L) and SGOT (49 IU/L) levels were above the normal limit. Alkaline Phosphatase and total protein were within normal limit. Renal function tests were normal (serum urea 18mg/dl, creatinine 0.54/dl, uric acid-4.7mg/dl, phosphate 3 mg/dl). Serum calcium (8.6mg/dl), albumin (3.3gm/dl) and electrolytes were within normal limit.

Thyroid Function was normal after appropriate treatment (TSH 4.2 µIU/ml, FT3- 2.9 peg/ml FT4-1ng/Dl). Vitamin D 1, 25 dihydroxycholecalciferol was insufficient at 11-year age (50nmol/L).

Genetic test revealed homozygous pathogenic variant of gene mutation in exon 3 of the EPM 2A gene.

History of medication: Carbamazepine (CBZ) was introduced at 10-year age with no seizure improvement. Later, Sodium Valproate (VPA), oxcarbamazepine, lemotrizin, topiramate, levotiracetam, Flunarizine and clobazam were used in variable combinations at different clinics without significant improvement. At one point she was on combination of five AEDs for 4 months.

Treatment out of the country: In India, "levotiracetam, topiramate, sodium valproate" combination was maintained by the epileptologist who also suspected PME. Diagnosis of LD was confirmed in India with the genetic test.

Recently the case history was reviewed by neurologist in Australia, while she had increasing seizures, visual hallucination, developed poor vision, and the family was referred to us.

We tapered off topiramate and levetiracetam, continued with VPA, added nitrazepam (NTZ). Three months later remarkable improvement was reported.

Since we introduced Zonisamide as an adjunctive therapy, her seizure frequency and intensity are well controlled for last three months.

First record at 10 year age revealed focal discharges with normal background activity and normal reactivity to eye closure. At 13 yr age transient discharges with spike-waves focal and generalized was noted with slowing of the background activity (image 1). Images 2 and 3: case diagnosed with LD at 13 yr of age, EEG in wake state showing repeated transient bursts with focal predominance, Background slowing and poor response on eye closure at 14 yr age.
Progressive Myoclonic Epilepsy

Images 4: Case with LD MRI of brain of the showing prominent cortical sulci and mildly dilated ventricles.
Discussions:
Our confirmed case of LD was an intelligent, normally functioning child till 10 year of age. First symptom with complex partial seizures, provoked by flickering light, was noted at 10 year age. Later she developed multiple types of seizure including myoclonous and secondarily generalized major attacks. She started having tremor, progressive deterioration of motor and cognitive function, dysarthria, ataxia and rapid weight gain. EEG revealed focal discharges with poorly reactive slow background activity. Clinical suspicion of PME, and diagnosis was confirmed by one of the experienced child neurologist and epileptologist in India three years later. PME or neurodegenerative disorder should have been suspected without delay, particularly while there was no response to multiple AEDs and there was functional regression noted in a child with completely normal developmental skills. The commonest diagnostic mistake in such a case at early state is juvenile myoclonic epilepsy (JME), idiopathic generalized epilepsy (IGE) or complex partial seizures\textsuperscript{1,2,38}, differentiated clinically with the fact that IGE or JME would not present with dementia. The PME presents with progressive functional

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<tr>
<th>Category</th>
<th>Description</th>
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<tr>
<td>At 10 year age</td>
<td>Photosensitive, complex partial seizures, 1\textsuperscript{st} noticed at 10 year age. EEG: Occipital discharges, generalized discharges on photic stimulation, other activities normal</td>
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<tr>
<td>At 11 yr age</td>
<td>Poorly controlled seizures, myoclonous noted, discrete jerking in sleep, school performance started regressing,</td>
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<td>At 12 year</td>
<td>Secondarily generalized tonic clonic seizures with loss of consciousness, at 1-3 month interval. Discrete jerking in sleep and wake state several times daily. Slow in her daily activities noticed</td>
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<td>At 13 year</td>
<td>Increasing frequency and intensity of GTCsz and myoclonous Motor incoordination, frequent fall, tremor, regressing memory and writing skills. Stopped schooling Remarkable weight gain, Hypothyroidism diagnosed EEG: focal and generalized spike wave discharges with slowing of background activity</td>
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<td>At 14 year age</td>
<td>Seizures increasing instead of multiple combination of AEDs Frequent daily attacks, Dependent for her daily living activity. Almost home-bound. Mild, infrequent Seizure at present for last three months after adding Zonisamide EEG: frequent transient bursts of spike-wave complexes, focal discharges in between. Non-reactive and slowing of the background, sleep pattern absent.</td>
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<td>Other test</td>
<td>SSEP: NAD, VEP: Large potential suggestive of PME MRI: prominent sulci and ventricles. Hyppocampal volume loss Genetic test: homozygous gene mutation in exon 3 of the EPM 2A gene SGOT and SGPT: just above the normal limit Vit. D 1,25 dehydrocolecalciferol: 50 nmol/l at 11 yr age Renal function test, s.electrolyte, STP: normal Thyroid function tests are normal (on oral treatment)</td>
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deterioration and other neurological sign symptoms in a normal individual. Usually there is negative myoclonus with sudden loss of leg muscle tone leading to frequent fall. At times increasing myoclonic jerks may build to a “crescendo myoclonus” or a major convulsion, after which sometimes the condition improves for a few days. The clinical phenomena including seizures in LD type of PME occur due to neuronal accumulation of Lafora bodies, this is not so in IGE or in JME.

The characteristic neurophysiological phenomena in LD, can be noted prior to the clinical symptoms, while background activities, reactivity to eye closure and photic stimulation remain normal in IGE and JME. In LD Somatosensory and VEP shows giant potentials resulting from cortical hyper-excitability due to impaired cortical inhibitory mechanisms in LD. Progressive prolongation of the central latencies and of brainstem auditory responses are noted during disease progression.

In a nutshell, PMEs(LD) differ from JME or IGE on the following aspects: i) complex phenotype including epilepsy plus movement disorder; ii) progressive neurological disability; iii) poor respond to AEDs; iv) slowing of background electroencephalographic (EEG) activity; v) presence of giant evoked potentials.

Wrong selection of AED might aggravate and alter the seizure phenomena, as noted in our case (CBZ, Ox CBZ, LMTZ). The present case had visual hallucination as a feature of PME at the early stage; she later developed visual field defect, which was clinically proved to be the side-effect of topiramate. Topiramate is used to control partial and primary generalized epilepsy in adults and children above two year of age. However ocular side effect of topiramate that may occur within 2 weeks of initiation of this drug is well accepted and should inform the parents about the side-effect to prevent irreversible iatrogenic damage.

The following three levels of evidence would help the clinicians for early suspicion and diagnosis of LD:

1. The clinical evidence from the detail history of the disease progression, i.e., seizure, myoclonous, visual agnosia or hallucination, age of onset, response to antiepileptic medication; motor and cognitive functional regression, consanguineous parents, if any affected family member. The history of AEDs should be taken meticulously to explore possibility of starting inappropriate AED.

2. Neurophysiological evaluation including EEG and evoked potentials. Thorough evaluation of multiple EEGs with progression of the condition, would provide complementary evidence, to distinguish between LD and other PMEs, e.g., Unverricht-Lundborg disease (EEG changes are less prominent); or juvenile ceroid-lipofuscinosis, in which single-flash responses are very prominent on EEG. The costlier tests should be justified by the appropriate clinical and neurophysiological evidence. Other tests such as MRI is not informative in LD.

3. Demonstration of LBs in sweat gland duct cells on axillary skin biopsy is pathognomonic test for LD. It may be very helpful in a situation where genetic testing is not available, or not entirely conclusive.

The next challenge is declaration of the specific diagnosis, adding extra burden to the family of the proband and should not be underestimated. There are certain issues need to be addressed during family counseling:

Feelings of guilt among the parents that must be alleviated with a few simple statements, that the inheritance is bilateral results from a very uncommon co-occurrence of abnormal genes, even in consanguineous marriages, persons with a single abnormal gene will not have the disease.

The possible occurrence of LD in healthy younger sibling remains uncertain in most of the cases, and whether siblings should be subject to molecular screening is still debatable. There is no treatment recommended in pre-symptomatic LD cases, to prevent or delay the appearance and progression of symptoms. Having provided all the relevant information, the clinician in charge of the patient should come to an agreement with the family and obtain their informed consent for the procedures performed on non-affected family members. If the family shows reluctance towards genetic testing, a simple EEG recording for a younger sibling may provide information on the potential risk of LD.

Unfortunately the AED-effect is partial, they have no major influence on the progression of motor, cognitive and behavioral symptoms. Valproic acid is effective at least for some time in suppressing GTCS, photic sensitivity, and myoclonus. Other AEDs used are phenobarbital (PB), primidone (PRM), and levetiracetam (LEV). Lamotrigine (LTG) is not
advisable in the context of myoclonic epilepsy, but may help transiently. Other helpful drugs include topiramate (TPM), with special attention to visual side effect, and zonisamide (ZNS), both have marked antimyoclonic effects. Additional relief can be obtained, often transiently, with ethosuximide, felbamate, methsuximide, and benzodiazepines (BZD). The latter (clobazam, clonazepam, and diazepam) should be used with caution as there is a marked initial effect followed by quick tolerance. Usually AED treatment progresses to polypharmacy with the LD progression. A suitable combination of two AEDs works for some time; needs re-combination after a few months, depending on the paradoxical aggravating effect of some AED, however, is difficult to pinpoint. Finally, there are recent single case reports of rather dramatic beneficial effects of ‘Perampanel’, a newly approved AED, in 2012.46,47

Social and family support in LD, is as important as medical treatment. Our case was fond of music, she gets tremendous support at home with restriction to use VIDEO game, stopped schooling to reduce her frustration there. She might get benefit from professional psychological support. Physical therapy should aim at preserving ambulation.

The general outcome of LD is gloomy; however, schooling and social activity should be maintained with professional and family cooperation. Regular follow up at the neurology service center should be organized at 6-12 months interval. Inpatient service might be required in case of acute infection or status epilepticus. The patient may become wheelchairbound and later bedridden in later stage.

There is a hope on the horizon for people diagnosed with Lafora disease by the initiative taken in advanced countries to treat LD with coordinated efforts. It is predicted that specific drug targeting the gene would be ready for human trial, possibly within the next few years48,49.

Conclusion:
Early suspicion of PME is possible by thorough history taking and, rational diagnostic workout with the use of the available investigation tool. That would help the clinicians to avoid untowards drug effect. With the hope of genetic therapy for potential cure or halt of the disease progression in near future we should give importance on suspicion and confirmed diagnosis of the LD without delay.

References:


