Journal of Bangladesh College of Physicians and Surgeons
Vol. 43, No. 4, October 2025

Phenotype, EEG, neuroimaging and Genetic profile of Progressive Myoclonic Epilepsy in Bangladesh: An Observational Study

K FATEMA[a], MM HOSSAIN[b], M ISMAIL[c]

Abstract:

Background: *Progressive myoclonic epilepsy (PME) is an epilepsy syndrome characterized by myoclonus, cognitive deficit and ataxia. Common PMEs are Unverricht–Lundborg disease, myoclonic epilepsy with ragged-red fiber (MERRF) syndrome, Lafora body disease, neuronal ceroid lipofuscinoses, and sialidases. This study was conducted to obtain baseline information on PME in terms of phenotype, EEG, MRI of the brain, and overall genetic profile.*

Methodology: *This retrospective observational study was conducted in the Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The duration of the study was from January 2020 to December 2023. Children diagnosed as PME on the basis of phenotype, EEG, imaging and genotype were included in this study. The genetic diagnosis was done by next-generation sequencing.*

Result: *A total of 11 patients were analyzed in this study. The age of onset ranges from 6 months to 5 years. Consanguinity of the parents was present in 8 cases; one patient had a positive family history of a similar type of illness. The key clinical features were seizure, ataxia, neuroregression, visual impairment, dystonia etc. EEG features showed focal epileptic discharges (6), generalized discharges (5), with progressive deterioration of background in most of the cases. In MRI, 8 out of 11 patients had cerebello-cerebral atrophy. In all cases, next-generation sequencing was done; of them, three cases had KCTD7 gene mutation, three had CLN6 gene mutation causing Neuronal ceroid lipofuscinosis, another three had TPP1 gene mutation and the remaining two had MFSD8(-) gene mutation.*

Conclusion: *This study highlighted the pattern of genotype and phenotype of children with PME in Bangladesh*

Keywords: *Progressive Myoclonic Epilepsy, genetic profile, phenotype.*

(J Bangladesh Coll Phys Surg 2025; 43: 269-276)
DOI: https://doi.org/10.3329/jbcps.v43i4.85002

Introduction:

Progressive myoclonic epilepsy (PME) is a complex syndrome that is characterized by progressive myoclonus, cognitive deficit and ataxia.[1] These are genetically and phenotypically heterogeneous complex groups of neurodegenerative diseases.[2]

PME may affect all ages; however, most cases present in late childhood and adolescence. Patients usually present with seizures, which start benignly, then gradually it become severe. Along with seizures, there are myoclonus, which are often stimulus sensitive, segmental or arrhythmic. Neurological deterioration consists of cognitive decline, ataxia, myopathy, neuropathy, and visual impairment.[2,3]

The major types of PME are Unverricht–Lundborg disease, myoclonic epilepsy with ragged-red fiber (MERRF) syndrome, Lafora body disease, neuronal ceroid lipofuscinoses, and Sialidoses.[4] PME has autosomal dominant, recessive and mitochondrial inheritance. Diagnosis of specific forms of PME is challenging because of genetic heterogeneity, phenotypic similarities, and an overlap of signs and symptoms with other epileptic and neurodegenerative diseases.[5] Because of recent developments in molecular

a. Prof. Kanij Fatema, Professor, Department of Pediatric Neurology, Bangladesh Medical University, Dhaka, Bangladesh.

b. Dr. Mohammad Monir Hossain, Assistant Professor, Department of Paediatric Neurology, National Institute of Neuroscience and Hospital, Dhaka, Bangladesh.

c. Dr. Maymuna Ismail, MD Phase B Resident, Department of Pediatric Neurology, Bangladesh Medical University, Dhaka, Bangladesh.

Address of Correspondence: Prof. Kanij Fatema, Professor, Department of Pediatric Neurology, Bangladesh Medical University, Dhaka, Bangladesh. E-mail: maiomonami@gmail.com. Cell: +8801713097751. Orchid ID: 0000-0002-2465-053X.

Received : 16.06.2025 **Accept :** 27.08.2025

genetics, their natural history and biological basis may soon be better understood.

There are only a few anecdotal case reports of these entities from Bangladesh. This study has been done to highlight the clinical, electrophysiological, neuroimaging and genetic profiles of the pediatric population diagnosed as PME.

Methodology

This retrospective observational study includes 11 children who were admitted and diagnosed as Progressive myoclonic epilepsy based on clinical features, EEG, MRI of brain and next-generation sequencing in the Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The duration of the study was from January 2019 to December 2023.

Initially, children were evaluated through detailed history and clinical examination. History related to seizure type, frequency, age at onset, perinatal details, family history, developmental history etc were noted. In every case a 30 minutes sleep and awake EEG and neuroimaging (MRI of brain) were done. EEG reporting was done by an experienced pediatric neuro-physiologist and neuroimaging was reviewed by an expert neuro-radiologist. In suspected case metabolic test (basic metabolic screening, Tandem mass spectrometry-TMS, Gas chromatography mass spectrometry-GCMS) were done.

The genetic test was done by Next generation sequencing (NGS). Selective capture and sequencing of the protein coding regions of the genome/genes was performed. Mutations identified in the exonic regions were generally actionable compared to variations that occur in non-coding regions.

Result:

The age of onset of the 11 patients with PME ranged from 6 months to 5 years, mean age of diagnosis was 5 ±2 year and age of onset mean was 2 ±0.7 year. Severn patients were female and the rest were male. Regarding the birth history, 9 patients had an uneventful birth history, one patient had a history of perinatal asphyxia and another one had neonatal sepsis. Before the onset of the ailment, 7 patients had normal development, while four patients had developmental delay. Eight out 11 had consanguineous parents, while only one patient had a positive family history of a similar type of illness. (Table I)

Table I

Demographic characteristics of the children with PME (n-11)

Demographic characteristics	n (%)
Age of diagnosis in year (mean)	5+2
Age of onset in year (mean)	2+0.7
Sex	
Male	5 (45.45)
Female	7 (63.63)
Developmental status prior to disease onset	
Normal	7 (63.63)
Developmental delay	4 (36.36)
Birth history	
Normal	9 (81.81)
Neonatal sepsis	1 (9.09)
Perinatal asphyxia	1 (9.09)
Consanguinity	
Present	8 (72.72)
Absent	3 (27.27)
Family history	
Present	1 (9.09)
Absent	10 (90.90)

Regarding the initial clinical features, the predominant features were seizure, ataxia, neuroregression and visual impairment. Seven patients had neuroregression, mostly in motor and speech domains. The predominant type of seizure was a myoclonic seizure. Other types of seizures were generalized tonic and focal clonic seizures. Four patients had dystonia, while others had tremor, titubation and head nodding. Cognitive decline and ataxia were invariably present in all the cases. (Table II). Ten out of 11 cases had visual abnormalities. Eight patients had optic atrophy, other eye abnormalities were macular degeneration, squint and retinitis pigmentosa. (Table II)

In all patients MRI of brain was done. In eight patients both cortical and cerebellar atrophy (Fig 1) was found. However, in most of the patients cerebellar atrophy was more than cerebral atrophy and most prominent in posterior regions. Regarding the other features, white matter change was present in 2 patients in the form of

Table II

Clinical profile of the children with Progressive myoclonic epilepsy (n-11)

Cases	Initial clinical features	Seizure type	Movement disorders	Behavioural disorder	Cognitive status	Ophthalmologic abnormality
Case 1	Focal Seizure Neuroregression	Focal Myoclonic Generalized tonic	Ataxia Titubation	Restlessness	Cognitive decline	Optic atrophy
Case 2	Ataxia, seizure Neuroregression	Myoclonic	Ataxia Dystonia	Irritability	Cognitive decline	Macular degeneration
Case 3	Seizure Cognitive decline Visual impairment	GTCS Myoclonic epilepsy	Ataxia Dystonia	Hyperactivity	Cognitive decline	Optic atrophy and retinitis pigmentosa
Case 4	Seizure, drooling	GTCS	_	Autistic features	Poor cognition	Optic atrophy
Case 5	Neuroregression Drop attacks, focal seizure, tremor of limbs	Focal seizure Myoclonic seizure	Ataxia Tremor	Hyperactivity	Cognitive decline	Nothing significant
Case 6	Seizure, developmental delay	Generalized seizure	Dyskinesia behavior	Autistic	Cognitive delay	Squint, pale optic disc
Case 7	Seizure, neuroregression	Focal seizure	Head nodding	Hyperactivity	Cognitive decline	Optic atrophy,
Case 8	Neuroregression, Dystonia Low vision	Myoclonic seizure	Dystonia	-	Cognitive decline	Pale optic disc, Optic atrophy
Case 9	Low vision, seizure	Generalized seizure	-	-	Cognitive delay	Optic atrophy
Case 10	Myoclonic jerks, developmental delay regression, hand wringing movement	Generalized tonic , myoclonic	_	_	Cognitive & speech decline	Temporal pallor
Case 11	Speech delay Ataxia Regression of motor skill Visual problem	Generalized, myoclonic seizure	Ataxia	Hyperactivity	Cognitive delay and regression	Primary optic atrophy

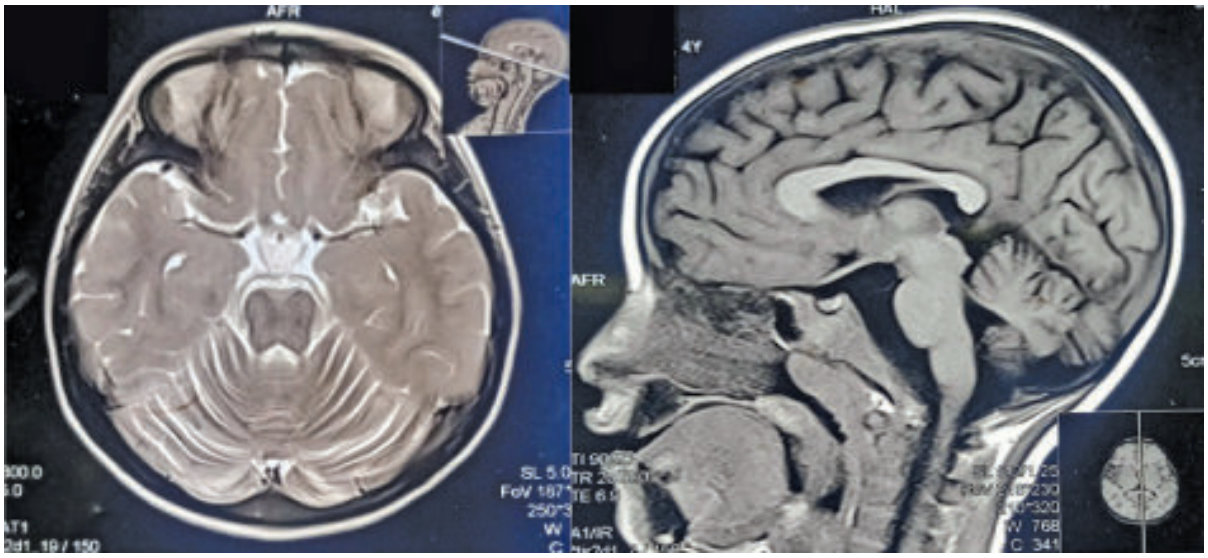

Figure 1: MRI of brain showing atrophy of cerebellum and cerebrum in a case of PME

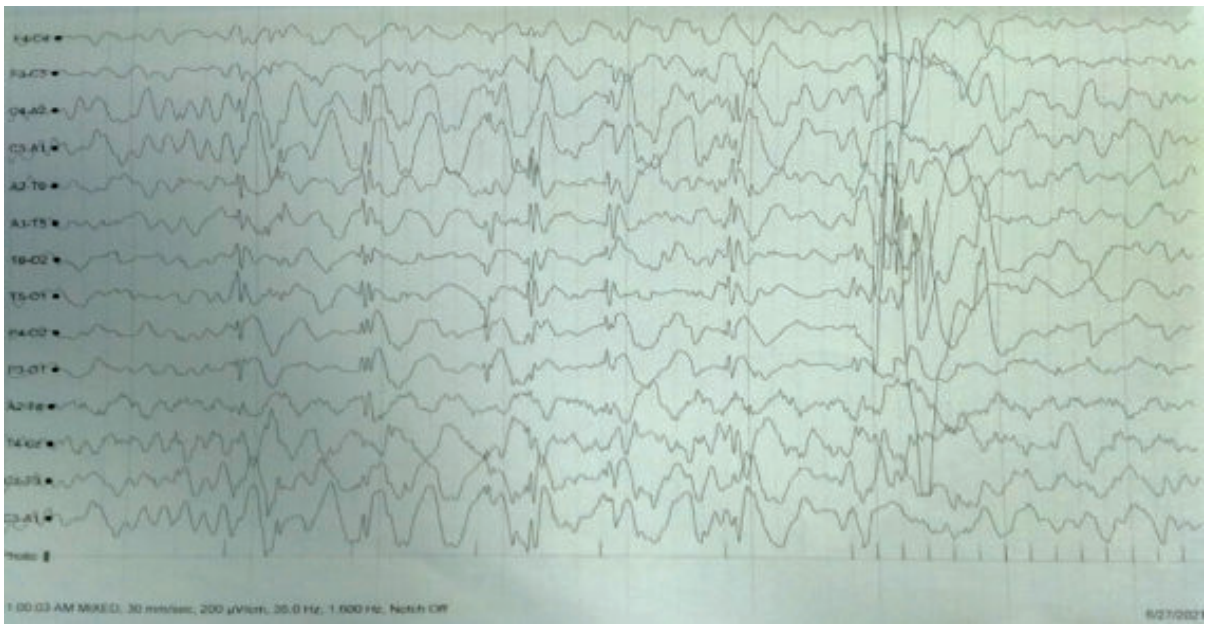

Fig.-2: *EEG of a case of PME showing photic stimulation at 1 Hz triggering posterior spike, polyspike wave paroxysms.*

hypomyelination and T1 hyperintensity. Basal ganglia hyperintensity and brainstem atrophy was present in one patient each**.** (Table 3**)**

In all cases at least 2 EEG were done, 3rd EEG was done in 5 cases. In first EEG, background was abnormal in 8 cases and normal in 3 cases. Abnormalities observed in the background were paucity of sleep marker, no posterior dominant alpha wave in awake state, diffuse slowing with attenuation and discontinuity. Regarding

Table III

Neuroimaging (MRI of Brain) profile of Cases (n-11)

MRI of brain finding of the cases	n(%)
Cortical atrophy	9 (81.81)
Cerebellar atrophy	8 (72.72)
White matter change	3(27.27)
Gliosis	1 (9.09)
Brainstem atrophy	1 (9.09)

the epileptic discharges, 6 patients had focal epileptic discharges, rest had generalized epileptic discharges with polyspikes. In 2nd and 3rd EEG deterioration of background and epileptic discharges have been observed in most of the cases. **(**Table IV**)** In case of 2 patients, there were posterior dominant epileptic discharges after slow (1 hertz) photic stimulation. (Fig 2)

In next-generation sequencing of the cases, four cases were Neuronal ceroid lipofuscinosis-6, 2 cases were Neuronal ceroid lipofuscinosis-2, two cases were Neuronal ceroid lipofuscinosis-2, 3 cases were Progressive myoclonic epilepsy 3(CLN14). Details of the genetic profile have been given in Table V. **(**Table 5**)**

Table - IV

EEG findings of the children with PME (n-11)

	First EEG		Follow up EEG 1	Follow up EEG 2
Cases	Background	Epileptic discharge		
Case 1	Normal	Focal with secondary generalization	Background disturbed, generalized epileptic discharges, polyspikes	Grossly abnormal background, intermittent attenuation, polyspike followed by slow wave discharges
Case 2	Abnormal	Generalized epileptic discharges, polyspikes	Disturbed background, generalized epileptic discharges, polyspikes with intermittent attenuation	Not done
Case 3	Abnormal Diffuse slowing	Focal epileptic discharges	Diffuse slowing with near continuous focal epileptic discharge	Not done
Case 4	Abnormal	Epileptic discharges over B/L temporo parieto occipital region with secondary generalization	Focal epilepsy	Focal epilepsy
Case 5	Paucity of sleep marker, generalized slowing	Epileptic encephalopathy	Epileptic encephalopathy	Not done
Case 6	Normal	Focal discharge -	Focal epileptic discharge with poor background	Diffuse slowing of background with widespread focal discharge
Case 7	Devoid of sleep marker	Focal epileptic discharges	Diffuse encephalopathy with focal epileptic discharges	Not done
Case 8	Normal	Focal epileptiform discharges over right posterior temporal and occipital region	Focal epilepsy with diffuse slowing	Focal epileptic discharges with periods of attenuation of background
Case 9	Background devoid of sleep marker, diffuse slowing	Generalized epileptiform discharges	Background poorly organized, frequent generalized epileptic discharges	Not done
Case 10	Abnormal	Epileptic encephalopathy	Epileptic encephalopathy	Generalized epileptic discharges with poor background
Case 11	Disturbed	Repeated burst of generalized epileptic discharges, polyspikes	Generalized epileptic discharges, poor background	Not done

Table V

Genetic Profile of the cases (n -11)

Cases	Chromosome	Exon no	Variance	Gene	Zygocity	Inheritance	Disease	Significance
Case 1	7	4	c.505C>T (p.Arg169Trp)	KCTD7 mutation	Homozygous	Autosomal recessive	Progressive myoclonic epilepsy 3 , with or without intracellular inclusions(CLN14)	US
Case 2	7	2	c.190A>G, (p. Thr64Ala)	KCTD7 gene (CLN14)	Homozygous	ARD	Progressive myoclonic epilepsy 3(CLN14)	US
Case 3	8	9	c.850G>C (p.Ala284Pro)	MFSD8(-)	Homozygous	ARD	Neuronal ceroid lipofuscinosis 7	US
Case 4	6	7	c.794_796del (p.Ser265del)	CLN6(-)	Homozygous	ARD	Neuronal ceroid lipofuscinosis-6	LP
Case 5	6	2	c.195dup (p.Met66Hisfs Ter66)	CLN6(-) CPT2	Homozygous	ARD	Neuronal ceroid lipofuscinosis-6	P
Case 6	11	6	c.617G>A (p.Arg206His)	TPP1(-)	Homozygous	Autosomal recessive	Neuronal ceroid lipofuscinosis-6	LP
Case 7	7	4	c.505C>T (p.Arg169Trp)	KCTD7(+)	Homozygous	ARD	Progressive myoclonic epilepsy 3, with or without intracellular inclusions	US
Case 8	11	5	c.503_504insTG GA (p.Phe169fs)	TPP1	Homozygous	ARD	Neuronal ceroid lipofuscinosis type 2	LP
Case 9	8	11	c.1235C>T (p.Pro412Leu)	MFSD8(-)	Homozygous	ARD	Neuronal ceroid lipofuscinosis 7	LP
Case 10	15	15	C794_796del(p.Ser265del)	CLN6(-)	Homozygous	ARD	Neuronal ceroid lipofuscinosis 6	LP
Case 11	11	5	c.503_504insTG GA (p.Phe169fs)	TPP1	Homozygous	ARD	Neuronal ceroid lipofuscinosis type 2	LP

P, pathogenic; F, LP, likely pathogenic; ARD, autosomal recessive disorder; US, uncertain significance;

Discussion:

PME is a rare group of genetic epilepsy with predominantly generalized epilepsy, neuroregression, ataxia and cognitive deficit.[6] It is often challenging to make a definite diagnosis of specific forms of PME as genetic tests are expensive and facilities are unavailable in most of the centers. This is the first case series of PME from Bangladesh with genetic profile. The predominant genotype of this case series was Neuronal ceroid lipofuscinosis-6.

Out of 11 patients of this study, 63.63% (7) patients were female. All the patients were less than 5 year at the time of onset and age range at diagnosis was 2-8 year. Nine out of 11 had uneventful birth history, while one had perinatal asphyxia and one had neonatal sepsis. About 72.7% had consanguinity and one patient had positive family history of same type of illness. In a related study done by Zhang et al , the age range of onset of disease of PME was 3 months to 12 years, a female predominance was seen in this case series also.[6] In a study done in south India, consanguinity was present in about 61.8% cases however, they found male predominance in their cases.[1]

Regarding the initial clinical features, almost all the patients in this study had seizure, mostly myoclonic in nature. Other types of seizure were generalized tonic clinic seizure and focal seizure. Seizure was mostly generalized in the study by Sinha et al.[1] Myoclonic seizure were fragmentary, asymmetric and disabling like some other studies.[1] Other manifestations were ataxia, visual impairment, cognitive decline, dystonia etc. Ataxia was present in 5 out of 11 patients. Behavioural disorders were present in 8 patients in the course of the illness in the form of hyperactivity, autistic features and irritability. All the patients had cognitive decline. In the study by Sinha H et al they found myoclonus, cognitive decline and neurological deficits in most of the cases.[1] In a case report from Bangladesh, visual hallucination along with ataxia, generalized seizure and cognitive decline was seen in a case of Lofora body disease.[8]

The most common ophthalmologic abnormality in this study was optic atrophy. Other findings were macular degeneration, retinitis pigmentosa etc. This findings have similarities with the study by Zeman et al and Sinha et al where the neuro-ophthalmic abnormalities were primary optic atrophy , macular degeneration and retinitis pigmentosa. [1, 2]

In this study, most of the patients had cerebello-cerebral atrophy with most prominent atrophy in the posterior regions. Other findings were hypomyelination, T1 hyperintensity, basal ganglia lesion and brainstem atrophy. In a study done by Zhang et al, out of 38 patients, 4 patients had cerebral atrophy, 14 had cerebral and cerebellar atrophy, 6 had cerebellar atrophy, 2 had brain atrophy with abnormal signals in cerebellar while 12 had normal findings.[7] In another study by Franceschetti S et al, the predominant MRI findings cerebello-cerebral atrophy and cerebral atrophy. While a few patients had nonspecific T2 hyperintensities.[5]

There is variability in EEG in various PME. It also depends on the disease progression. In most of the cases, the background is normal at the onset of the disease. Then, gradually there is diffuse slowing of the background.[11,12] The epileptic discharges are mostly generalized spikes, polyspikes activity. However, in some of the cases, focal or multifocal epileptic discharges are found. In Lafora disease, occipital discharges are found. Photosentivity particularly in low flash frequencies (<6 Hz) are important characteristics of Neuronal ceroid lipofuscinosis.[8] In this study, almost all patients showed deterioration of background activities evidenced by background slowing in repeat EEG. The predominant type of epileptic discharge initially was focal.

Till date, more than 30 genes have been linked with PME. The common genes linked are as follows: PPT1, TPP1, CLN5, CLN6, MFSD8, KCNC1, KCTD7, TBC1D24, DRPLA, GOSR2 etc.[7-10] In this study, 3 cases had KCTD7 gene mutation causing PME 3 (CLN14). Three cases had CLN 6 gene mutation causing Neuronal ceroid lipofuscinosis 6. While TPP1 gene mutation was found in 3 cases which caused NCL2. Whereas 2 cases of MFSD8(-) gene mutation was found which was linked to NCL 7. All cases were inherited as autosomal recessive fashion. We did not include here cases without positive genetic yield. In a study by Zhang J et al, 78.9% (30/38) children reached genetic diagnosis, and 13 genes related to PME were identified. [7] While in a study done by Muona et al. 31% genetic diagnosis was done.[14]

Conclusion:

PME is a group of neurogenetic disorders with heterogeneity in phenotype and genotype. Although clinical phenotype, eye findings, EEG, MRI of brain play important role in the diagnosis, but confirmation is obtained with the genetic diagnosis by next generation sequencing or whole exome sequencing. This is the first study of PME with genetic diagnosis from Bangladesh. The genetic mutation found in relation with PME here were KCTD7, TPP1. MFSD8 and CLN6. Further, prospective study is suggested to obtain the genetic landscape of PME in this part of geographic area.

Limitation of the study: As this is a retrospective study, this does not portray the total NGS yield in suspected cases. Furthermore, in most of cases, parental genetic study was not done.

IRB number: BSMMU/2020/1042

Conflict of interest:

Nothing to declare

References:

1. Sinha S, Satishchandra P, Gayathri N, Yasha TC, Shankar SK. Progressive myoclonic epilepsy: A clinical, electrophysiological and pathological study from South India. J Neurol Sci. 2007 Jan 15;252(1):16-23. doi: 10.1016/j.jns.2006.09.021. Epub 2006 Dec 12. PMID: 17166519.

2. Holmes GL. Drug Treatment of Progressive Myoclonic Epilepsy. Paediatr Drugs. 2020 Apr; 22(2):149-164. doi: 10.1007/s40272-019-00378-y. PMID: 31939107; PMCID: PMC7901803.3vailable at: https://doi.org/10.1016/j.jns.2006.09.021.

4. Delgado-Escueta AV, Ganesh S, Yamakawa K. Advances in the genetics of progressive myoclonus epilepsy. Am J Med Genet. 2001 Summer; 106(2):129-38. doi: 10.1002/ajmg.1575. PMID: 11579433.

5. Berkovic SF, Cochius J, Andermann E, Andermann F. Progressive myoclonic epilepsies: clinical and genetic aspects. Epilepsia 1993;34: 19–30.

6. Franceschetti S, Michelucci R, Canafoglia L, Striano P, Gambardella A, Magaudda A, et al. Collaborative LICE study group on PMEs. Progressive myoclonic epilepsies: definitive and still undetermined causes. Neurology. 2014 Feb 4;82(5):405-11. doi: 10.1212/WNL.000000 0000000077. Epub 2014 Jan 2. PMID: 24384641; PMCID: PMC3917687.

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. Zeman W, Donanne S, Dyken P, Green J. The NCL (Batten–Vogt syndrome). In: Vinken PJ, Bruyn GW, editors. Handbook of Neurology, vol. 10. Amsterdam: North Holland Publishers; 1970. p. 588–679.