

Progressive Myoclonus Epilepsies

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Abstract

Keywords

- ▶ progressive myoclonus epilepsy
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- ▶ sialidosis
- ▶ Gaucher disease

The progressive myoclonus epilepsies (PMEs) comprise a group of rare and heterogeneous disorders defined by the combination of action myoclonus, epileptic seizures, and progressive neurologic deterioration. Neurologic deterioration may include progressive cognitive decline, ataxia, neuropathy, and myopathy. The gene defects for the most common forms of PME (Unverricht–Lundborg disease, Lafora disease, several forms of neuronal ceroid lipofuscinoses, myoclonus epilepsy with ragged-red fibers [MERRF], and type 1 and 2 sialidoses) have been identified. The prognosis of a PME depends on the specific disease. Lafora disease, the neuronal ceroid lipofuscinoses, and the neuropathic form of Gaucher disease have an invariably fatal course. In contrast, Unverricht–Lundborg disease has a much slower progression, and with adequate care many patients have a normal life span. The specific diseases that cause PME are diagnosed by recognition of their age of onset, the associated clinical symptoms, the clinical course, the pattern of inheritance, and by special investigations such as enzyme measurement, skin/muscle biopsy, or gene testing.

Progressive myoclonus epilepsies (PMEs) are neurodegenerative diseases and are among the most disabling forms of epilepsy. They are clinically and genetically heterogeneous, characterized by the core features of action myoclonus, epileptic seizures, and progressive neurologic decline.¹ Typically, the myoclonus shows a focal or segmental distribution, and is characterized by an arrhythmic, asynchronous, and asymmetric occurrence. Generalized tonic-clonic seizures predominate, although there may also be other types of seizures such as absence, tonic, and focal seizures. Most molecularly characterized PMEs are inherited in an autosomal recessive manner, but rare cases show autosomal dominant or mitochondrial inheritance.^{2,3} The diagnosis of specific forms of PME is challenging because of genetic heterogeneity, phenotypic similarities, and an overlap of symptoms with other epileptic and neurodegenerative diseases (▶ **Table 1**). Consequently, a substantial proportion of PME cases still remain without a molecular diagnosis.^{2,3}

Unverricht–Lundborg Disease (EPM1)

Progressive myoclonus epilepsy type 1 (EPM1) of the Unverricht–Lundborg type is an autosomal recessive neurodegenerative disorder that has the highest incidence among the progressive myoclonus epilepsies worldwide.¹ Progressive myoclonus epilepsy type 1 is characterized by stimulus-sensitive myoclonus and tonic-clonic epileptic seizures. As EPM1 progresses, patients develop additional neurologic symptoms including ataxia, dysarthria, intention tremor, and decreased coordination.⁴ Progressive myoclonus epilepsy type 1 is caused by 14 known mutations in the cystatin B (CSTB) gene.^{5–7}

At disease onset (6–16 years), EPM1 patients present primarily with myoclonic and/or generalized tonic-clonic seizures. Most patients show involuntary action-activated or stimulus-sensitive myoclonus (i.e., triggered by light, physical activity, noise, cognitive stimulus, and/or stress).⁴

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Table 1 Diagnostic investigations in different progressive myoclonus epilepsies (PMEs)

1. Unverricht–Lundborg disease (EPM1)	Gene test: EPM1 (<i>CSTB</i>) mutation analysis
2. Lafora body disease (EPM2)	Skin biopsy: Lafora bodies
	Gene tests: EPM2A or EPMP2B(<i>NHLRC1</i>) mutation analysis
3. Neuronal ceroid lipofuscinoses (NCL)	Skin biopsy: Granular osmophilic deposit
	Leukocyte enzyme analyses: PPT1, TPP1, CTSD
	Gene tests: CLN1/ <i>PPT1</i> , CLN2/ <i>TPP1</i> , CLN3, CLN4/ <i>DNAJC5</i> , CLN5, CLN6, CLN7/ <i>MFSO8</i> , CLN8, CLN10/ <i>CTSD</i> , CLN11/ <i>GRN</i> , CLN12/ <i>ATP13A2</i> , CLN13/ <i>CTSF</i> , CLN14/ <i>KCTD7</i> mutation analysis
4. Sialidosis	Urine: Sialo-oligosaccharides
	Leukocyte enzyme analysis: Neuraminidase
	Gene test: <i>NEU1</i> mutation analysis
5. Myoclonus epilepsy and ragged-red fibers (MERFF)	Plasma lactate and pyruvate
	Muscle biopsy: Ragged-red fibers
	Gene test: MT-TK mutation analysis
6. Type 3 neuronopathic Gaucher disease	Leukocyte enzyme analysis (β -glucocerebrosidase)
	Gene test: GBA mutation analysis
7. Dentatorubral-pallidolusian atrophy	Gene test: <i>DRPLA</i> mutation analysis
8. Action myoclonus-renal failure syndrome (AMRF; EPM4)	Gene test: <i>SCARB2/LIMP2</i> mutation analysis
9. PME-ataxia syndrome (EPM5)	Gene test: <i>PRICKLE1</i> mutation analysis
10. North Sea PME (EPM6)	Gene test: <i>GOSR2</i> mutation analysis

This asynchronized myoclonus occurs primarily in the proximal muscles of the extremities; it may be focal or multifocal, and it may generalize to myoclonic seizures or status myoclonicus.

Approximately one-third of the patients become wheelchair bound due to progressive myoclonus and ataxia. An earlier age at onset for EPM1 and longer disease duration are associated with more severe action myoclonus and also lower performance IQ.⁸ Patients with more severe myoclonus report more marked disability and more difficulties in everyday activities. Patients with EPM1 may experience emotional lability, depression, and a mild intellectual decline over time, but overall their cognitive functions, such as verbal abilities and memory, are less impaired than their motor functions.

The diagnosis should be considered in any previously healthy child who, between the ages of 6 to 16 years, presents with at least one of the following four symptoms: (1) involuntary, stimulus, and/or action-activated myoclonic jerks; (2) generalized tonic-clonic seizures; (3) mild neurologic signs in motor function or coordination; (4) photosensitivity, with generalized spike-and-wave and polyspike-and-wave paroxysms, and background slowing on the electroencephalogram (EEG), with concurrent deterioration of neurologic symptoms, such as myoclonus and ataxia.⁴ The clinical examination should include funduscopy, and an evaluation of walking, coordination, handwriting, school performance, and emotional state. An examination of the myoclonus should entail an evaluation of the myoclonus at rest, with action, and in response to stimuli including light, noise, and/or stress.⁴

At disease onset, brain magnetic resonance imaging (MRI) is typically normal. However, voxel-based morphometry may show cortical and thalamic atrophy and thinned cortical thickness in the sensorimotor areas.^{9,10} Abnormalities in the EEG (background slowing, spike-wave discharges, polyspike discharges during REM sleep and photosensitivity) are more pronounced at initial diagnosis, when disease onset may be accompanied by generalized tonic-clonic seizures. Some patients at presentation have focal epileptiform discharges, primarily in the occipital region. In general, EEG abnormalities diminish as the disease stabilizes.⁴ Navigated transcranial magnetic stimulation also shows significant neurophysiological changes in cortical excitability.¹¹

The clinical diagnosis should be complemented with genetic testing, which is commercially available. The gene responsible for Unverricht–Lundborg disease was initially mapped to the long arm of chromosome 21, band q22.3. The *CSTB* gene is approximately 2.5 kb in length and contains three small exons. The most common mutation (~90%) consists of the expansion of a dodecamer repeat in the promoter region of the *CSTB* gene. The general consensus has been that Finnish patients display a more severe clinical phenotype than patients from the Mediterranean region.¹² Earlier it was reported that although the expanded alleles in Finnish patients were longer, the actual length did not correlate with the clinical disease severity or with the age of the EPM1 onset.¹³ Recently, with more detailed phenotyping of the patients, it has been shown that the actual size of the longer *CSTB* expansion mutation allele is likely to have a modulating effect on the age at disease onset, myoclonus severity, and cortical

neurophysiology.⁸ Only a minority of EPM1 alleles (~14%) harbor mutations within the transcriptional unit of CSTB. Most of the compound heterozygous EPM1 patients exhibit a more severe phenotype.^{6,14} Cystatin B is a small, 98 amino acid protein and a member of a superfamily of cysteine proteinase inhibitors. It is found in all tissues examined so far and is thought to protect against inappropriate intracellular degradation by proteinases that leak from lysosomes.

The disease course is inevitably progressive; however, with improved prognosis through better targeting of antiepileptic drugs and with more accurate molecular genetic diagnostics, it has become evident that the phenotype of EPM1 is more heterogeneous than previously assumed. The rate of deterioration especially in terms of walking capacity seems to vary even within members of the same affected family. Only a proportion of patients become wheelchair bound and some have significant daily and weekly fluctuations for years or decades before losing their ability to walk. A considerable number of cases seem to have myoclonus that is so mild that the diagnosis is markedly delayed or the condition is misdiagnosed as focal epilepsy or juvenile myoclonic epilepsy. There is also anecdotal evidence of rare forms of EPM1 without the full symptomatology— patients with late-onset myoclonia without epileptic seizures or patients with so-called progressive myoclonic ataxia without epileptic seizures who may have EPM1. The relative intensity of the various symptoms can also vary between individuals even within the same family. Generalized tonic-clonic seizures are usually controlled with treatment, even if the myoclonic jerks may become severe enough to inhibit routine activity.¹² In the past, life expectancy was shortened; many individuals died between 8 and 15 years after the onset of disease, usually before the age of 30 years. With better pharmacological, rehabilitative, and psychosocial supportive treatment, life expectancy is much higher, approaching normal. The oldest genetically verified EPM1 patients in Finland have lived into their 70s with modern medical care.⁴

Lafora Disease (EPM2)

Lafora disease is an autosomal recessive PME with an adolescent onset. Most patients with Lafora disease have mutations of the EPM2A gene encoding laforin or *NHLRC1*/EPM2B encoding malin.¹⁵ Lafora disease is clinically characterized by medication-refractory generalized tonic-clonic or visual seizures and spontaneous and stimulus-sensitive myoclonus; this is followed by rapidly progressive dementia with apraxia and visual loss. Patients finally become wholly incapacitated and usually die within a decade of symptom onset.

The EEG becomes disorganized early in the disease course and is characterized by a slow background with superimposed generalized high-voltage spike-wave and polyspike-wave complexes.¹⁶ Multifocal, predominantly posterior, epileptiform discharges appear in addition to the generalized bursts. In the final stages of the illness, the EEG is highly disorganized and the epileptiform discharges are almost continuous. Because of similarities at onset, patients may initially be diagnosed with juvenile myoclonic epilepsy. The

presence of a slow background rhythm, drug-resistant seizures and neurologic deterioration in a patient diagnosed with juvenile myoclonic epilepsy or absence epilepsy should raise suspicion and lead to more investigation.

The diagnosis of Lafora disease is established by the presence of the characteristic periodic acid-Schiff- (PAS-) positive cytoplasmic inclusion Lafora bodies.¹⁵ Lafora bodies contain branched polysaccharides (polyglucosans) and have been identified in multiple tissues, including brain, spinal cord, liver, skin, skeletal muscle, heart, and retina. Because Lafora bodies can be seen in the myoepithelial cells of the secretory acini of the apocrine sweat glands and in the eccrine and apocrine sweat duct cells, an axillary skin biopsy is often diagnostic. Recent studies have shown that Lafora bodies are pathogenic. Preventing their formation in Lafora disease mice completely prevents the disease, including both neurodegeneration and the progressive myoclonus epilepsy.¹⁷

Traditional exclusion criteria for Lafora disease included an age at onset before 6 or after age 20 years, evolution over more than one decade, and the absence of cognitive decline. Several authors have since reported Lafora disease patients with a slowly progressive course.^{18,19} In a recent Italian series, patients who maintained >10 years gait autonomy were labeled as “mild” and were compared with the remaining Lafora disease patients with a typical course.²⁰ Mild Lafora disease patients had *NHLRC1* mutations and most carried the homozygous or compound heterozygous p.D146N missense mutation. This mutation was found in none of the patients with typical Lafora disease. The occurrence of specific *NHLRC1* mutations in patients with mild Lafora disease should be taken into account in clinical practice for appropriate management and counseling. The D146N missense mutation lies in the first *NHLRC1* domain and is known to affect ubiquitination of glycogen synthesis activator protein PTG and interaction with laforin.²¹ Because of clinically atypical features, some patients with mild Lafora disease could escape a correct diagnosis because adult patients with mild PME traditionally have not undergone diagnostic workup for Lafora disease.

There have been recent descriptions of early-onset Lafora disease presenting at 5 years of age with dysarthria, myoclonus, and ataxia.²² The combination of early-symptom onset and early dysarthria strongly suggests late infantile-variant neuronal ceroid lipofuscinosis on clinical grounds, rather than Lafora disease. The pathology, however, shows Lafora bodies instead of ceroid lipofuscinosis. The subsequent course is a typical PME, though much more protracted than any infantile neuronal ceroid lipofuscinosis, or Lafora disease, with patients living into their fourth decade. The mutation, c.781T > C (F261L), is in a gene of unknown function, *PRDM8*. The *PRDM8* protein interacts with laforin and malin and causes translocation of the two proteins to the nucleus.

Neuronal Ceroid Lipofuscinoses

Neuronal ceroid lipofuscinoses are the most common group of neurodegenerative disorders associated with lysosomal storage.²³ In the pregenetic era, they were divided into infantile, juvenile, and adult based on the following features:

age of onset, the order of presentation of the main symptoms (myoclonus and seizures, cognitive and motor decline, and retinal pathology and visual loss), and electron microscopic features.²⁴ The length of survival is related to the specific type, but they all lead to early death. Some patients cannot easily be categorized because of significant variation in the age of onset and severity of the disease progression. Molecular genetics has emerged as a useful tool for enhancing subtype classification of neuronal ceroid lipofuscinoses.²⁵ There are 14 genetic forms (CLN1 to CLN14) described to date and 360 etiological mutations, most of which have been included in the neuronal ceroid lipofuscinoses mutation database²⁶ (www.ucl.ac.uk/ncl/mutation).

Although the neuronal ceroid lipofuscinoses are considered in the differential diagnosis of PMEs, myoclonic seizures may be infrequent during their disease course of some forms. This highlights the neuronal ceroid lipofuscinoses as comprising genetically distinct disorders with differing natural history.²⁷ However, in the late phases of progressive neurodegeneration and brain atrophy, most patients experience some form of myoclonus, tremor, or involuntary movements.²⁸

Sialidosis

Sialidosis is an autosomal recessive lysosomal storage disease caused by the genetic deficiency of the enzyme α -N-acetylneuraminidase-1 (coded by the *NEU1* gene on chromosome 6p21)²⁹ and are classified on the basis of their phenotype and onset age.³⁰ Patients with the late and milder type 1, which is known as “cherry-red spot myoclonus syndrome,” typically develop myoclonic epilepsy, visual impairment, and ataxia in the second or third decade of life. The infantile sialidosis (type 2) is characterized by dysmorphic features and cognitive delay, followed by myoclonus starting during the second decade of life. Action myoclonus leads to severe disability in both types of sialidosis.³¹

The macular cherry-red spot is a typical finding. The clinical diagnosis is usually supported by increased urine-bound sialic acid excretion and confirmed by genetic analysis or the demonstration of neuraminidase enzyme deficiency in cultured fibroblasts.³⁰ Sialidosis and a *NEU1* gene defect has been recently shown also in patients with milder isolated action myoclonus presenting in adulthood in the absence of other typical clinical and laboratory findings, such as macular abnormalities and increased urine-bound sialic acid levels.³²

Myoclonus Epilepsy and Ragged-Red Fibers (MERRF)

Myoclonus epilepsy and ragged-red fibers (MERRF) is a mitochondrial syndrome classically characterized by myoclonus, generalized seizures, and ataxia, with variable onset and associated with various mtDNA point mutations, mainly the 8344A > G change in the mitochondrial tRNA(L)(ys) gene (MT-TK).³³ Recently, using a genotype-based approach, it was reported that the great majority of 8344A > G patients (80%) did not show a full-blown MERRF clinical picture.³⁴ In adult

subjects with the 8344A > G mutation, myoclonus was linked to ataxia more than to generalized epilepsy; therefore, the MERRF syndrome resulting from the 8344A > G mutation could be better defined as a myoclonic ataxia rather than a myoclonic epilepsy. On the other hand, *POLG* mutations may be a rather common cause of mitochondrial myoclonus.³⁵ Therefore, myoclonus is not strictly linked to MERRF syndrome, having been detected in other typical mitochondrial encephalopathies, such as MELAS and Alpers syndromes.

Type 3 Neuronopathic Gaucher Disease

Gaucher disease, a lysosomal storage disorder, results from inherited deficiency of lysosomal glucocerebrosidase due to homozygous mutations.³⁶ The result is widespread accumulation of macrophages engorged with predominantly lysosomal glucocerebroside. In type 1 Gaucher disease, a complex multisystem phenotype arises involving the liver, spleen, bone marrow, and occasionally the lungs; in neuronopathic type 2 and chronic type 3 disease there is also progressive neurodegenerative disease.³⁶ Type 3 patients especially can also present with myoclonus and PME.³⁷ Recombinant human acid β -glucosidase GBA (rhGBA) infusion is an effective therapy for type 1 Gaucher disease, but its effect on type 3 Gaucher disease is still controversial.³⁸

Dentatorubral-Pallidolusian Atrophy

Dentatorubral-pallidolusian atrophy (DRPLA) is a progressive disorder of ataxia, choreoathetosis, and dementia.³⁹ The clinical presentation varies depending on the age of onset. The myoclonus epilepsy form is characterized by onset of myoclonus, epilepsy, cognitive decline, ataxia, and choreoathetosis in the first two decades of life.³⁹ The EEG background is usually normal, sometimes with atypical spike-wave discharges and photosensitivity. At postmortem, the major neuropathologic changes consist of combined degeneration of the dentatorubral and pallidolusian systems.

Dentatorubral-pallidolusian atrophy, as opposed to other PMEs, is an autosomal dominant disorder caused by an unstable expansion of CAG repeats in exon 5 of the DRPLA gene on chromosome 12 coding for polyglutamine tracts. The repeat size varies from 7 to 23 in normal individuals and shows an expansion of 49 to 75 in DRPLA patients. The repeat size correlates inversely with age of onset of symptoms and with disease severity. Patients with an earlier onset tend to have the progressive myoclonus epilepsy phenotype and larger expansions.⁴⁰

The Action Myoclonus-Renal Failure Syndrome

The myoclonus-renal failure syndrome (EPM4) has been identified to be caused by pathogenic variants in *SCARB2*.⁴¹ It typically presents at ages 15 to 25 years either with neurologic symptoms (including tremor, action myoclonus, infrequent generalized seizures, and ataxia) or with proteinuria that progresses to renal failure.⁴² Despite severe

neurologic disability due mainly to action myoclonus, cognition is preserved in patients who survived as long as 14 years after renal transplantation.

Progressive Myoclonus Epilepsy-Ataxia Syndrome (EPM5)

Progressive myoclonus epilepsy-ataxia syndrome (EPM5) has been reported in association with a homozygous missense mutation in *PRICKLE1*.⁴³ Children present with ataxia at 4 to 5 years of age, and later develop a progressive myoclonus epilepsy phenotype with mild or absent cognitive decline.

North Sea Progressive Myoclonus Epilepsy

The condition bears the clinical and electrophysiological hallmarks of a progressive myoclonus epilepsy due to a homozygous p.G144W mutation in *GOSR2*, termed “North Sea” progressive myoclonus epilepsy (EPM6) due to the proximity of the patient families to the shores of the North Sea.⁴⁴ The disorder appears to have arisen as a founder mutation in Northern Europe. In addition to the PME phenotype predominantly myoclonus and epileptic seizures, there is also early-onset ataxia (average 2 years of age), areflexia, and elevated serum creatine kinase. Independent ambulation is lost in the second decade, and affected individuals develop scoliosis by adolescence. Their cognition is not usually affected.

Myoclonus Epilepsy and Ataxia Due to Pathogenic Variants in the Potassium Channel

The disorder myoclonus epilepsy and ataxia due to pathogenic variants in the potassium channel (MEAK), caused by a recurrent de novo missense mutation in *KCNK1*, resembles at disease onset EPM1.³ MEAK presents at the ages of 6 to 15 years with myoclonus. The later disease course is characterized by moderate-to-severe incapacitating myoclonus, infrequent tonic-clonic seizures, ataxia, and mild, if any, cognitive decline. The clinical course for MEAK is generally more severe than for EPM1. Identification of this mutation highlights the usefulness of exome sequencing as a diagnostic tool in affected PME individuals previously subjected to negative molecular analyses³ because it identified a dominantly inherited recurrent de novo mutation in contrast to the recessive inheritance model of most PMEs.

Treatment

Progressive myoclonus epilepsies are severe, usually fatal or very disabling diseases. Most patients are healthy before the onset of the progressive disease and their brains are intact. Today, we can diagnose many of the PMEs exactly but have incomplete understanding of the gene defects; we also know that these gene defects do not always explain the full pathogenesis of various PMEs and do not facilitate curative treatments. However, this should be the goal of the research.

Patients need lifelong clinical follow-up and psychosocial support, including evaluation of the drug treatment and comprehensive rehabilitation. Meanwhile, symptomatic pharmacological and rehabilitative management are the mainstay of patient care. The antiepileptic and antimyoclonic drug, valproate, is the drug of choice.^{4,45–47} Clonazepam, the only drug approved by the Food and Drug Administration (FDA) for the treatment of myoclonic seizures, is used as add-on therapy.^{4,45–47} High-dose piracetam has been formally studied and appears useful in the treatment of myoclonus only.^{47,48} Levetiracetam seems to be effective for both myoclonus and generalized seizures.^{49,50} Topiramate and zonisamide may be also used as add-on treatment.^{51–53}

In mitochondrial diseases, however, valproate as well as other antiepileptic drugs that may interfere with the mitochondrial function (zonisamide and topiramate), should be avoided, valproate especially due to increased risk of serious liver damage.^{54,55} In all PME patients, phenytoin should be avoided because it has an aggravating effect on the neurologic symptoms and on the cerebellar degeneration.⁵⁶ This is also true for fosphenytoin in the acute setting. Sodium channel blockers (carbamazepine, lamotrigine, oxcarbazepine, phenytoin) and GABAergic drugs (tiagabine, vigabatrin) as well as gabapentin and pregabalin should in general be avoided, as they may aggravate myoclonus and myoclonic seizures.⁵⁷

In situations where myoclonic jerks are exacerbated into series or into status myoclonicus, patients should avoid all loud noises and bright lights; the patient should be treated in a quiet room as peacefully as possible. Emergency treatment includes intravenous benzodiazepines (diazepam, lorazepam, clonazepam, midazolam), valproate, and levetiracetam. General anesthesia is rarely needed.

Brivaracetam, a SV2A ligand that differs from levetiracetam by its mechanism of action profile, has significant antiepileptic activity in experimental models of epilepsy and myoclonus.^{58,59} It has been granted orphan drug designation by the FDA for the treatment of symptomatic myoclonus, and by the EMA (European Agency for the Evaluation of Medicinal Products; European Union) for treating progressive myoclonic epilepsies. Brivaracetam is being investigated as an add-on treatment for EPM1 in adults. Vagus nerve stimulator therapy may reduce generalized seizures, but the outcome for myoclonic jerks and cerebellar function was more variable.⁶⁰

Conclusion

The diagnosis of the specific form of PME is challenging, but this should be the goal. After diagnosis, genetic counseling provides information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members. There are also support groups for individuals and families, providing information, support, and contact with other affected people. Appropriate and adequate pharmacological treatment of the symptoms, rehabilitation, and social as well as psychological support are of utmost importance. Patients with PMEs have to cope with a lifelong disease and its consequences.

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