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Progressive myoclonic epilepsies—English Version

Current state of knowledge

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Abstract

Progressive myoclonic epilepsies (PMEs) are a heterogeneous group of diseases leading to increasingly severe and usually therapy-refractory myoclonic and other epileptic seizures in initially normally developed children and adolescents and, exceptionally, in adults. Additional as well progressive symptoms consist of ataxia and cognitive impairment up to dementia. The 12 forms that have been genetically differentiated to date are briefly reviewed, and disorders and genes that are further associated with PMEs are named. Therapeutic aspects are briefly mentioned.

Keywords
Epilepsy syndromes · Genetics · Lafora disease · Progressive myoclonic epilepsies · Unverricht-Lundborg syndrome

"Progressive myoclonic epilepsy" (PME) is a term that was first proposed in 1903 by the Swedish neurologist, psychiatrist, and racial biologist Herman Lundborg [1, 2] for what has now become a heterogeneous group of epilepsy syndromes characterized by progressive myoclonic as well as bilateral (generalized) tonic–clonic and other seizures, ataxia, and mostly cognitive decline through to dementia. Although for many years only the Unverricht–Lundborg form and Lafora disease were distinguished from each another, 12 different forms are now known. These will be briefly presented here, not least since PMEs often receive little attention in adult neurology.

1. *Epilepsy, progressive myoclonic 1A* (EPM1A; OMIM #254800 [3]):
   This classical form was first described by the German internist and neurologist Heinrich Unverricht and the aforementioned Herman Lundborg in 1891 [4] and 1901 [5], again in 1903 [2]:
   - Epidemiology: rare; worldwide occurrence, predominantly in Finland (1:20,000) and Mediterranean countries.
   - Etiology: mutation in the *CSTB* gene [6].
   - Onset: around the age of 10 (6–13) years.
   - Seizures: onset usually with bilateral tonic–clonic seizures; usually 1.5 years later asymmetric and proximally emphasized myoclonia, occasionally, absence or focal seizures as well.
   - Clinical–neurological aspects: initially within the normal range, over time increasing ataxia, dysarthria, and tremor as well as cognitive decline (through to dementia).
   - EEG: baseline activity already slowed in the preclinical phase, generalized high-amplitude spike-wave and polyspike-wave activity, and usually photosensitivity.
   - Imaging: atrophy of pons (base), medulla, and cerebellum as well as mild generalized brain atrophy [7], in addition frequently hyperostosis frontalis [8].
   - Neuropsychology: disorders of abstract thinking, attention, planning, word fluency, constructive practice, visuospatial memory, and learning [9].
   - Other diagnostic investigations (formerly): skin biopsy with examination

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of sweat glands for typical vacuoles [10].
- Treatment: antianxiety medications, usually combination therapy; valproate or valproic acid, levetiracetam [11], and perampanel [12], avoiding phenytoin due to unfavorable effect on ataxias. Case reports have described a favorable effect for *N*-acetylcysteine [13].
- Disease course: after initial increase especially of myoclonia (maximum around 3–7 years), subsequent stabilization and sometimes even decline; meanwhile, patients often reach the age of 60 years.
- Other, former names: Baltic myoclonus, Mediterranean myoclonus, Ramsay–Hunt syndrome, Unverricht–Lundborg disease.

2. *Epilepsy, progressive myoclonic 1B* (EPM1B; OMIM #612437 [14]):
This variant has first been described in 2005 by the Australian neurologist and epileptologist Samuel ("Sam") Berkovic [15] with causative mutations in the *PRICKLE1* gene [16]. The clinical picture in an Arab family was compatible with that of EPM1A, but no mutations of the *CSTB* gene were detectable. Onset with myoclonic or bilateral tonic–clonic seizures at an average age of 7.5 years, with an increase in myoclonia during the course and additional ataxia in all. Some patients became wheelchair-bound, while others were able to walk unassisted. A cognitive impairment was not described.
3. *Epilepsy, progressive myoclonic 2* (EPM2; OMIM #254780 [17]):
This form has first been described in 1911 by the Spanish neuropathologist Gonzalo Rodriguez Lafora [18]:
   - Epidemiology: less common than progressive myoclonic epilepsy 1A.
   - Etiology: causative mutations in the *EPM2A* genes (former name: laforin [19]; approximately 70% of cases); *NHLRC1* (former name: malin [20]; approximately 25% of cases); other genes are probably involved [21]; an animal model has been developed [22].
   - Pathogenesis: Polysaccharide metabolic disorder with deposition of "Lafora" or "inclusion bodies" consisting of polyglucosans in brain, liver, and sweat gland cells (detectable on biopsy in skin and muscle [23]).
   - Clinical presentation: two subtypes have been described [24]:
     a. *Lafora disease, classic:* onset in childhood and adolescence (6–19 years, peaking around 15 years) with stimulus-induced bilateral (generalized) tonic–clonic, absence, and myoclonic seizures (perioral myoclonus usually absent!), occasionally also focal (occipital) seizures with visual hallucinations (especially in patients with *EPM2A* mutations) or status epilepticus, followed by dementia-related decline and neurological deterioration including resting and action myoclonus.
     b. *Lafora disease, atypical:* onset in childhood with dyslexia and learning disability, followed by epilepsy and neurological deterioration
   - EEG: baseline activity already slowed in the preclinical phase, increasingly frequent paroxysmal irregular spike-wave activity, often also photosensitivity (EEG changes may be useful to distinguish heterozygous trait carriers from healthy homozygotes [25]).
   - Other neurophysiological aspects: increased SEP and VEP amplitudes especially at onset, later also delayed SEP and AEP latencies; early on, also pathological electroretinogram.
   - Imaging: MRI initially unremarkable, atrophy in the further course [26]; spectroscopically significant reduction in NAA/creatine ratios in numerous regions [27] as well as disturbed glucose metabolism in PET [28].
   - Treatment: initially, valproate or valproic acid is advised; of the new antiseizure drugs, levetiracetam [25] and perampanel [29] are promising; in light of animal experiments, treatment with metformin has also been attempted, but so far without convincing results [30].
   - Disease course: increase in myoclonia and ataxia, dysarthria, and rapidly progressive dementia; usual survival < 10 years.

Other name: Lafora (body) disease.

4. *Epilepsy, progressive myoclonic 3 with or without intracellular inclusions* (EPM3; OMIM #611726 [31]):
This form has first been described in 2007 by the Belgian neurologist, neuropediatrician, and epileptologist Patrick Van Bogaert [32] with causative mutations in the *KCTD7* gene [33]. Clinically in three members of a consanguineous Moroccan family after initially normal development, onset of epileptic seizures between 16 and 24 months of age; these were multifocal myoclonias aggravated by movement and bilateral (generalized) tonic–clonic seizures; all three patients had dementia. The eight patients in a later publication also presented with myoclonic and other epileptic seizures and ataxia; the mean age of onset was 19 months, and within 2 years there was progressive loss of intellectual and motor abilities [34]. Former name: Ceroid lipofuscinosis, neuronal, 14.
5. *Epilepsy, progressive myoclonic 4 with or without renal failure* (EPM4; OMIM #254900 [35]):
This form was first described by the Canadian neurologist and epileptologist Frederick ("Fred") Andermann together with his wife Eva and others in 1981 [36], and then more extensively in 1986 [37]. Causative mutations in the *SCARB* gene [38]. Clinical onset in the second or third decade of life involving progressive renal failure associated with tremor, cerebellar signs, and rare bilateral tonic–clonic seizures [39]. Other former names: action myoclonic (progressive) renal failure syndrome, Andermann syndrome II, myoclonus nephropathy syndrome.
Epilepsy, progressive myoclonic 5 (EPM5: reclassified as Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO; OMIM #607459 [40]). Causative mutations in the *POLG* gene.

6. *Epilepsy, progressive myoclonic 6* (EPM6; OMIM #614018 [41]):
This form was first described in 2011 by the research group of the Australian neurologist and epileptologist Samuel ("Sam") Berkovic in patients with descent from the North Sea countries [42]. Causative mutations in the *GOSR2* gene [43]. Clinical onset of ataxia at an average age of 2 years, followed by myoclonic seizures at an average age of 6.5 years, as well as multiple other seizure types including bilateral tonic–clonic, absence, and drop seizures as they progress. Scoliosis always develops in adolescence, sometimes also additional skeletal deformities (pes cavus and syndactyly). In addition, serum creatine kinase levels are always elevated (median over 700 IU) accompanied by normal muscle biopsies. EEG demonstrates pronounced generalized spike-and-wave discharges with posterior dominance and photosensitivity, frequently also focal abnormalities. In the further course at 13 years of age on average, wheelchair requirement, as well as frequent deaths as early on as in the third or early fourth decade [44]. Former name: North Sea progressive myoclonus epilepsy (NPME).
7. *Epilepsy, progressive myoclonic 7* (EPM7; OMIM #616187 [45]):
This form has been first described in 2015 [46] with causative mutations in the *KCNC1* gene [46]. Clinically similar to EPM1A with initially normal development, onset of myoclonia at around 10 years of age, followed by onset of rare bilateral (generalized) tonic–clonic seizures, only mild cognitive impairment, and EEG evidence of generalized epileptiform discharges. A significant improvement in symptoms with fever is clinically striking. Former name: Myoclonus epilepsy and ataxia due to a potassium channel mutation (MEAK).
8. *Epilepsy, progressive myoclonic 8* (EPM8; OMIM #616230 [47]):
This form was first described in 2009 by the Italian neurologist and epileptologist Edoardo Ferlazzo [48] with causative mutations in the *CERS1* gene [49]. Onset in a family of Algerian origin between the ages of 6 and 16 years, unusually severe course with myoclonia, bilateral tonic–clonic seizures, and moderate to severe cognitive impairment.
9. *Epilepsy, progressive myoclonic 9* (EPM9; OMIM #616540 [50]):
This form has been first described in 2015 [51] with causative mutations in the *LMNB2* gene [51]. Clinical presentation in two siblings of an Arab-Palestinian family after normal development up to the age of 6–7 years, myoclonic seizures with falls; in the further course, deterioration of walking until wheelchair use and additional occurrence of tonic–clonic seizures. In addition, action myoclonus affecting the limbs and bulbar muscles, no impairment of cognitive function despite worsening epilepsy. MRI in one patient showed complete agenesis of the corpus callosum, ventricular enlargement, as well as a left interhemispheric cyst and simplified frontal gyration.
10. *Epilepsy, progressive myoclonic 10* (EPM10; OMIM #616640 [52]):
This form was first described in 2012 in three patients from an Arab-Palestinian family [53] with causative mutations in the *PRDM8* gene [53]. Clinically, in two of these patients, early-onset disease at 5–7 years of age with dysarthria, myoclonia, and ataxia. The combination of early onset and early dysarthria suggests a late infantile variant of neuronal ceroid lipofuscinosis, but pathologically Lafora bodies were found and the further course corresponded to typical PME with increasing gait disturbances, frequent falls, and eventually wheelchair use or even bedriddenness and partial loss of speech. In addition, bilateral tonic–clonic seizures also emerged, as did psychiatric disorders. In the third patient onset occurred in adulthood and no bilateral (generalized) tonic–clonic seizures were observed [54].
11. *Epilepsy, progressive myoclonic 11* (EPM11; OMIM #618876 [55]):
This form has been first described in 2020 in four patients aged 11–28 years [56] with causative mutations in the *SEMA6B* gene [56]. Clinically, childhood developmental milestones were mostly normal until the age of 2 years; onset of epilepsy between 1.5 and around 6 years of age, onset of regression between 2 and 4 years of age. Between the ages of 10 and 14 years, wheelchair requirement is usual, linguistic communication only possible with a few words to two-word sentences, if at all. Frequent microcephaly, epileptic seizures were (bilateral) generalized tonic–clonic, absence, and atonic seizures; in addition, rigidity and/or myoclonia as well as ataxia and intention tremor; mild cerebellar atrophy on MRI [56].
12. *Epilepsy, progressive myoclonic 12* (EPM12; OMIM #619191 [57]):
This form has been first described in 2021 [58] with causative mutations in the *SLC7A6OS* gene [58]. Clinically, in the six patients aged 22–43 years from two unrelated families of Portuguese and Turkish origin, respectively, onset between the ages of 11 and 21 years; four patients with bilateral (generalized) tonic–clonic seizures, the other two with myoclonia. During the further course, all developed myoclonia and all but one bilateral tonic–clonic seizures. Additional features were cerebellar ataxia, often with dysarthria or dysmetria, and a decline in independent walking, with wheelchair use in four patients aged 17–30 years. Three patients had mild cognitive impairment manifesting mainly as attention deficit disorder, and several had comorbid psychiatric disorders including depression, anxiety, attention deficit disorder, and addictive disorders. On EEG, generalized polyspike-, polyspike-wave, and sometimes spike-wave discharges; on brain imaging, one of the two families had progressive cerebellar and cerebral atrophy [58].
13. Other diseases that may present with the clinical picture of PME:

A number of other diseases may present as PME, such as:

- Dentatorubral-pallidoluysian atrophy (DRPLA [59])
- Familial encephalopathy with neuroserpin inclusion bodies (FENEK [60])
- Gaucher disease type 3 [61]
- Gerstmann–Sträussler disease/ Gerstmann–Sträussler–Scheinker disease [62]
- Lipodystrophy, congenital generalized, type 2 [63]
- Kufs disease or neuronal ceroid lipofuscinosis 4 [64]
- Leigh syndrome [65]
- MELAS syndrome (acronym for myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; due to *MTDN6* mutations [66])
- Menkes disease [67]
- MERRF syndrome (acronym for myoclonic epilepsy with ragged red fibers; [68])
- Mucolipidoses [69]
- Sialidosis type I or neuraminidase I [70]
- Spinal muscular atrophy with progressive myoclonic epilepsy [71]
- SREAT (Hashimoto's encephalopathy [72])
- Ceroid lipofuscinoses, neuronal [73]

In addition, numerous other causative genes have been described in patients presenting with PME: *AFG3L2* [74], *ALG10* [75], *ASAH1* [75], *ATP6V0A1* [76], *CACNA1A* [75], *CACNA2D2* [74, 75], *CAMTA1* [75], *CHD2* [75], *CLN6* [74, 75, 77], *DHDDS* [74, 78, 79], *DYNC1H1* [75], *GBA* [75], *NEU1* [74, 75], *NUS1* [75], *PEX19* [75], *RARS2* [75], *SACS* [74, 80], and *STUB1* [74].

Therapeutic options include antianxiety medications and, in individual cases, the ketogenic diet [81] or modified Atkins diet [82]; the neurostimulation methods of vagus nerve stimulation [83] and deep brain stimulation [84] are also used.

Practical conclusion

- **Progressive myoclonic epilepsies are clinically characterized by myoclonia and other epileptic seizures, usually in association with ataxia and cognitive decline that are also progressive.**
- **Some of the 12 genetically distinct forms described to date do not begin until later adolescence or adulthood.**
- **From a diagnostic perspective, genetic testing is the method of choice; neurophysiological findings can substantiate the suspected diagnosis.**
- **Differentiation of the various forms is also of prognostic and therapeutic relevance.**
- **Medication usually requires combination therapy, and positive experiences with diets and neurostimulation procedures have also been reported.**

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Declarations

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No studies on humans or animals were conducted by the author for this article. For the studies listed, the ethical guidelines stated therein apply in each case.

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