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REVIEW

Progressive myoclonic epilepsies: review of clinical, molecular and therapeutic aspects

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Abstract The progressive myoclonic epilepsies (PME) are a rare group of inherited neurodegenerative diseases with debilitating evolution, resistance to treatment and poor prognosis. However, advances in molecular genetics have enabled *better* understanding of the pathogenesis of these diseases, bringing hope for improved treatment options in the future. This manuscript is an overview of the clinical and molecular findings in patients with PME. Furthermore, it describes therapeutic approaches that are currently recommended in the literature.

Keywords Epilepsy · Myoclonus · Lafora · Unverricht · NCL · MERRF

Introduction

The progressive myoclonic epilepsies (PME) are an unusual and heterogeneous group of epilepsies with debilitating progression, resistance to conventional treatment and poor prognosis. It is estimated that these diseases are responsible for up to 1% of epileptic syndromes in children and adolescents around the world [1, 2].

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The diagnosis of PME, like all epileptic syndromes, is done through analysis of electroencephalographic and clinical findings. In the early stages of the PME, such data can mimic the features of other epileptic syndromes, such as idiopathic generalized epilepsies or juvenile myoclonic epilepsies, but the therapeutic failure and the progressive worsening of the neurological signs and electroencephalography (EEG) data points in the direction of PME.

Likewise, the clinical features of patients with idiopathic generalized epilepsy may strongly suggest PME if they are inappropriately treated and intoxicated with antiepileptic drugs, presenting cognitive changes and ataxia.

Despite its broad spectrum of manifestations, PME share some clinical findings, such as myoclonus, multiple types of seizures, delay or regression of psychomotor development (especially cognitive) and cerebellar signs. However, the age of onset, first symptoms and presence of seizures, myoclonus, cerebellar signs and dementia, vary widely according to its etiology.

Progressive myoclonic epilepsies usually begin in childhood and adolescence, and its evolution is variable, with some forms of slow progression and others with refractory seizures and death within a few years.

Myoclonus, which are typical findings of the syndrome, presents variable morphology in different patients or even in the same patient at different moments. They may be focal or segmental, arrhythmic, asynchronous, asymmetric and massive. In PME, they are typically precipitated by posture, action or external stimuli such as light, sound and touch. They are also more apparent on the face and distal extremities. Massive bilateral myoclonus including the proximal muscles of the limbs may also occur [1–3].

There are several types of seizures, most often myoclonic seizures and generalized tonic clonic seizures

prevail, but others like absences, atypical absences, tonic seizures or focal seizures may also occur.

Neurological deterioration is variable depending on the etiology and may lead to disabling manifestations such as dementia, cerebellar ataxia, neuropathy and myopathy.

Beyond these common characteristics and according to underlying disease, other clinical manifestations might be crucial for the etiological diagnosis, such as the existence of partial visual seizures in Lafora disease or the presence of myopathy, neuropathy or deafness, suggesting myoclonic epilepsy with ragged red fibers (MERRF) [1–3] Table 1.

The ophthalmologic evaluation is also essential for these patients, since some signals detected on fundoscopy may suggest a specific diagnosis. As an example, the finding of retinal dystrophy, possibly with retinitis pigmentosa, suggests a mitochondrial disease or neuronal ceroid lipofuscinosis. On the other hand, the finding of a macular cherry-red spot is consistent with a diagnosis of sialidosis [1].

There are six main causes of PME which have different forms of genetic inheritance. The conditions include autosomal recessive Unverricht-Lundborg's disease (EPM1), Lafora disease (EPM2), neuronal ceroid lipofuscinosis and storage diseases such as sialidosis. Dentatorubral-pallidoluysian atrophy (DRPLA) is a disease of trinucleotide repeat, whereas myoclonic epilepsy with ragged red fibers (MERRF) is an example of mitochondrial inheritance disease [1–3].

Unverricht-Lundborg disease

Unverricht-Lundborg disease, also called progressive myoclonic epilepsy type 1 (EPM1), is an autosomal recessive disease described by Unverricht in 1891 and Lundborg in 1903 [4, 5]. Its prevalence is estimated in 1–20,000 live births and mutations in the gene encoding cystatin B (CSTB), a cysteine protease inhibitor, are responsible for the EPM1 defects [1, 3, 6–8].

Clinical and electroencephalographic aspects

The age of onset of EPM1 symptoms varies between 6 and 15 years and the severity of progression is variable. Patients have no neurologic deficit at first and gradually evolve with progressive ataxia, intention tremor, dysarthria and mild dementia. However, the manifestations tend to stabilize after the age of 40 [2, 6, 9].

Myoclonus is the first symptom in most patients, and it might be triggered by sensory stimuli (proprioceptive, auditory and visual). The jerks are usually severe, irregular, asynchronous and predominate in the morning upon awakening, occurring in any segment of the body [1–3, 9]. The tonic clonic seizures are very common and absence seizures have also been observed [2, 9, 10].

The EEG findings are not very specific. The background activity might be normal in the early years, but evolves with generalized slowing associated with epileptiform discharge bursts. Photoparoxysmal responses and photosensitivity reactions are characteristic and, unlike other PME, the sleep electroencephalographic patterns remain normal [2, 10].

The findings on magnetic resonance imaging (MRI) of the brain might be normal or show nonspecific findings such as atrophy of the basal pons, spinal cord, cerebellar hemispheres and, less frequently, diffuse brain atrophy [11].

Molecular aspects

EPM1 is closely related to the chromosome 21q22.3, a region where the gene for cystatin B is located [12]. Human CSTB belongs to family 1 of cystatins, a superfamily of cysteine protease inhibitors known to inhibit several cysteine proteases of the family of papain (cathepsins) in vitro through reversible binding [13].

Cystatin B is widely expressed in different tissues and it is assumed that it generates abnormal apoptosis and neurodegeneration by inhibiting cathepsins in vitro. However, its in vivo function has not yet been established [13, 14].

The main neuropathological finding in mice with a deficiency of CSTB is a significant loss of cerebellar granule cells by apoptosis, with less marked apoptosis in neurons of the hippocampal formation and entorhinal cortex in younger animals of 2–4 months of age. In older mice, gliosis occurs in the hippocampal formation, entorhinal cortex, neocortex, and striatum. There is also diffuse gliosis in the white matter [15, 16].

Ten different mutations in CSTB leading to EPM1 have been described. The main mutation is an expansion of unstable dodecameric repetition (CCCCGCCCCGCG) in the promoter 5′ untranslated region. The extent of normal alleles (repeats) is two to three copies, but expanded alleles associated with the disease phenotype contain at least thirty copies [17].

There are also other mutations that affect one or two nucleotides in CSTB, generating disease in some patients. Affected individuals may have dodecameric expansions in both alleles, expansions in one and point mutations in other or, more rarely, a point mutation in both alleles [18].

An Arab family with a phenotype similar to EPM1 was described, but with clinical signs starting earlier and without mutations in the CSTB gene, called EPM1B. The underlying locus has been described on chromosome 12 implying that there might be a greater genetic heterogeneity behind EPM1 [19].

Table 1 Summary of PME features

Disease	Age at onset (years)	Seizures	Cerebellar signs	Dementia	Fundoscopy	EEG: slowing of background activity	EEG: epileptiform discharges	Inheritance	Diagnosis
ULD	6–15	Myoclonic	Mild/late	Mild/later or absent	Normal	Yes Sleep patterns remain normal	Diffuse epileptiform Discharges	AR	CSTB gene mutation
Lafora's disease	12–17	Myoclonic and occipital	Early	Early/severe	Normal	Yes	Diffuse spike and wave 6–12 Hz	AR	Lafora bodies in skin biopsy or EPM2A mutation
MERRF	Variable	Myoclonic	Variable	Variable	Retinal dystrophy and retinitis pigmentosa, optic atrophy	Yes	Focal discharges and bursts of generalized spike and wave of 2–5 Hz	Maternal	Ragged red fibers in muscle biopsy or MTTK mutation
NCL	Variable	Variable	Variable	Rapidly progression	Macular degeneration, except in Kuf's disease	Yes	Focal and generalized discharges	AR	Typical inclusions or Mutation in TPP1, CLN3 and CLN5
Sialidosis	Variable	Myoclonic	Progressive	Type II: learning disability	Cherry-red spot	Low voltage, beta rhythm	Trains of positive spikes associated with myoclonus	AR (except Kuf's disease—AD)	Neuraminidase deficiency in fibroblasts or leucocytes
DRPLA	–	–	–	–	–	Normal background	Spike and wave photoparoxystic discharges	AD (anticipation)	Abnormal CAG repetition

ULD Unverricht Lundborg disease; *MERRF* myoclonic epilepsy with ragged red fibers; *NCL* neuronal ceroid lipofuscinosis; *DRPLA* dentatorubralpallidoluysian atrophy; *EEG* electroencephalography; *AR* autosomal recessive; *AD* autosomal dominant

Lafora's disease

Lafora's disease (LD) is a recognized cause of PME and has an autosomal recessive pattern of heritance. It is characterized by the presence of epilepsy, myoclonus, dementia and the pathognomonic inclusion bodies (of Lafora), which are PAS (periodic acid Schiff) positive polyglucosans, found within neurons and cells of the heart, skeletal muscle, liver and sebaceous gland ducts [1, 2].

Clinical and eletroencephalographic aspects

The onset of symptoms usually occurs between 12 and 17 years with epileptic seizures that progressively deteriorate to status epilepticus [20]. Among the most common types of seizures found in LD, we highlight myoclonic, occipital with transitory blindness or visual hallucinations, atypical absences, atonic seizures and complex partial seizures [1, 2].

There are no neuropsychomotor development abnormalities before the beginning of seizures. Nevertheless, cognitive decline, dysarthria and ataxia will appear early. Affective and mood disorders are also common in the beginning of the disease and dementia evolves gradually. Most patients die 10 years after the beginning of the symptoms [1, 2, 25].

In an initial phase in LD, EEG shows organized background activity with generalized multiple spike and wave discharges, sometimes triggered by low frequencies in the photic stimulation. Moreover, the background activity and sleep elements suffer progressive deterioration [21].

In longitudinal studies of EEG, the pattern of spike and wave discharges at a frequency of 3 Hz, found in the early stages, increases to 6–12 Hz with disease progression [22].

There was significant neuronal loss in *postmortem* studies. Many regions of the central nervous system are involved, including the cerebral cortex, cerebellum, basal ganglia, thalamus and hippocampus [20].

Regarding diagnosis, the major clinical milestones of LD are the short interval of age at initiation of symptoms, the rapid progression to dementia and death, and the pattern of seizures, frequently of occipital semiology [1, 2, 20].

Lafora bodies are present in neurons but they can also be seen in several other tissues such as skin, liver and muscle. However, conveniently, the diagnosis is made through the analysis of the eccrine ducts of the sebaceous glands in skin biopsies [1, 2, 20].

Molecular aspects

Over 80% of patients with the disease have a mutation in the gene EPM2A on chromosome 6q24. The EPM2A gene encodes a 331 amino acid protein called laforin, which belongs to the family of tyrosine phosphatases [23, 24]. The function of laforin is unknown but it is speculated to have an involvement in the regulation of protein translation and hyperfunction of glycogen synthase, contributing to the deposition of polyglucosans near the endoplasmatic reticle [6, 23].

The EPM2A gene consists of four exons, where more than 20 mutations have been described. However, only three mutations were found in more than two unrelated families and there is no established relation between type of mutation and clinical presentation [1, 23].

Recently, a new locus was mapped to the LD, NHLRC1 (EPM2B) in a region on 6p22. This region encodes several proteins, including kinesin, which plays an important role in axonal and dendritic transport in neurons [25, 26].

Myoclonic epilepsy with ragged red fibers

Mitochondrial diseases and abnormalities of oxidative phosphorylation were recognized in 1962 by Luft, and in 1963 the histological findings characteristic of mitochondrial myopathy were described [27, 28]. Ten years later, Tsairis et al. described the myoclonic epilepsy with ragged red fibers (MERRF), admitted as a distinct entity in 1980 [29, 30]. However, only in 1990 was the description of a point mutation in the gene for tRNA lysine (A8344G) made; it was subsequently found in approximately 80% of patients [31, 32].

Clinical findings

Common clinical manifestations of MERRF include myopathy, neuropathy, deafness, dementia, short stature, and optic atrophy. Less commonly are cardiomyopathy, retinitis pigmentosa, pyramidal signs, ophthalmoparesis, multiple lipomas and diabetes mellitus. Myoclonus and cerebellar ataxia are constant. However, MERRF's syndrome clinical spectrum can vary, showing even intrafamilial variation in age of onset, severity and evolution [33].

EEG shows a slow background activity with bursts of generalized spike and wave frequency of 2–5 Hz. Focal discharges can also be seen [34]. Brain MRI shows atrophy and calcifications in basal ganglia. Signal intensity changes of gray matter in T2-weighted images can also be seen, and deep brain nuclei are more involved than the cerebral cortex [35, 36].

Muscle biopsy shows great proliferation of mitochondria, seen as ragged red fibers through morphological studies with modified Gomori trichrome (interruption of the muscle fibers by the accumulation of mitochondria). Biochemical studies of respiratory chain enzymes in muscle usually show decreased activity [37].

Molecular aspects

Mitochondria have their own DNA (multiple copies per organelle) consisting of 16,569 base pairs arranged in a circular bifilamentar molecule that encodes two ribosomal RNAs, 22 transporter RNAs and 13 polypeptides involved in oxidative phosphorylation. There are also over 90 genes in nuclear DNA that encode polypeptides to be transported to the mitochondria to participate in the processes of oxidative phosphorylation [33].

Mitochondrial DNA (mtDNA) is inherited exclusively through the maternal line; their transcription occurs in the mitochondria themselves and, unlike nuclear DNA, mtDNA contains no introns. Furthermore, since each cell itself has a population of mtDNA molecules, a single cell can contain a few molecules of other mutant and normal mtDNA (heteroplasmy). All these peculiarities explain the great number of mutations and the wide spectrum of manifestations of mitochondrial diseases.

The molecular defect most commonly found in patients with MERRF is a substitution of guanine by adenosine at nucleotide pair 8344 (A8344G) in the gene for tyrosine tRNA (MTTK) of mitochondrial DNA. It is found in more than 80% of patients with MERRF [38].

Another mutation identified that is far less common is a substitution of tyrosine for cytosine (T8356C) in the same gene. The exchange of guanine by adenosine (G8363A) leading to a phenotype of MERRF has also been described [38, 39].

Analysis of mtDNA mutations in muscle and leukocytes are also useful to confirm the diagnosis.

Neuronal ceroid lipofuscinosis

Neuronal ceroid lipofuscinosis (NCL) are a group of neurodegenerative disorders that present accumulation of lipopigments in tissues known as auto-fluorescent ceroid lipofuscin [1–3]. The heritage of all types is autosomal recessive, except for the adult form that is autosomal dominant [1–3, 40].

Clinically, it is characterized by progressive loss of visual acuity up to blindness, refractory epilepsy, motor and cognitive deficits, behavioral disorders and early death. The classification of NCL is based on age of onset, disease progression and pathology analysis of the deposited material.

Electron microscopy analysis of lysosomal storage material demonstrates four types of inclusions: osmiophilic granular deposits (GROD), curvilinear (CV), fingerprint-like (FP) and rectilinear (RL) [1–3].

Magnetic resonance imaging findings are nonspecific and include cerebral and cerebellar atrophy, hyperintense signal on T2-weighted images in the lobar white matter and thinning of the cerebral cortex [40–42]. There are no specific electroencephalographic features, and definitive diagnosis is made through the detection by microscopy of intracellular inclusions, which can be located in eccrine cells and also in the conjunctiva, or muscle biopsy [1, 2, 40].

Eight different genes have been linked to various forms of the disease. However, there are five types of NCL that may cause PME. The classic late infantile NCL (type 2) is the most recognized form, and the other variants described in the literature as possible causes of PME are: juvenile NCL (type 3), adult NCL (type 4), late infantile Finnish variant NCL (type 5) and late infantile variant NCL (type 6).

Neuronal ceroid lipofuscinosis variant forms

Late infantile form determined by CLN2 gene

The late infantile form is the form traditionally considered a PME. The gene (CLN2) is located on chromosome 11p15 and it encodes protein tripeptidyl peptidase 1 (TPP1). Several mutations were identified, but the substrate around the TPP1 is not yet clear [2, 40, 43, 44].

The late infantile form of NCL features symptom onset between 2.5 years and 4 years old. The first manifestations tend to be epileptic seizures, often intractable, followed by dementia, ataxia, spasticity and visual acuity disturbances that appear later. The fundoscopy shows macular degeneration and tapered vessels. Death occurs within 5 years after initiation of symptoms [1–3, 43, 44].

The lysosomal inclusion types are of curvilinear bodies in most cases. The detection of diminished activity of TPP1 in fibroblasts or leukocytes can confirm the diagnosis, with subsequent genetic analysis [2, 43, 44].

Finnish variant late infantile NCL determined by CLN5 gene

A variant form of the late NCL has been found in Finland presenting some peculiar features. The age of onset of symptoms in this form was around 5 years, and included manifestations such as hypotonia. Visual disturbances and ataxia were also detected and had slow progression. Myoclonic seizures and tonic clonic seizures occurred only later, by the age of 8 years old [1, 2, 43, 45, 46].

The associated gene, CLN5, is found almost exclusively in Finland and was mapped on chromosome 13q21–32. It encodes a transmembrane protein of 407 amino acid residues of still unknown function. The most common mutation is a deletion in exon 4 and the inclusion types are of fingerprint and rectilinear complex [1, 2, 43, 45, 46].

Late infantile NCL Egyptian/Indian variant determined by CLN6 gene

A variant of late infantile NCL related to gene CLN6 occurs at 5–7 years with visual loss, and epilepsy and death around the third decade of life. Ultrastructural studies demonstrate various types of inclusion bodies. CLN6 was mapped on chromosome 15q21–23. The encoded protein function is uncertain and there is not a most common mutation in the disease [1, 2, 43, 47].

Juvenile NCL determined by CLN3 gene

Batten disease is the juvenile form of NCL. It begins at 4–10 years, often with decreased visual acuity. Gradually, extrapyramidal signs, dementia, myoclonus and epileptic seizures appear, followed by blindness in the second decade of life. Death occurs approximately 8 years after the beginning of the disease [2, 48–50]. The gene associated with this disease, CLN3, is located on the short arm of chromosome 16, and encodes a protein of 438 amino acid residues, the function of which is unknown [40].

Adult form of NCL determined by CLN4 gene

The classical adult variant (Kuf's disease) is caused by mutations in CLN4, a symbol assigned to an unidentified gene of autosomal recessive and autosomal dominant forms of inheritance. Kuf's disease may have its beginning in adolescence or adulthood with myoclonus, dementia, ataxia and extrapyramidal signs. There are no visual changes or eye abnormalities. Definitive diagnosis is accomplished by ultrastructural studies demonstrating mixed inclusions [1–4, 40].

Sialidosis

Type 1 sialidosis (myoclonic syndrome with cherry red spot) is caused by a deficiency of alpha-neuraminidase, has autosomal recessive inheritance, and its gene, NEU1, is located in the chromosome 6p21.3 [1, 2, 51].

It begins with juvenile or adult action and intention myoclonus, tonic clonic seizures and slowly progressive visual loss with bilateral cherry red spots in the macula at fundoscopy. There are also signs of pyramidal liberation and ataxia. Its evolution is slow, without mental deterioration [51, 52].

EEG shows background activity with low voltage and beta rhythm. Intense myoclonus occurs associated with trains of positive spikes of low amplitude in the vertex. The MRI findings may be of cerebellar atrophy, followed by cerebral and pontine atrophy [1, 2, 51–53].

The histopathological study reveals neuronal lipidosis and vacuolated Kupffer cells. The diagnosis is made by chromatography of urine that shows high levels of sialylated oligosaccharide that should have been hydrolyzed by sialidase [1, 2, 51–54].

Dentatorubral-pallidoluysian atrophy

Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare neurodegenerative autosomal dominant disorder, described initially in Japan where it is most prevalent, but also found in other ethnic groups around the world [1, 2, 55].

DRPLA is caused by an unstable expansion of CAG repeats in the gene 12p13.31. There is anticipation phenomenon and inverse correlation between the expanded CAG repeats and the age at onset [56, 57].

There are three clinical forms described: a choreoatetoid form, a pseudo-Huntington form and a PME form. Patients with onset before 20 years always have the phenotype of PME, characterized by ataxia, seizures, myoclonus and dementia [1, 2, 55].

EEG shows normal background activity and spike and wave photoparoxystic discharges. MRI findings include atrophy of parasagital structures in the cerebellum and brainstem, particularly the pontine tegmentum. The pathological changes consist of degeneration of the rubral and dentato-pallidoluysian systems.

The diagnosis can be confirmed by identification of an abnormal number of repetitions CAG [1, 2, 55].

Treatment

The treatment of PME is strictly supportive and there have been no particular advances recently in this area. Rehabilitation measures will be imposed according to patients' features. Conventional treatment with antiepileptic drugs like carbamazepine, phenytoin and lamotrigine should be avoided, since they can worsen PME's symptoms substantially, either with seizure aggravation, or cognitive deterioration [1, 2].

Valproic acid should be preferred to control the myoclonus. However, this drug causes the inhibition of carnitine uptake and should not be used in the mitochondrial disorders [58–60].

The literature also describes good response to clonazepam, high doses of piracetam and levetiracetam in myoclonus treatment of EPM1 patients [59–61]. By contrast, studies with phenytoin showed that it might significantly worsen myoclonus and trigger cerebellar atrophy [62]. The improvement of the myoclonus in one patient with EPM1 treated with stimulation of the vagus nerve has also been reported [63].

Furthermore, there is some evidence that zonisamide may play an important role in the management of PME, acting in the reduction of the myoclonus and in the control of generalized and myoclonic seizures in patients previously refractory to other antiepileptic drugs [64, 65].

Patients with mitochondrial disorders may be treated empirically with combinations of antioxidant vitamins and cofactors, like coenzyme Q10 and L-carnitine supplementation, with some response [66].

Finally, it is important to say that although there have been no particular advances recently, future treatments with enzyme replacement and gene therapy may help in modifying the quality of life and prognosis for these patients.

Conclusion

Although a rare group of epilepsies, PME are of great interest, mainly because of the diagnostic challenge and degree of disability generated in patients. The evolution of histological and molecular techniques has allowed an increasingly early diagnosis in these patients. However, there have been no particular advances recently in the treatment of this group of disorders.

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