Progressive myoclonic epilepsies: a review of genetic and therapeutic aspects

Amre Shahwan, Michael Farrell, Norman Delanty

The progressive myoclonic epilepsies (PMEs) are a group of symptomatic generalised epilepsies caused by rare disorders, most of which have a genetic component, a debilitating course, and a poor outcome. Challenges with PME arise from difficulty with diagnosis, especially in the early stages of the illness, and further problems of management and drug treatment. Recent advances in molecular genetics have helped achieve better understanding of the different disorders that cause PME. We review the PMEs with emphasis on updated genetics, diagnosis, and therapeutic options.

Progressive myoclonic epilepsies (PMEs) are characterised by myoclonic seizures, tonic-clonic seizures, and progressive neurological deterioration, typically with cerebellar signs and dementia. In different disease entities, various types of seizures and neurological symptoms also occur, which may guide the clinician to the most likely cause. Myoclonus in PME is typically fragmentary and multifocal, and is often precipitated by posture, action, or external stimuli such as light, sound, or touch. It is particularly apparent in musculature of the face and distal extremities. Bilateral massive myoclonic jerks that tend to involve muscles of proximal limbs may also occur. With the disabling myoclonus there is the risk of injury and impairment of activities of daily living. The age of onset, presenting symptoms, predominance of symptoms as seizures, or myoclonus over cerebellar signs and dementia vary substantially across the different disorders. There are five main causes of PME that have been more accurately defined with recent advances in genetic studies (panel 1).

Unverricht-Lundborg disease
Unverricht-Lundborg disease (ULD), or epilepsy progressive myoclonus type 1, is an autosomal-recessive disorder that was described by Unverricht in 1891, and by Lundborg in 1903. It is the most common PME. It was initially recognised as a geographic cluster in Finland, where the prevalence is one in 20 000 births. Clusters of a phenotypically and sometimes genetically identical disorder occur in southern Europe and north Africa, and sporadically worldwide.

Clinical picture and investigations
The age of symptom onset in ULD is 6–15 years. Symptoms progress insidiously. Stimulus-sensitive myoclonic jerks are an essential feature for the diagnosis of the disease and are the first symptom in at least half of patients. The myoclonus is generally quite severe and shares the common characteristics of myoclonus in other PMEs. Generalised tonic-clonic seizures are the presenting feature in many patients, but in rare cases these may not occur. Absence seizures may also be observed. Neurological examination is initially normal, but patients later develop ataxia, incoordination, intention tremor, and dysarthria. Progression to ataxia and mild dementia is typically a late feature. However, this is not constant and progress in the genetic basis of the disorder has led to finding atypical evolutions even within the same family, with some affected individuals displaying severe cognitive involvement. With advances in antiepileptic drug development and their use, the prognosis of the disease has improved significantly and patients now live into their sixties.

The EEG background may be normal during the first years of the disease. EEG features may mimic completely that of idiopathic generalised epilepsy at the beginning of the disease. With progress of the illness, it becomes abnormal with diffuse slow background activity and generalised high-voltage spike and wave, and polyspikes and wave paroxysms, ranging from a slow frequency of 2–3 Hz to faster frequencies of 4–6 Hz, which reach a maximum anteriorly. Photosensitivity is typical. MRI of the brain may be normal or can show reduced bulk of the basis pontis, medulla, and cerebellar hemispheres, and less often, cerebral atrophy.

Genetics and diagnosis
ULD is linked to chromosome 21q22.3. Further linkage disequilibrium and historical recombination breakpoint mapping placed the associated gene, CSTB (formerly CLN5), on chromosome 21q22.

Panel 1: Definite diagnosis of specific types of PME

<table>
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<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Mutation Details</th>
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</thead>
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<tr>
<td>Unverricht-Lundborg disease</td>
<td>CSTB</td>
<td>Gene mutation</td>
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<td>Lafora disease</td>
<td>LAFB</td>
<td>Skin biopsy or EPM2A mutation</td>
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<tr>
<td>Myoclonic epilepsy with ragged red fibres</td>
<td>RAG1</td>
<td>Ragged red fibres in muscle biopsy or MTTK mutation</td>
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<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>CLN3/CLN5/CLN22</td>
<td>Typical intracellular inclusions or mutation in TPP1, CLN3, and CLN5</td>
</tr>
<tr>
<td>Sialidoses</td>
<td>SIA1</td>
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</tr>
<tr>
<td>Dentatorubral-pallidolusian atrophy</td>
<td>DPPA</td>
<td>Abnormal CAG repeats</td>
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known as EPM1), between regions D21S2040 and D21S1259. CSTB encodes cystatin B, a cysteine protease inhibitor. The main mutation in CSTB, even among patients of different ethnic origins, is an unstable expansion of a dodecamer repeat (CCCCGCCCCGCG) in the 5’ untranslated promoter region. The range of normal alleles (repeats) is two to three copies, but expanded alleles associated with the disease phenotype contain at least 30 copies. Five other mutations that affect one or two nucleotides in CSTB cause the disease in a few patients. Affected individuals may have expansion of the dodecamer on both alleles, expansion on one and point mutation on the other, or, rarely, a point mutation on both alleles. Cystatin B inhibits the papain family of cysteine proteases, which are involved in the initiation of apoptosis. The exact pathophysiology of the disease remains unknown. Presumably, with mutations in cystatin B and loss of its inhibition of cysteine proteases, apoptosis proceeds abnormally and neurodegeneration results. A multiprotein complex has been identified to interact with cystatin B in vitro. Immunofluorescent confocal microscopy showed that the same proteins are present in the granule cells of the developing cerebellum and the purkinje cells of adult rat cerebellum, which raises the possibility that a cystatin B multiprotein complex may have a specific cerebellar function. For diagnosis, clinical suspicion is paramount. Detection of the mutation in the cystatin B gene can be used to confirm the diagnosis (panel 1).

Treatment
There is no specific treatment for ULD, and palliative and rehabilitative management is therefore the mainstay of patient care. For seizure and myoclonus control, valproic acid has traditionally been the drug of choice, especially if started early in the course of the disease. Clonazepam may also help as an add-on therapy. High-dose piracetam also helps in many patients. Levetiracetam had a substantial beneficial effect on a female patient with ULD. She was able to walk assisted and write her name, after being wheelchair bound with severe stimulus-evoked and action-induced multifocal myoclonus. The antmyoclonic effect of levetiracetam in 13 patients with ULD was most effective when started early in the course of the disease. Zonisamide has been used with success. Phenytoin may significantly worsen myoclonus and precipitate cerebellar signs and cerebellar atrophy. Myoclonus in a patient treated with vagus-nerve stimulation also improved.

Lafora’s disease
First described by Lafora and Gluelkin in 1911, Lafora’s disease is characterised by epilepsy, myoclonus, dementia, and Lafora bodies, which are periodic-acid–Schiff-positive intracellular polyglucosan inclusion bodies found in neurons, heart, skeletal muscle, liver, and sweat-gland duct cells.

Clinical picture and investigations
In most patients, the onset of progressively worsening seizures occurs age 12–17 years. Before that, physical and mental development is within normal limits. Many patients experience isolated febrile and non-febrile convulsions earlier in childhood. At onset it may be difficult to distinguish Lafora’s disease clinically from typical idiopathic generalised epilepsy with no evidence of cognitive decline, particularly juvenile myoclonic epilepsy. Seizure types in Lafora’s disease include myoclonus, occipital seizures with transient blindness and visual hallucinations, atypical absences, and atonic and complex partial seizures. As the disease progresses, seizures become more intractable and status epilepticus of any seizure type is not unusual. Cognitive decline, dysarthria, and ataxia appear early. Emotional disturbance is common early in the disease and dementia develops gradually. Later, patients are disabled with continuous myoclonus. Most patients die within 10 years of onset. Early in Lafora’s disease, the EEG has a well-organised background with multiple spike-and-wave discharges, and photosensitivity is common; however, induced epileptiform discharges may occur only at low frequency (1–6 Hz) of photic stimulation. Erratic myoclonus may be seen without EEG correlation. Spike-and-wave discharges are not accentuated during sleep. During the next few months to years, the background deteriorates and sleep features are lost. Multifocal epileptiform abnormalities, mainly occipital in location, appear in addition to generalised bursts. In longitudinal EEG studies, the spike-and-wave pattern changes from a frequency of 3 Hz in the early stages to faster frequencies of 6–12 Hz as the disease progresses. Lafora bodies, are present in neurons, but can be seen in many other tissues such as skin, liver, and muscle, although diagnosis is most conveniently made by examination of the eccrine ducts of the sweat glands in a skin biopsy specimen. Lafora bodies may range in size from a barely visible 1 μm dot to a large, rounded intracytoplasmic basophilic structure (figure 1).

Genetics and diagnosis
Lafora’s disease is an autosomal recessive disorder. Up to 80% of patients with the disorder have a mutation in the EPM2A gene on chromosome 6q at locus 24. The gene encodes laforin, a dual-specificity protein tyrosine phosphatase, primarily associated with ribosomes. The function of laforin is largely unknown but involvement in translational regulation and protein folding may underlie the molecular basis of the disease. Laforin may also cause glycogen synthase hyperfunction, contributing to the endoplasmic-reticulum-associated polyglucosan depositions seen in the disease. More recently, a new Lafora’s disease locus, NHLRC1 (formerly EPM2B), has been mapped to a 2·2 Mbp region at 6p22, a region that codes for several proteins, including kinesins, which play a major part in axonal...
and dendritic transport in neurons (table 1). Evidence for a third locus for Lafora’s disease, yet to be identified, has been recently reported. The narrow age of onset, progressive dementia, rapid and relentless progression to death, and frequent occipital seizures are clinical clues to diagnosis. Diagnosis is confirmed by detecting Lafora bodies in skin biopsy specimens, but this is likely to be superseded by analysis of the EPM2A gene, yielding a known mutation in 80% of patients with Lafora’s disease.

Treatment
Treatment for Lafora’s disease remains palliative. Advances in gene, protein, or stem-cell therapies may allow replacement of the defective protein in the future. Knockout mouse and natural canine models of the disease may yield new insights into pathogenesis, and may facilitate the testing of new therapeutic approaches. Meanwhile, on the basis of the knowledge that Lafora bodies are carbohydrate compounds, an international collaborative clinical trial based at the US National Institutes of Health has been begun to test whether carbohydrate restriction will diminish Lafora-body formation and disease progression.

Myoclonic epilepsy with ragged red fibres
Myoclonic epilepsy with ragged red fibres (MERRF) is one of the common causes of PME. It may be sporadic or familial. Mitochondrial diseases can be both maternally and paternally inherited, but typical MERRF, and the syndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (known as MELAS), are maternally inherited.

Clinical picture and investigations
The syndrome of MERRF is characterised by myoclonus, generalised epilepsy, ataxia, and ragged red fibres in muscle biopsy (figure 2). The clinical spectrum can vary, and the syndrome exhibits intrafamilial variation in age of onset and clinical severity. Common clinical manifestations include myopathy, neuropathy, hearing loss, dementia, short stature, and optic atrophy. Less commonly, cardiomyopathy, pigmentary retinopathy, pyramidal signs, ophthalmoparesis, multiple lipomas, and diabetes mellitus can occur. There is an overlap with the syndrome of MELAS, but MERRF usually has a longer course and is associated with milder behavioural and cognitive deficits.

In patients with MERRF, the EEG shows generalised spike-and-wave discharges at 2–5 Hz, with background slowing that progresses as the disease advances. Focal epileptiform discharges can also be seen. Muscle biopsy shows ragged red fibres in over 90% of patients. Biochemical studies of respiratory-chain enzymes in muscle extracts usually show decreased activity. Brain

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Chromosome locus</th>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULD</td>
<td>AR</td>
<td>Ch21q22.3</td>
<td>CSTB</td>
<td>Cystatin B</td>
<td>Gysteine protease inhibitor</td>
<td>Unstable expansion of dodecamer repeat or point mutations</td>
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<tr>
<td>Lafora’s disease</td>
<td>AR</td>
<td>Ch6p24</td>
<td>EPM2A</td>
<td>Laforin</td>
<td>Dual specificity protein tyrosine phosphatase</td>
<td>More than 20 mutations</td>
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<tr>
<td>MERRF</td>
<td>Maternal</td>
<td>Mitochondrial DNA</td>
<td>MTTK</td>
<td></td>
<td>hTfNAlys</td>
<td>Mitochondrial function and metabolism</td>
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<tr>
<td>Classical late infantile</td>
<td>AR</td>
<td>Ch11p15</td>
<td>TPF1</td>
<td></td>
<td>Tripeptidyl peptidase 1</td>
<td>Multiple</td>
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<tr>
<td>Juvenile</td>
<td>AR</td>
<td>Ch6p</td>
<td>CLN3</td>
<td></td>
<td>Multiple</td>
<td>1.02 kbp deletion</td>
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<td>Adult (Kufs disease)</td>
<td>AR/AD</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Finnish-variant late infantile</td>
<td>AR</td>
<td>Ch13q21-q32</td>
<td>CLN5</td>
<td>–</td>
<td>CLN5; Finnish major</td>
<td>Multiple</td>
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<tr>
<td>Varant late infantile</td>
<td>AR</td>
<td>Ch15q21-23</td>
<td>CLN6</td>
<td>–</td>
<td>Multiple</td>
<td>–</td>
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<tr>
<td>Sialidoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>AR</td>
<td>Ch6p21.1</td>
<td>NEU1</td>
<td>Sialidase 1</td>
<td>Multiple</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>AR</td>
<td>Ch20</td>
<td>NEU1</td>
<td>Sialidase 1</td>
<td>Multiple</td>
<td></td>
</tr>
<tr>
<td>DRPLA</td>
<td>AD</td>
<td>Ch12q13.1</td>
<td>DRPLA</td>
<td></td>
<td>Atrophin 1</td>
<td>Unstable expansion of CAG repeats</td>
</tr>
</tbody>
</table>

MERRF=myoclonic epilepsy with ragged red fibres; NCL=neuronal ceroid lipofuscinoses; DRPLA=dentatorubral-pallidoluysian atrophy; AR=autosomal recessive; AD=autosomal dominant; –=unknown.
MRI may show brain atrophy and basal ganglia calcifications. Grey-matter signal changes on T2-weighted images are sometimes seen, with deep cerebral nuclei being more involved than the cerebral cortex. When signal changes are seen in the white matter, the peripheral white matter is the earliest to be involved.

Genetics and diagnosis
The most common molecular defect is an adenosine to guanine substitution at nucleotide pair 8344 (8344A→G) in the tRNA gene (MTTK) of mitochondrial DNA, and is present in 90% of typical MERRF patients. Another rare identified molecular cause of MERRF is a tyrosine to cytosine substitution (8356T→C) in the same gene, and another is a guanine to adenosine substitution (8363G→A). However, in some individuals, a mutation has not been identified. Clinical clues to the presence of MERRF include deafness, optic atrophy, myopathy, lipomas, intrafamilial variation in age of onset, and maternal transmission. Ragged red fibres and mutations in germline DNA (e.g., peripheral blood) can be used to confirm the diagnosis.

Treatment
There is no specific therapy for MERRF, but, as in many mitochondrial disorders, many patients are empirically treated with combinations of antioxidant vitamins and cofactors including coenzyme Q$_0$ and L-carnitine. Valproic acid causes inhibition of carnitine uptake, so must be used with caution and combined with L-carnitine supplementation.

In most patients, mutant and wildtype mitochondrial DNA molecules coexist (heteroplasmy), and there is a threshold amount of mutant mitochondrial DNA necessary for the disease to be expressed clinically. Antigenomic peptide nucleic acids that specifically inhibit replication of mutant but not wildtype mitochondrial DNA templates in vitro have been developed and expressed in cultured human myoblasts. Furthermore, mutant mitochondrial DNA predominates in mature myofibres, but is rare or undetectable in skeletal muscle satellite cells, a pattern that is thought to result from positive selection for the mutant mitochondrial DNA in postmitotic myofibres and loss of the mutant by genetic drift in satellite cells. This finding lends itself to new approaches for treatment, for example, by increasing the incorporation of satellite cells through regeneration after injury to myofibres by resistance exercise training, or by bupivacaine hydrochloride injection.

Neuronal ceroid lipofuscinoses
The neuronal ceroid lipofuscinoses (NCLs) are characterised by the accumulation of abnormal amounts of lipopigment in lysosomes (figure 3). There are five types of NCL that may cause PME: classic late infantile NCL (type 2) or Jansky-Bielschowsky disease; juvenile NCL (type 3), Spielmeyer-Vogt-Sjogren disease, or Batten disease; adult NCL (type 4), Kuf’s disease, or Parry disease; late infantile Finnish variant NCL (type 5); and late infantile variant NCL (type 6). Each form of the disease is genetically distinct, with an autosomal recessive inheritance in all except for the adult form, which may have autosomal dominant inheritance.

Classic late infantile NCL
Classic late infantile NCL usually has an onset between 2.5 and 4 years. Myoclonic, tonic-clonic, atonic, and atypical absence seizures are typically the first manifestation of the disease. Within a few months from onset, ataxia and psychomotor regression appear, whereas visual failure develops later. Optic fundi show attenuated retinal vessels and macular degeneration (table 2). Epilepsy is intractable and dementia and spasticity are relentlessly progressive, with death occurring about 5 years after onset.

EEG shows background slowing and disorganisation with generalised epileptiform discharges. Specific electrophysiological features are posterior spikes in response to low-frequency photic stimulation in EEG studies, and the giant visual evoked potentials elicited only with flash stimulation. The gene for this disease (TPP1) has been mapped to chromosome 11p15. This gene encodes the protein tripeptidyl peptidase 1 (TPP1). Multiple mutations that include missense, nonsense, deletion, insertion, and splicing mutations have been detected. TPP1 removes tripeptides from the N-terminal of proteins undergoing degradation in lysosomes. The specificity and substrate range of TPP1 is still not clear. Reduced or undetectable TPP1 enzyme activity in fibroblasts or leucocytes can be used to confirm the diagnosis.
Late infantile Finnish variant NCL

A variant of late infantile NCL has been found in Finland (NCL type 5). This variant differs from classic late infantile NCL (type 2) in that onset is later, at around age 5 years, and includes symptoms of clumsiness and hypotonia. This is followed by visual impairment at age 5–7 years, and then ataxia at 7–10 years. Myoclonic and tonic-clonic seizures usually appear at around 8 years of age. Progression is slower than in NLC type 2. EEG is similar to that in NCL type 2, but the substantial response to photic stimulation develops later, at age 7–8 years.

The gene associated with the disease, CLN5, is found almost exclusively in Finland and has been mapped to chromosome 13q21–q32. The most common mutation (Finnish major mutation or CLN5 Fin major) occurs in 94% of Finnish patients and is a 2 bp deletion in exon 4. The CLN5 gene encodes for a putative transmembrane protein of 407 amino acid residues, the function of which is unknown.

Late infantile variant NCL

A variant of late infantile NCL, sometimes called early juvenile NCL, Gypsy-Indian late infantile NCL, or NCL type 6, features an intermediate onset of symptoms at age 5–7 years and a course that leads to death in the mid twenties. The associated gene, CLN6, has been mapped to chromosome 15q21–23. The encoded protein and function are unknown. There is no major founder mutation for this disease; 18 mutations have been reported, including missense, nonsense, small deletions or insertions, and splice-site mutations. Cases reported in Costa Rica, Venezuela, Pakistan, and the Czech Republic show that families from the same country do not all share the same mutation.

Juvenile NCL

Juvenile-onset NCL, also known as Batten disease or NCL type 3, starts at age 4–10 years with visual failure. Dementia and extrapyramidal features develop gradually, and seizures are not a prominent manifestation of the disease. Most patients are blind by their second decade. The most common seizure type is generalised tonic-clonic; myoclonus is usually subtle. Behavioural and psychiatric problems, including psychosis and hallucinations are common. Fundoscopy reveals optic atrophy, macular degeneration, and attenuated vessels. Death occurs about 8 years after disease onset.

EEG shows a slow background with generalised spike and wave. Epileptiform abnormalities are accentuated during sleep but not with photic stimulation. The gene associated with this disease, CLN3, is located on the short arm of chromosome 16. The CLN3 gene encodes a protein of 438 amino-acid residues, the function of which is unknown. The most common mutation of more than 25 mutations identified is a 1·02 kbp deletion that removes exons 7 and 8, resulting in production of a truncated protein containing the original 153 N-terminal residues followed by 28 new amino acid residues.

Adult NCL

Adult NCL (Kuf’s disease, or NCL type 4), may have its onset in childhood or adolescence, despite its denomination. Myoclonus can first occur as late as age 30 years. Dementia, ataxia, and extrapyramidal signs may develop first. There are no ophthalmological abnormalities or visual failure. EEG shows generalised fast spike-and-wave discharges with photosensitivity.

Table 2: Some differentiating clinical characteristics of PME

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age at onset (years)</th>
<th>Prominent seizures</th>
<th>Cerebellar signs</th>
<th>Dementia</th>
<th>Fundi</th>
<th>Dysmorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULD</td>
<td>6–15</td>
<td>Myoclonus ++++</td>
<td>Mild and late</td>
<td>Mild and late or absent</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>Lafora’s disease</td>
<td>12–17</td>
<td>Myoclonus and occipital seizures</td>
<td>Early</td>
<td>Early and relentless</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>MERRF</td>
<td>Any age</td>
<td>Myoclonus + +</td>
<td>Variable</td>
<td>Variable</td>
<td>With or without optic atrophy or retinopathy</td>
<td>With or without cherry-red spot type II</td>
</tr>
<tr>
<td>NCL</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Rapidly progressive</td>
<td>Macular degeneration and visual failure, except Kuf’s disease</td>
<td>No</td>
</tr>
<tr>
<td>Sialidoses</td>
<td>Variable</td>
<td>Myoclonus ++++</td>
<td>Gradual</td>
<td>Absent in type I, learning difficulty in type II</td>
<td>Kuf’s disease</td>
<td>No</td>
</tr>
</tbody>
</table>
The disease is sometimes observed as a sporadic case, or as familial disease with autosomal recessive inheritance (most commonly), or with autosomal dominant inheritance (least commonly), suggesting genetic heterogeneity of the disease.57

**Diagnosis and treatment of NCL**

Diagnosis of NCL is typically suspected clinically (table 2) and supported by electrophysiological studies. Visual and ophthalmological abnormalities point to NCL forms other than type 4. MRI findings in NCL include cerebral and cerebellar atrophy, T2-hyperintensity of the lobar white matter, and thinning of the cerebral cortex.71 Definitive diagnosis currently relies on finding typical intracellular inclusions by electron microscopy,72 which can be located in eccrine secretory cells and also in conjunctival or muscle biopsy. Suction biopsy of rectal mucosa is also a reliable method to show the inclusions.73 The inclusions have different morphologies that point to individual types of NCL, being curvilinear in late infantile NCL and fingerprint figure in juvenile and adult NCL (figure 4).74–76

There is no specific treatment and like most other causes of PME the mainstay of treatment is supportive and palliative care. Antioxidant treatment in patients with juvenile NCL, with vitamins E and C and methionine, has been tried in one study but a definite benefit has not been confirmed.77 Gene therapy is still experimental. Treatment options for the future include delivering active TPP1 to CNS and retinal cells in a sufficient quantity and time to prevent cell loss. Theoretically, this can be achieved by enzyme augmentation therapy, allogenic stem-cell transplantation, and other forms of gene therapy.78

These strategies are based on the concept that the pro-TPP1 protein is taken up via mannose-6-phosphate receptors on both the producer and the neighbouring cells.79,80 Recently, virus-mediated gene transfer of TPP1 to the CNS of mice has been reported as a potential therapy for late infantile NCL.81

**Sialidoses**

Two sialidoses are rare causes of PME. Sialidoses type I (cherry-red spot myoclonus syndrome) is caused by deficiency of α neuraminidase. It has a juvenile or adult onset and produces a rather pure intention and action myoclonus. Slow progression and absence of mental deterioration or dysmorphism are characteristic of the syndrome. There is gradual visual failure, tonic-clonic seizures, ataxia, and a characteristic cherry-red spot in the fundus.82

Sialidoses type II is caused by a deficiency of both N-acetyl neuraminidase and β-galactosialidase, and is therefore also called galactosialidoses. The time of onset varies from the neonatal period to the second decade of life. Clinical features include coarse facial features, corneal clouding, hepatomegaly, skeletal dysplasia, and learning disability in addition to the myoclonus. EEG background shows low-voltage fast activity, but slowing can be seen in patients with dementia. Massive myoclonus is associated with trains of 10–20 Hz, small, vertex-positive spikes preceding the electromyographic artefact.83 MRI findings in sialidoses range from normal in the early stages to cerebellar, pontine, and cerebral atrophy as the disease progresses.84

The sialidoses are autosomal recessive disorders. The human sialidase gene (NEU1) is located inside the locus of the MHC on chromosome 6p21.3.85 Sialidase is targeted to the endosomal-lysosomal compartment as an integral membrane protein by vesicular transport, which involves association of the adapter proteins with a tyrosine-containing internalisation signal at the C-terminus of the enzyme.86 There are no major founder mutations for the sialidoses. Several mutations including five novel mutations have been described; the mutated protein may prevent substrate binding or impair the folding of the sialidase enzyme.79 More than 39 mutations in NEU1 have been described,87 including splice-site mutations, insertions and deletions, nonsense, and missense mutations. The most common of these are the missense mutations, which cause almost complete loss of enzyme activity. The analysis of these mutations reveals substantial molecular heterogeneity, reflecting the diversity of clinical phenotypes. Patients with a combination of a mild and a severe mutation have a clinically milder form of the disease, suggesting that a small percentage of normal sialidase activity may protect against severe phenotypes. Hence, enzyme replacement therapy is a possible approach to treatment in sialidoses.88 The gene responsible for galactosialidoses is located on chromosome 20.89 Protective protein

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**Figure 4:** Fingerprint intraneuronal inclusion typical of Kuf’s disease (electron micrograph) Reproduced with permission from Dustri Verlag.76
cathepsin A (PPCA), a lysosomal carboxypeptidase, is deficient in galactosialidoses. Enzyme-replacement experiments have been done on PPCA-deficient mice, which display symptoms similar to those of severe galactosialidoses. These mice received haematopoietic progenitors transduced with a bicistronic retroviral vector based on a murine stem-cell virus, which overexpresses PPCA and a fluorescent protein marker. Complete correction of the disease phenotype was seen up to 10 months after transplantation, and PPCA-positive cells derived from the bone marrow were detected in all tissue including the brain. The cherry-red spot should be sought when sialidoses is suspected clinically. Diagnosis is confirmed by the detection of high urinary sialyloligosaccharides and by confirmation of the lysosomal enzyme deficiency in leucocytes or cultured fibroblasts.

**Dentatorubral-pallidoluysian atrophy**

Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare autosomal-dominant neurodegenerative disorder, characterised by various combinations of cerebellar ataxia, choreoathetosis, myoclonus, epilepsy, dementia, and psychiatric symptoms. First described in Japan, where it is most prevalent, molecular diagnosis has allowed detection of the disease in other ethnic groups. There is substantial heterogeneity in clinical presentation, even in the same family. There are three clinical forms: an ataxochooreathetoid form, a pseudo-Huntington form, and a PME form. Patients with onset before age 20 years often present with the phenotype of PME, characterised by ataxia, seizures, myoclonus, and progressive intellectual deterioration.

DRPLA is an autosomal-dominant disorder, caused by unstable expansion of CAG repeats of a gene at 12p13.31. The discovery of the DRPLA gene has made it possible to analyse the diverse clinical presentations on the basis of the size of the expanded CAG repeats. There is also an inverse correlation between the age at onset and the size of the expanded CAG repeats. DRPLA is characterised by prominent anticipance with a mean acceleration of age at onset of 2.5 years (SD 2.4) in paternal transmission and 14 years (SD 4) in maternal transmission. MRI findings include atrophy of mid-sagittal structures of the cerebellum and brain stem, particularly the pontine tegmentum. There is strong inverse correlation between the age at diagnosis by MRI and the areas of atrophy in patients with large expanded CAG repeats. However, cerebral white-matter involvement is associated with the duration of the illness rather than with the size of the CAG repeats.

Diagnosis is confirmed by identifying the abnormal CAG repeats.

**Other rare causes of PME**

The action-myoclonus renal-failure syndrome, an autosomal recessive disorder, was described in French Canadians with PME, severe progressive action myoclonus, dysarthria, ataxia, and renal failure. A juvenile form of Huntington’s disease may also cause PME. Familial encephalopathy with neuroserpin inclusion bodies is a rare autosomal-dominant disease that causes progressive dementia and, in some cases, a familial form of PME. It is caused by mutation in the gene coding for the serine protease inhibitor (serpin) on chromosome 3q26. Inclusion bodies are distributed throughout the cerebral cortex and substantia nigra. Non-infantile neuropathic Gaucher’s disease, atypical inclusion body disease, neuraxonal dystrophy, coeliac disease, juvenile GM1 gangliosidosis, Hallervorden-Spatz disease, and Alzheimer’s disease beginning in the third or fourth decade are other very rare causes of a PME phenotype.

**Conclusion: diagnosis and treatment of PME**

The PMEs are rare disorders, that typically have a genetic cause. Most PMEs are autosomal-recessive disorders, except for adult NCL (Kuf’s disease), DRPLA, juvenile Huntington’s disease, familial encephalopathy with neuroserpin inclusion bodies, and MERRF. The mode of inheritance, especially if dominant, can give a clue to diagnosis.

In the early stages of PME, clinical and EEG features may mimic idiopathic generalised epilepsy syndromes, especially juvenile myoclonic epilepsy, but failure of therapy and progressive neurological and EEG deterioration point to a diagnosis of PME. Conversely, the clinical picture of patients with idiopathic generalised epilepsy may mimic PME, if they are inappropriately treated and intoxicated with antiepileptic drugs, with resultant ataxia, impaired cognitive function, and poorly controlled seizures. However, photosensitivity may require photic stimulation at a lower frequency than that in idiopathic generalised epilepsy. A full history of the illness, developmental history in children, comprehensive family history when possible, and thorough clinical examination are imperative to obtain clues to diagnosis.

Although laboratory and pathological studies are still required for some of the PME disorders, the revolution in molecular genetics has allowed a definitive diagnosis of some PMEs such as Unverricht-Lundborg disease, MERRF, DRPLA, and most patients with Lafora’s disease. Reaching a definite diagnosis has significant implications for management and genetic counselling.

Treatment of PME disorders remains essentially that of managing seizures and myoclonus together with palliative, supportive, and rehabilitative measures. Treatment of myoclonus and seizures in PME can prove to be difficult as both tend to be refractory and resistant to conventional antiepileptic medications. Controlled clinical studies could be used to assess the antiepileptic drug efficacy in PME in large groups of patients, but are not possible because the incidence of these disorders is rare. Hence, available data on the efficacy of newer
antiepileptic medications in PME are primarily anecdotal or observational, based on responses of individuals or very small groups of patients.105

Commonly used antiepileptic drugs for management of myoclonus (panel 2) include combinations of valproic acid, benzodiazepines, phenobarbital, and more recently, piracetam, zonisamide, and levetiracetam. Vagus-nerve stimulation may also have a role but needs to be further investigated and can not yet be considered as a routine treatment. Care must be taken to avoid antiepileptic medications that clearly worsen myoclonus. These include vigabatrin, carbamazepine, phenytoin, and gabapentin. Lamotrigine has an unpredictable effect on myoclonus and must be used with caution.106–108

Through recent advances in molecular genetics, several gene loci, mutations, and proteins involved in the pathogenesis of PME disorders have been identified. Future treatments with gene therapy and enzyme replacement may help to modify and improve the course of these progressive disorders.

Panel 2: Drugs and PME

**Used for treatment**
- Valproic acid
- Benzodiazepines
- Phenobarbital
- Piracetam
- Levetiracetam
- Zonisamide

May aggravate myoclonus
- Phenytoin
- Carbamazepine
- Gabapentin
- Vigabatrin
- Tiagabine

**Use with caution**
- Lamotrigine in all cases
- Valproic acid in MERRF

Authors’ contributions
AS designed and wrote the review and collected the data. MF revised the review and provided the neuropathological figures. ND developed the initial idea, contributed to the design of the review, and revised the paper at its different stages of development for important intellectual content.

Conflicts of interest
ND has received unrestricted educational and research grant support from the following pharmaceutical companies: UCB Pharma, Elan Pharma, GlaxoSmithKline, Jansen Cilag, Pfizer and Novartis. He is or has also been a member of Elan Advisory Board (Ireland), UCB Pharma Advisory Board (UK), Eisai Advisory Board (Europe), Irish advisory boards of Jansen Cilag and GlaxoSmithKline, and the European advisory board of Pfizer. He has also received speaker’s honoraria from UCB Pharma and Jansen Cilag. The decision to write and submit this review was entirely his, and was not in any way influenced or initiated by any pharmaceutical company. MF is not employed by any pharmaceutical companies nor does he receive any funds from pharmaceutical or other commercial companies, nor does he have ownership of stocks in such companies. AS is not employed by any pharmaceutical company nor does he receive any funds from pharmaceutical or commercial companies, nor does he have ownership of stocks in such companies.

Role of the funding source
There is no funding allocated for this study and it is entirely the sole efforts of the participating authors.

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