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Review

The best evidence for progressive myoclonic epilepsy: A pathway to precision therapy

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A B S T R A C T

Progressive Myoclonus Epilepsies (PMEs) are a group of uncommon clinically and genetically heterogeneous disorders characterised by myoclonus, generalized epilepsy, and neurological deterioration, including dementia and ataxia. PMEs may have infancy, childhood, juvenile or adult onset, but usually present in late childhood or adolescence, at variance from epileptic encephalopathies, which start with polymorphic seizures in early infancy. Neurophysiologic recordings are suited to describe faithfully the time course of the shock-like muscle contractions which characterize myoclonus. A combination of positive and negative myoclonus is typical of PMEs. The gene defects for most PMEs (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. PMEs are uncommon disorders, difficult to diagnose in the absence of extensive experience. Thus, aetiology is undetermined in many patients, despite the advance in molecular medicine. Treatment of PMEs remains essentially symptomaticof seizures and myoclonus, together with palliative, supportive, and rehabilitative measures. The response to therapy may initially be relatively favourable, afterwards however, seizures may become more frequent, and progressive neurologic decline occurs. The prognosis of a PME depends on the specific disease. The history of PMEs revealed that the international collaboration and sharing experience is the right way to proceed. This emerging picture and biological insights will allow us to find ways to provide the patients with meaningful treatment.

1. Definition and history of progressive myoclonus epilepsies

The Progressive Myoclonus Epilepsies (PMEs) are a group of uncommon clinically and genetically heterogeneous disorders (mainly autosomal recessive), characterised by myoclonus, generalized epilepsy, and progressive neurological deterioration, including dementia and ataxia [1]. PMEs are disorders with debilitating evolution, resistance to treatment and poor prognosis, and it is estimated that these diseases are responsible for up to 1% of epileptic syndromes in children and adolescents around the world. The rarity and complexity of the disorders that cause PMEs have resulted in a confusing literature since the first description, a century ago (Table 1) (Table 2). The recent history of PMEs begins in 1989 with a consensus statement published in the wake of the Marseille PME workshop. The consensus helped to define the various types of PMEs known at that time and set the agenda for a new era of genetic research, which soon led to the discovery of many PME genes [2,3].

Here, we review the main advances in the field and also address the potential pathways for a targeted, personalized approach for their treatment.

2. Unverricht-Lundborg disease (ULD) (OMIM #254800)

ULD is the purest type of PMEs, with only few symptoms associated with epileptic seizures and myoclonus [4]. It is the most common, less severe form of PME, with an autosomal recessive inheritance and it occurs in late childhood or adolescence. Sex distribution is equal. Although it occurs worldwide, its prevalence is higher in some geographic areas (Finland, Mediterranean region, Reunion Island) and in areas with a high rate of consanguinity [1,5]. Its worldwide prevalence is unknown; in Finland, approximately 4 in 100,000 people are affected.

ULD has been related to mutations in the *CTSB* (cystatin B) gene, located in 21q22.3. Cystatin B protects the cell from endogenous proteases and its deficiency causes hyperexcitability and impaired neuronal function of cortical networks. An unstable minisatellite repeat expansion of a dodecamer (CCCCGCCCCGCG) in the 5-prime

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Table 1
Summary of PMEs clinical features.

DISEASE	AGE AT ONSET (YEARS)	SEIZURES	CEREBELLAR SIGNS	DEMENTIA	FUNDOSCOPY	EEG FEATURES	DIAGNOSTIC CLUES	NEUROIMAGING
ULD	6–15	Myoclonic	Mild/late	Mild/late or absent; psychosis (visual and auditory hallucinations)	Normal	Diffuse epileptiform discharges	CSTB gene mutation	Usually normal
Lafora's disease	12–17	Myoclonic and occipital	Early	Early/severe	Normal	Diffuse spike and wave 6–12 Hz	Lafora bodies in skin biopsy or EPM2A mutation	Possible posterior hypometabolism in early stages
MERRF	Variable	Myoclonic	Variable	Variable	Retinal dystrophy and retinitis pigmentosa, optic atrophy	Focal discharges and bursts of generalized spike and wave of 2–5 Hz	Ragged red fibers in muscle biopsy or MTTK mutation	Normal or progressive cerebral atrophy
NCL	Variable	Variable	Variable	Rapid progression	Macular degeneration, except in Kuf's disease	Focal and generalized discharges	Typical inclusions or Mutation in TPP1, CLN3 and CLN5	Cerebral and cerebellar atrophy
Sialidosis	Variable	Myoclonic	Progressive	Type II: learning disability	Cherry-red spot	Trains of positive spikes associated	Neuraminidase deficiency in fibroblasts or leucocytes	Cerebellar, pontine and cerebral atrophy (late stage)

Abbreviations: ULD Unverricht-Lundborg disease; MERRF myoclonic epilepsy with ragged red fibers; NCL neuronal ceroid lipofuscinosis; AR autosomal recessive; AD autosomal dominant; EEG electroencephalography.

untranslated region of the gene (601145.0003) could be the most likely source of the disorder [6].

In addition to the expanded repeat mutation and the 2 or 3 repeats found in alleles considered to be normal, alleles with 12–17 repeats, termed 'premutational', were identified and shown to be transmitted unstably to the offspring. These 'premutational' alleles were not connected with a clinical phenotype [7].

Point mutations identified in EPM1 patients were found as compound heterozygous with the 12-bp repeat expansion allele, or sometimes homozygous. All EPM1 patients had residual gene activity; patients with null point mutations in homozygous state were not found, probably because they are not viable [7].

CSTB belongs to the family 1 of the protease inhibitor superfamily. Human CSTB (also known as stefin 1, stefin B, or neutral cysteine protease), inhibits in vitro several cathepsins (B, H, L and S), by tight reversible binding. The main function of cathepsins is non-selective degradation of intracellular proteins to peptides and amino acids, but they also participate in antigen procession and apoptosis. In lymphoblastoid cells of EPM1 patients, decreased inhibitory activity of CSTB has been shown to correlate with enhanced activity of cathepsins B, L and S, providing in vivo evidence for cathepsin regulation by CSTB. The physiological functions of CSTB, however, are likely not limited to cathepsin binding. Cystatin B has also been shown to inhibit apoptosis in cerebellar cells. Data obtained in mice suggest that EPM1 should be classified as a primary neurodegenerative disorder, with CSTB having an endogenous neuroprotective role in different neuronal populations. Despite this progress, the molecular pathogenesis of EPM1 as well as the normal physiological function of CSTB still remains to be elucidated [8]. Oxidative stress is correlated with many neurological conditions and several case reports have suggested that antioxidant therapies, including *N*-acetylcysteine, may alleviate symptoms in ULD patients [9]. Glial activation and particularly microglial activation may also contribute to the pathogenesis of the disease. The observed microglial activation precedes the onset of myoclonus and is followed by gliosis and neuronal loss [10].

Myoclonus is present since the early stages, with diffuse myoclonic jerks at awakening. Myoclonus is typically distal, triggered by action, sensory stimulation or surprise. Over months or few years, myoclonus becomes movement-related and increases with stress, causing major disability [4]. Generalized tonic-clonic seizures (GTCSs) are usually grounds for an initial referral but in general they are a less prominent source of disability than myoclonus and in most patients become a relatively minor feature over time [11]. GTCS typically occur at awakening or during sleep. With disease progression, they may evolve into cascade seizures, characterized by increasingly intense and violent myoclonic jerks, culminating into a GTCS. GTCS usually decrease spontaneously with advancing age. Other kind of seizures are rare. Ataxia, impaired walking and instability upon standing are associated with myoclonus and they usually decrease when myoclonus is fully controlled.

Cognitive impairment may be from mild to moderate [4,5]. In some studies, it has been demonstrated a loss of attention, short-term memory and executive functions [5].

Psychiatric comorbidities are frequent in ULD patients. A variety of neuropsychological disorders have been documented in ULD patients in various combinations [11,12].

The most typical EEG findings in ULD patients are represented by normal or moderately slow background activity, generalized fast spike or polyspike and wave discharges at 3–5 Hz, both spontaneous and induced by intermittent photic stimulation (IPS), mainly between 10 and 15 flashes/s. Focal EEG abnormalities prevalent over the central and the posterior regions may be detected [13], particularly during REM sleep with evidence of typical vertex and central fast spikes [14]. EEG abnormalities, tend to decrease over time after an average of 15 years of disease.

Photosensitivity is a nearly constant feature of ULD (from 88% to

Table 2
Molecular genetics of PME.

DISEASE		INHERITANCE	CHROMOSOME LOCUS	GENE	PROTEIN	FUNCTION
ULD		AR	Ch21q22.3	CSTB	Cystatin B	Cysteine protease inhibitor
LD		AR	Ch6q24 Ch6p22	EPM2A EPM2B	Laforin Malin	Dual specificity protein tyrosine phosphatase
MERRF		Maternal	Mitochondrial DNA	MTTK	tRNALys	Mitochondrial function and metabolism
NCL	Classical late infantile	AR	Ch11p15	TPP1	Tripeptidyl peptidase 1	–
	Juvenile	AR	Ch6p	CLN3	–	–
	Adult (Kufs disease)	AR/AD	–	–	–	–
	Finnish-variant late infantile	AR	Ch13q21-q32	CLN5	–	–
	Variant late infantile	AR	Ch15q21-23	CLN6	–	–
Sialidosis	Type I	AR	Ch6p21.3	NEU1	Sialidase 1	–
	Type II	AR	Ch20	NEU1	Sialidase 1	–

Abbreviations: MERRF myoclonic epilepsy with ragged red fibres; NCL neuronal ceroid lipofuscinoses; DRPLA dentatorubral-pallidoluysian atrophy; AR autosomal recessive; AD Autosomal dominant; – unknown.

100% in different studies). Unlike other PMEs but similar to patients with idiopathic generalized epilepsies and PPR, photosensitivity in ULD tends to disappear over the years, its prevalence decreasing to ~30% after 15 years of disease [15].

Outcome in adults ranges from independent active life with minimal impairment to severe disability and wheelchair-bound or even bed-ridden patients.

3. Sialidosis (OMIM# 256550)

Sialidosis is an autosomal recessive lysosomal storage disorder due to isolated neuraminidase (sialidase) deficiency leading to a defect in the degradation of glyco-proteins and accumulation of sialic-acid-containing oligosaccharides and glycol-peptides. It was first reported as 'cherry-red spot-myoclonus syndrome' because of the characteristic aspect of the fundus oculi, resulting from storage material in perifoveal ganglionic cells [16].

Sialidosis is caused by mutations in the gene encoding neuraminidase, NEU1. It is classified on the basis of the patients' phenotype and onset age [17]. NEU1 is localized in 6p21.33 and encodes lysosomal neuraminidase. To date, > 40 NEU1 disease-causing mutations have been identified. Most of these are missense mutations that do not affect NEU1 mRNA synthesis or stability [18]. Besides point mutations, also small deletions can be causative: an 11-kb deletion encompassing the entire coding and promoter regions of the NEU1 gene was identified in 2 patients with sialidosis [19].

Two types of sialidosis can be distinguished: type I and type II sialidosis. Severe type II is caused by inactivate sialidase, while in the milder form there is some residual activity [17].

Sialidase is part of a multienzyme complex containing other lysosomal enzymes such as: cathepsine A, b-galactosidase and *N*-acetylgalactosamine-6-solfate sulfatase. Sialidase removes terminal sialic acid molecules from oligosaccharides and glycoproteins, and its deficiency causes macromolecular storage and urinary sialy-oligosaccharides exertion [20]. The accumulation of the sialic acid-rich substrates contributes to the pathogenesis, and light and electron microscopy reveals vacuolations in the neurons and in the perineuronal and interfascicular oligodendroglia, but also in the endothelial cells. Diffuse neuronal intracytoplasmic storage of lipofuscin-like pigment is detectable in the neocortex, thalamus, brainstem and spinal cord, as well in extra-nervous organs [21].

Sialidosis type I (also known as cherry-red spot myoclonus syndrome) presents with the typical clinical features of the PMEs, a slowly progressive syndrome characterized by late-onset, decreased visual acuity associated with bilateral macular cherry-red spot (that may fade later in the course of the disease) in childhood or juvenile age, nystagmus, cerebellar ataxia, action myoclonus and generalized tonic-clonic seizures. The onset of the disease is typically with gait abnormalities, decreased visual acuity, or both. Young onset cataract formation has also been detected [21]. Myoclonus is the most prominent clinical aspect and it may be precipitated by voluntary movements, the thought of movement, passive joint movements, light, touch or sound stimuli. Leg tremors and generalized seizures may also occur. A few vacuolated lymphocytes and histiocytes may be present in peripheral blood and bone marrow (BM) smears, respectively. At the ultrastructural level, swollen lysosome are visible in BM cells and in Kupffer cells of the liver [18].

Sialidosis type II may present dysmorphic features (coarse facial features, short trunk, barrel chest, spinal deformity and skeletal dysplasia) and sometimes it is associated with hepatomegaly, corneal clouding and hearing loss[HYPERLINK \l "Ref21″ \o "[21] S. Franceschetti and L. Canafoglia, Sialidoses, (in eng), Epileptic Disord, vol. 18, no. S2, pp. 89–93, Sep 2016, doi: 10.1684/epd.2016.0845.″ \h 21]. Type II sialidosis is further classified in three subtypes: congenital or hydropic with onset in utero, infantile with onset between birth and 12 months, and juvenile with onset past 2 years of age [18]. Patients with the congenital form show severe non-immune hydrops fetalis and ascites. The clinical presentation at birth includes facial oedema, inguinal hernias and hepatosplenomegaly. All patients have major dysmorphism, including coarse face, vertebral deformities, visceromegaly with enlargement of spleen and liver, dysostosis multiplex, and severe mental retardation. Renal involvement has also been described. Both the infantile patients with longer survival and the juvenile cases develop macular cherry-red spots and myoclonus and may also have hearing loss and angiokeratoma.

The penetrance and degree of severity of the symptoms in these patients correlate closely with the type of NEU1 mutations involved and, in turn, the levels of residual enzyme activity [18].The typical macular change (red-cherry-spots) depends on ganglionic degeneration and may lead to late visual failure; however it can be clinically undetectable for many years and may disappear in the late stages of the disease. Two distinct forms of myoclonic activity, namely massive myoclonic jerks and facial myoclonus, are recognizable. Action myoclonus is the main characteristic of "late" type I sialidosis, but may also occur in patients with type II sialidosis [21]. The second form of myoclonic activity is restricted to the lower face and mouth and interferes with speech. It is intermittent and often asymmetrical. This facial myoclonus occurs independently of the massive myoclonic jerks. MRI findings are normal in the early stages, while in the late stages cerebellar, pontine and cerebral atrophy can appear [21].

Diagnosis is usually supported by increased urinary bound sialic acid excretion and confirmed by the genetic analysis or by the neuraminidases deficiency in cultured fibroblast. Sialidosis type II should be differentiated from other storage disease sharing similar features and sialidosis type I should be differentiated from other types of PME.

4. Neuronal ceroid lipofuscinosis (NCLs)

The neuronal ceroid lipofuscinoses (NCLs) are the most common cause of dementia in children. They are a group of genetically-

Table 3
Genetic classification of NCLs.

LOCUS NAME	GENE SYMBOL	LOCUS	PROTEIN NAME	PHENOTYPIC SPECTRUM	CAUSING DEFECT
CLN1	PPT1	1p34.2	Palmitoyl protein thioesterase 1	I, LI, J, A	lysosomal enzymes
CLN2	TPP1	11p15.4	Tripeptidyl peptidase 1	LI, J, P	lysosomal enzymes
CLN3	CLN3	16p11.2	CLN3	J, P	transmembrane proteins
CLN4	DNAJC5	20q13.33	DnaJ homolog	A (Parry disease) subfamily C member 5	–
CLN5	CLN5	13q22.3	CLN5	LI, J, P, A	–
CLN6	CLN6	15q23	CLN6	LI, P, A (Kufs type A)	transmembrane proteins
CLN7	MFSD8	4q28.2	Major facilitator superfamily	LI, J domain-containing protein 8	transmembrane proteins
CLN8	CLN8	8p23.3	CLN8	LI, P	transmembrane proteins
CLN9	n/a	unknown	Unknown	unknown	–
CLN10	CTSD	11p15.5	Cathepsin D	C, LI, J, A	lysosomal enzymes
CLN11	GRN	17q21.31	Granulins	A	–
CLN12	ATP13A2	1p36.13	Probable cation-transporting	J ATPase 13A2	–
CLN13	CTSF	11q13.2	Cathepsin F	A (Kufs type B)	lysosomal enzymes
CLN14	KCTD7	7q11.21	BTB/POZ domain-containing	I protein KCTD7	–

Abbreviations: Aadult; C congenital; I infantile; J juvenile; LI late-infantile; P protracted; – unknown.

determined neurodegenerative conditions linked by the characteristic accumulation of abnormal storage material (NCL-specific lipopigments [22] in neurons and other cell types, and a degenerative disease course [23]. NCLs are characterized by a progressive decline of cognitive and motor capacities, retinopathy evolving into blindness, variable cerebellar atrophy, and myoclonic epilepsy, leading to significantly decreased life expectancy [24]. The characteristics of these symptoms can vary and the age at disease onset ranges from birth to young adulthood [23]. The incidence in USA and Scandinavian countries is 1:12.500 while the world-wide incidence is 1:100.000 [25].

More than a dozen genes containing nearly 400 mutations related to underlying human NCLs have been identified. These genes belong to the neuronal ceroid lipofuscinosis (CLN) family Table 3.

Traditionally, NCL diseases were classified according to the age at disease onset (congenital, infantile, late infantile, juvenile, adult) and sometimes also according to the respective authors [23]. An internationally developed new NCL nomenclature clearly identifies each NCL disease both genetically and clinically [23].Very recently, a new nomenclature has been discussed and subsequently proposed which is gene-based and specific to phenotypic variation arising from different mutations. This is an axial diagnostic classification system that includes seven axes: affected gene (CLN gene symbol), mutation diagnosis, biochemical and clinical phenotype, ultrastructural features, level of functional impairment and other remarks (additional genetic, environmental, or clinical features). NCL classification according to the affected gene, combined with the age at onset, is sufficient for general use [24].

The unifying finding in NCL patients is the accumulation, in neurons and other cell types, of autofluorescent storage material (lipopigment accumulations) revealed upon electron microscopy (EM), despite having diverse underlying biochemical aetiologies [26]. NCLs are considered as lysosomal storage diseases (LSDs), however many distinct characteristics are observed. In fact, the accumulating material in NCLs is not a disease specific substrate and the main storage material is the subunit C of mitochondrial ATP synthase or sphingolipid activator proteins A and D. The precise function of the NCL proteins as well as the disease mechanisms is largely unknown[HYPERLINK \l "Ref27″ \o " [27] A. Jalanko and T. Braulke, Neuronal ceroid lipofuscinoses, (in eng), Biochim Biophys Acta, vol. 1793, no. 4, pp. 697–709, Apr 2009, doi: 10.1016/j.bbamcr.2008.11.004.″ \h 27]. Under the electron microscope, the accumulated material takes different forms: granular osmiophilic deposits (GRODs), curvilinear profiles (CLP), fingerprint profiles (FPP), as well as rectilinear complex (RLC) or so called 'condensed forms'. The ultrastructural findings do not absolutely correlate with clinical presentation, and the same NCL may contain more than one pattern of inclusion. Furthermore, the appearance of the pathological inclusions can depend on the tissue examined [24].

NCL have a recognizable phenotype that correlates with the progressive grey matter neurodegenerative process involving the cortex, deep grey nuclei, cerebellum, and retina. The age at disease onset can range from birth to adulthood. The main alerting symptoms are the combination of two or more among dementia, visual loss, epilepsy, and motor deterioration. The order in which symptoms occur is variable and depends both on age at onset and on genetic form. In a young child, first symptoms are developmental slowing followed by standstill, then later regression of psychomotor development, or epilepsy. In a school child, first symptoms are usually visual loss and behaviour change, followed by dementia [23].

The first approach to diagnosis should consider age at onset and type of clinical presentation [23]. Suggestive situations can be divided in four typical groups: **(1)** very young infants, including new-borns with congenital epilepsy and microcephaly, **(2)** young children with developmental standstill or regression and severe epilepsy, **(3)** school children with visual loss, followed by dementia and epilepsy, and **(4)** young adults with non-specific mental, motor or behavioural abnormalities. In each of these groups, a characteristic set of NCL types can be expected, caused by variable mutations in the known NCL genes Table 4.

5. Neuroserpinosis (PME associated with neuroserpin inclusion bodies) (OMIM #604218)

Familial encephalopathy with neuroserpin inclusion bodies (FENIB) is a conformational proteinopathy, characterised by neuronal inclusion bodies composed of neuroserpin, a serine protease inhibitor (SERPIN). FENIB is responsible for progressive myoclonic epilepsy and/or presenile dementia. FENIB should be considered in cases of progressive myoclonic epilepsy and dementia particularly where there is family history of neuropsychiatric diseases [28].

FENIB is due to mutations in *SERPINI1* gene, located on chromosome 3q26, which encodes for a serine protease inhibitor, neuroserpin (NS). Genotype-phenotype correlations are remarkably strong with clinical features increasing in severity (S49 P, S52R, L47 P, H338R, G392E to G392R, from the less to the most severe). Clinical severity refers to an earlier onset of the symptoms and an increasing contribution of the epileptic component of the syndrome [28].

The Serine protease inhibitors (serpins) are a super-family of proteins that inhibits a wide range of proteases. Mutations may render serpins prone to aggregation and direct toxicity is a consequence of the intracellular accumulation of serpin aggregates (polymers) and may result in death of the synthetic cell. There may also be associated loss-of-function effects caused by the deregulated hyperactivity of the target proteases and this may underpin the development of epilepsy. Cytotoxicity is seen exclusively in neurons of the central nervous system and this aggregation causes gain-of-function neuronal dysfunction. NS

Table 4
Diagnostic algorithm for NCL diseases.

CLINICAL PRESENTATION	NECESSARY DIAGNOSTIC		POSSIBLY AFFECTED GENES
Newborn with epilepsy and microcephaly.	Enzyme testing for cathepsin D (CtsD) (leucocytes or fibroblasts).	If pisitive for CTSD deficiency:	CLN10
		If negative: further enzyme testing for PPT1 and TTP1.	
Young child (> 6 months) with developmental standstill or regression and/or newly occurring severe epilepsy of unknown cause.	Enzyme testing for PPT1 and TPP1 (dry blood spots or leucocytes or fibroblasts).		
	PPT1 deficient:		CLN1
	TPP1 deficient:		CLN2
	If PPT1 and TPP1 enzyme activities are normal: Electron microscopic examination (skin biopsy or lymphocytes).		
	If storage material is present: genetic testing.		CLN5, CLN6, CLN7, CLN8, CLN14
School child with visual loss and/or dementia and epilepsybetween ages 4 and 7.	Search for lymphocyte vacuoles (light microscopy of blood smear).		
	If lymphocyte vacuoles are present:		CLN3
	If no lymphocyte vacuoles, enzyme testing for PPT1, TPP1 and CtsD.		
	PPT1 deficient:		CLN1
	TPP1 deficient:		CLN2
	CTSD deficient:		CLN10
	If PPT1 and TPP1 enzyme activities are normal: Electron microscopic examination (skin biopsy or lymphocytes).		
	If storage material is present:		CLN5, CLN6, CLN7, CLN8, CLN12
Young adult with non-specific mental, motor or behavioral abnormalities.	Enzyme testing for PPT1, TPP1 and CtsD.		
	PPT1 deficient:		CLN1
	TPP1 deficient:		CLN2
	CTSD deficient:		CLN10
	CTSF deficient:		CLN13
	If enzyme activities are normal: Electron microscopic examination (skin biopsy or lymphocytes).		
	If storage material is present: genetic testing (eventually in special cases even without detection of storage material), consider possible mode of inheritance.		If autosomal dominant: CLN4. If autosomal recessive: CLN6, CLN11, CLN13

also inhibits tPA and plays physiological roles in the development of the central nervous system [29], in learning, in memory and also in such pathological events as stroke [30]and epilepsy [31]. NS is also thought to regulate the sensitivity of neurons to glutamatergic excitatory neurotransmission at the NMDA (*N*-methyl-D-aspartate) receptor. The epileptic component of FENIB may be due to dysfunction of the NS/tPA pathway [28].The rate of aggregation of the least clinically-aggressive NS mutant, S49 P, is more than 10 times higher than that of the wild type protein, whereas the association rate constant for tPA is essentially unchanged [32]. The next most severe mutation, S52R, results in a further tenfold increase in the polymerization rate and the loss of effective tPA inhibition [33]. NS polymers gradually become entangled in the neuronal endoplasmic reticulum (ER) and form inclusions, known as Collins bodies.

To date, only a few families and exceptionally rare non-familial cases of progressive myoclonic epilepsy linked to the SERPINI1gene have been described.

Belorgey et al. reported 2 unrelated Caucasian families, carrying 2 different heterozygous mutations (S49 P and S52R) [32]; he also described a small family with 2 affected siblings with S49 P mutation.

Davis et al. reported two patients with the disorder, a 23-year-old man with an 8-year history of progressive myoclonic epilepsy, dementia, tremor, and dysarthria, and a 13-year-old girl with progressive myoclonus epilepsy, intractable seizures, myoclonus, and dementia who died at the age of 19 during status epilepticus [34]; Gourfinkel-An et al. subsequently described a small French family with a heterozygous S52R missense mutation at position 273 in exon 2, the same as in the two families from the United States [35]; S49 P mutation have diffuse small intraneuronal inclusions of neuroserpin with an onset of dementia between the ages of 45 and 60 [34]. Patients show cognitive decline, deficits in attention and concentration, response regulation difficulties, and impaired visuospatial skills. Memory is also impaired. In adulthood, generalized seizures and, later on, status epilepticus are frequent. Slow speech, diplopia, nystagmus, dysarthria, and myoclonus in the extremities were also described. At last stages of the disease there are loss of self-sufficiency and dementia [32]. People with the S52R, L47 P and H338R variants have larger and more numerous intraneuronal inclusions associated with progressively earlier onset of symptoms, during early adulthood (S52R, L47 P) and adolescence (H338R) [36]. Neuro-histology is dominated by eosinophilic, PAS-positive intraneuronal inclusions in the brain [32]. The French family described by Gourfinkel-An et al. [35] with S52R mutation showed progressive myoclonic epilepsy associated with a frontal syndrome starting from the age of 18 with severe myoclonus, generalized tonic-clonic seizures, and absences. The EEG of one of the patients showed diffuse slow waves, spikes, and spike-wave discharges superimposed on a slow background, with photic sensitivity at around 1 Hz. Cerebral MRI revealed cortico-subcortical atrophy. Additionally, cerebellar symptoms and pyramidal signs were also present. Cognitive deterioration was severe [35]. L47 P mutation resulting in a proline to leucine amino acid substitution was recently reported by (Hagen et al., 2011) [36], in a patient with progressive myoclonus epilepsy and declining mental status starting in adulthood [36]. Generalized seizures occurred early with myoclonus and progressive gait disturbances. Neuroimaging revealed mild atrophy and multiple periventricular white matter lesions, consistent with demyelination [36].In the most severe cases, caused by the most polymerogenic mutations, namely G392R and G392E, the patients exhibit the earliest onset of symptoms, with rapidly-progressive symptomatology consisting in profound intellectual decline during childhood associated with severe, uncontrolled epilepsy, aggressive behaviour, intellectual decline, psychic seizures, and subtle seizures with eyelid myoclonus [28].

6. Spinal muscolar atrophy associated with progressive myoclonus epilepsy (SMA-PME) OMIM #613468

SMA-PME is a rare syndrome characterized by lower motor neuron disease associated with progressive myoclonic epilepsy caused by mutations in ASAH1 (*N*-Acylsphingosine Amidohydrolase), which encodes an acid ceramidase [37]. It has been described in childhood and is

inherited as an autosomal recessive trait [38]. Distal muscle weakness was defined in patients with PME; however, Jankovic and Rivera were the first to report the association of hereditary myoclonus and progressive distal muscle atrophy as a separate clinical entity in 1979 [39].

Functional studies in cultured fibroblasts showed that acid ceramidase was reduced in both overall amount and enzymatic activity. Ceramide level was doubled in the patient's fibroblasts. Ceramides are the precursors to complex sphingolipids, which are important for normal functioning of both the developing and mature brain.

A total of 11 affected individuals have been reported thus far, leading to a relatively precise phenotypic characterization [37,40]. The onset of the disorder occurs between 1 and 6 years of age with lower motor neuron disease leading to progressive muscle weakness and soon followed by the occurrence of clinical and EEG characteristics of myoclonus epilepsies. SMA-PME has an inevitable progressive course. The epileptic pattern is characterized by brief myoclonic seizures without loss of consciousness, generalized epileptic seizures and myoclonic jerks, absences with head drop or postural lapses in the upper limbs, atonic seizures. Electromyography (EMG) shows evidence of motor neuron disease despite only mild proximal muscle weakness, and a chronic denervation process while muscle biopsy shows neurogenic atrophy. The EEG shows subcortical myoclonic epileptiform abnormalities which are sensitive to hyperventilation, paroxysmal activity consisting of frequent, diffuse bursts of sharp waves and polyspike and wave complexes. Brain MRI is most often normal or displays mild supratentorial and subtentorial cortical atrophy. Myoclonic seizures are most often refractory to antiepileptic drugs. Variable degrees of cognitive impairment (usually mild) occur [41].Taking into account ongoing therapeutic research for Farber disease, a disease allelic to SMA-PME, screening for *ASAH1*or acid ceramidase activity should be proposed for the diagnosis and future treatment of patients with PME or SMA.

7. MEAK: PME-Ataxia due to potassium channel mutation (OMIM #616187)

This is the most recently described subtype of PME and is caused by a recurrent *de novo* heterozygous mutation in the *KCNC1* (Potassium Channel, Voltage-Gated, Shaw-Related Subfamily, Member 1) gene, which encodes for the Kv3.1 protein (a subunit of the Kv3 subfamily of voltage-gated potassium channels) [42]. MEAK was first described in 2015, when a cohort of 84 unconfirmed, unrelated PME patients was extensively investigated and mutations in the *KCNC1*gene [43] were identified.

KCNC1encodes the highly conserved potassium ion channel subunit of the Kv3 subfamily of voltage-gated tetrameric potassium ion channels [44]·.Previous studies have shown that loss of Kv3 function disrupts the firing properties of fast-spiking neurons [45,46], affects neurotransmitter release [47], and induces cell death [48]. In MAEK the most affected neurons include inhibitory GABAergic interneurons [46] and cerebellar neurons.

MEAK patients generally have a normal early development. The first symptom is usually myoclonus, with an onset ranging from the age of 6–14 years. Myoclonus tends to progressively worsen with time causing gait disturbances. Learning difficulties before seizure onset are not common, while some patients develop mild cognitive impairment following seizure onset. Typical electroencephalographic features comprise generalized epileptiform discharges and, in some cases, photosensitivity. Brain imaging is either normal or shows cerebellar atrophy [42].The early clinical presentation and evolution of MEAK resembles that of Unverricht-Lundborg disease (ULD). MEAK might be clearly distinguished from ULD, as patients with MEAK usually suffer a more severe course.

8. Action myoclonus renal-failure syndrome (AMRF) (OMIM #254900)

AMRF is an autosomal recessive syndrome characterized by progressive myoclonus epilepsy sometimes associated with renal dysfunction. AMRF is caused by the loss of function of the gene *SCARB2* (Scavenger Receptor Class B, Member 2) (* 602257), which encodes LIMP2 (lysosomal integral membrane protein type 2).

LIMP2 is a ubiquitously expressed [49] glyco-protein located in lysosomal membranes. Overexpression of LIMP-2 causes an enlargement of early and late endosomes/lysosomes, impairs the endocytic membrane traffic. These findings support the idea that LIMP-2 plays a role in the biogenesis and maintenance of the endolysosomal system [49]. Moreover, LIMP-2 appears to display a role as a multifunctional receptor at the plasma membrane for the lysosomal delivery of acid hydrolase-glucocerebrosidase (GC) [50].

The predominant clinical manifestations of AMRF are progressive myoclonus epilepsy and renal failure [51–53]. Age of onset ranges between the late teens and early twenties. One of the most important neurological symptoms is the tremor, which starts in the fingers and hands, and it is exacerbated by fine motor activities. The patients later develop involuntary spontaneous action-activated myoclonic jerks and involuntary spontaneous myoclonic jerks at rest. Generalized tonic-clonic seizures occur in the majority of patients [49]. Other common features include ataxia, dysarthria due to cerebellar dysfunction, auditory defects [52] and a rare demyelinating peripheral neuropathy [54]. Cognitive function is preserved or only slightly affected until the final stages of the disease. Renal involvement is heralded by the appearance of proteinuria that can progress to a nephrotic syndrome and end-stage renal disease.

Death occurs usually within 7–15 years after disease onset. The absence of renal involvement in PME associated with SCARB2 mutations has also been described, particularly in Italian patients showing an invariably fatal course [55–57].

EEG shows generalized epileptiform abnormalities [53,56], and background activity slows progressively over the years. Intermittent photic stimulation can trigger bursts of generalized spike-polyspike-wave discharges, often associated with massive myoclonic jerks. Brain imaging studies are usually unremarkable or show diffuse cerebral atrophy and cerebellar atrophy. Widespread deposition of abnormal, extraneuronal brown pigment in the brain, with no neuronal loss or significant gliosis, has been reported [53]. It has been suggested that the pigment consists of lipofuscin-like oxidized lipid or proteolipid [53]. The patients without renal involvement showed different neurodegenerative changes, such as neuronal loss and gliosis in the brain [55].

9. Myoclonic epilepsy with ragged red fibers (OMIM #545000) and Alpers-Huttenlocher syndrome (OMIM #203700)

The two most common mitochondrial epilepsies are MERRF (myoclonic epilepsy with ragged red fibers) and AHS (Alpers-Huttenlocher syndrome, also known as hepatopathic poliodistrophy) [58].

MERRF is a maternally inherited mitochondrial disease and represents a phenotype that can be produced by mutation in more than 1 mitochondrial gene, e.g., MTTK (590060), MTTL1 (590050), MTTH (590040), MTTS1 (590080), MTTS2 (590085), MTTF (590070). Features of the MERRF syndrome have also been associated with mutation in the MTND5 gene (516005).The A-to-G mutation at nucleotide 8344 accounts for 80–90% of MERRF cases [59]. MERRF is a multisystemic disorder with onset occurring during childhood after a period completely normal development, characterized bymyoclonus, episodes of generalized epilepsy, progressive ataxia, and ragged-red fibers (RRF) with partial deficiency of cytochrome c oxidase [58]. Other clinical manifestations include hearing loss, peripheral neuropathy, cognitive decay, short stature, exercise intolerance, and optic atrophy and ataxia.

Less common clinical signs are cardiomyopathy, pigmentary retinopathy, pyramidal signs, ophthalmoparesis, and the appearance of multiple lipomas, particularly in the neck and upper trunk [58].The muscle biopsy shows RRF using modified Gomori trichrome stain [60]. The main neuropathological findings are selective neuronal loss, particularly affecting the dentate nucleus and the inferior olivary nucleus, and widespread gliosis and degeneration of myelinated tracts, including the superior cerebellar peduncles and posterior columns [61].

AHS is caused by homozygous or compound heterozygous mutation in the nuclear gene encoding mitochondrial DNA polymerase gamma (POLG; 174763) on chromosome 15q26. Few recessive mutations have been reported. AHS is characterized by onset in infancy or early childhood often with seizures and/or hypotonia, psychomotor retardation, intractable epilepsy, liver failure, developmental delay and regression, progressive microcephaly and cortical visual impairment with abnormal visual-evoked potentials. Brain MRI may be normal in the initial stage of disease or show progressive cerebral atrophy. Usually, patients die before the age of 3. Most patients experience status epilepticus and the main cause of death are refractory seizures and liver failure [62].

10. Autosomal recessive PME due to impaired ceramide synthesis (OMIM #616230)

Progressive myoclonus epilepsy due to impaired ceramide synthesis is an extremely rare condition, so far reported in a single family of Algerian origin. The patients presented an unusual, severe form of progressive myoclonus epilepsy, characterized by myoclonus, generalized tonic-clonic seizures and moderate to severe cognitive impairment.

This autosomal recessive condition is caused by a homozygous mutation in CERS1 (Ceramide Synthase 1). This gene encodes ceramide synthase 1, a transmembrane protein of the endoplasmic reticulum (ER), that catalyses the biosynthesis of C18-ceramides. The mutation decreases C18-ceramide levels. We cannot exclude that his represents a private mutation within this family.

11. GOSR2-Related PME/Ataxia (OMIM #614018)

Progressive myoclonic epilepsy-6 (EPM6) is an autosomal recessive neurologic disorder caused by mutations in GOSR2 (Golgi Snap Receptor Complex Member 2) (604027). It is characterized by onset of ataxia in the first years of life, followed by action myoclonus and seizures later in childhood, and loss of independent ambulation in the second decade. Cognition is not usually affected, although mild memory difficulties may occur in the third decade [63].

All patients with GOSR2-mediated PME so far reported have a homozygous mutation (c.430 G > T, p.Gly144Trp) in GOSR2 [63,64].

The clinical presentation is characterized by early-onset ataxia, followed by action myoclonus and seizures [65]. Areflexia, scoliosis in adolescence, elevated creatine kinase levels are other clinical features [1]. Mild cognitive decline in the late stages of the disease, and loss of independent ambulation in the second decade and relentless disease course may be observed [65]. All patients exhibited multiple seizure types, including generalized tonic-clonic seizures, absence seizures, and drop attacks [64]. Patients showed highly photosensitive generalized myoclonus that worsened with action or emotional stress [65]. EEG analysis revealed generalized spike-and-slow-wave discharges with a posterior predominance, often with a slow background. The generalized discharges are highly photosensitive [65]. Nerve conduction studies have been reported to be consistent with a mild, predominantly axonal peripheral neuropathy [64]. MRI have displayed essentially normal findings or generalized cerebral and cerebellar atrophy [64].

12. KCTD7-Related PME (OMIM #611726)

Progressive myoclonic epilepsy associated with KCTD7 mutations has been reported in 19 patients from 12 families; these families had variable ethnic origin and showed a high rate of consanguinity (5/12).

The disease is caused by homozygous mutations in *KCTD7*gene (potassium channel tetramerization domain-containing protein 7) at 7q11.21. KCTD7is a member of hyperpolarization of the resting membrane potential and decreases excitability in patch clamp experiments [66]. This is consistent with an epileptogenic effect of a *KCTD7* defect [66].

The disease starts in infancy, between five months and three years of age, after a period of normal or slightly delayed psychomotor development. Patients typically show an initial severe epileptic disorder, with abundant epileptiform discharges on EEG and myoclonic seizures in the foreground, associated with cognitive regression and ataxia. The seizures are described as either myoclonic or generalized tonic-clonic seizures, and they can be precipitated by fever. Other types of seizures (atonic seizures and atypical absences) have also been reported. Epilepsy is drugs resistant. Progressive ataxia was reported in all but one patient. Continuous multifocal myoclonus aggravated by action has been observed in more than half of the cases [67]. After a few years, the disease tends to stabilize, and long survival can be expected. It has been hypothesized that the epileptic disorder may influence the neurological regression observed in patients [68]. All patients have cognitive decline leading to severe dementia. Differential diagnosis may be with the classic late-infantile form of NCL and the rare presence of associated opsoclonus can evoke opsoclonus-myoclonus syndrome. Concerning complementary examinations, EEGs were described to be abnormal and the most common findings were very frequent multifocal and/or generalized spike-waves associated with an excess of slow activity. EEG abnormalities were more prominent in the posterior areas, and intermittent light stimulation evoked generalized or posterior epileptiform discharges. KCTD7-related epilepsy could be considered as an epileptic encephalopathy, a condition in which epileptic activity may contribute to progressive neurological decline, such that effective antiepileptic intervention might improve developmental outcome [69].

13. Gaucher's disease type III (OMIM # 231000)

Gaucher's type III involves a storage of glucocerebroside in various organs. It generally onsets in childhood. The disease is due to a mutation in the GBA (glucosidase beta acid) gene on chromosome 1q21, with a L444 P substitution most common in type III [1].The first symptoms are often saccadic horizontal eye movements and supranuclear gaze paralysis, which can be associated with strabismus, along with generalized or focal seizures. It is usual to observe, in these patients, ataxia, moderate intellectual impairment and low oculo-manual dexterity. Another typical finding is hepatosplenomegaly. The typical PME phenotype is present in only a minority of cases. The EEG shows a normal to slow background activity and bursts of predominantly posterior or multifocal or polyspike waves, with sensitivity to photic stimulation. The somatosensory EP are abnormally enlarged with hearing loss. Diagnosis is due with biopsy or with genetic test. There are increased levels of chitotriosidase in plasma. A life expectancy of more than 10 years can usually be predicted [1].

14. Lafora disease (LD) (OMIM #254780)

Lafora disease is an autosomal recessive progressive myoclonus epilepsy and it was the second of the PMEs to be identified in 1911 by Gonzalo Lafora, depending on the mutations of two genes: EPM2A (Epilepsy, progressive myoclonic 2A)(* 607566), located in chromosome 6q24, that encodes for the Laforin dual specificity phosphatase and EPM2B (NHLRC1, Nhl Repeat-Containing 1 Gene)(*608072) in chromosome 6p22.3 that encodes the Malin ubiquitin E3 ligase, both involved in the complex and not yet completely understood glycogen metabolism leading to the deficiency of Laforin and Malin, respectively. They both seem to contribute equally to the pathogenic variants'

phenotypes. It is particularly frequent in Mediterranean countries (Spain, Italy, France), Northern Africa, Southern India, Pakistan and Middles East, found in 250 families and of these 42% are caused by mutations in EPM2A and 58% by mutations in EPM2B. The prevalence seems to be close to 4 cases per million persons. However, the prevalence may be higher, because of the missed and undiagnosed patients. [70,71].

The most pathogenic variants include the following loss of function mutations: splice site, missense, nonsense and small intragenic deletions and insertions [72].A third gene, PRDM 8 (Pr Domain-Containing Protein 8, *616639), has been reported and it is associated with early childhood onset phenotype [73].The most common *EPM2A* mutation is the R241X mutation, that has been found in the 17% of the patients with EPM2A mutation, and large deletions make up 10–15%. The most common *EPM2B* mutations are the missense mutation P69A and the frameshift mutation G158fs16.

Clinically, LD is a fairly homogenous disease with onset in adolescence (range: 8–19 years; peak: 14–16 years) in otherwise neurologically normal individuals.and neurological decline soon after, but the timing and severity of symptoms can be variable, even within the same families [74]. Genotype-phenotype correlations do not reveal substantial differences between patients with EPM2A and EPM2B mutations, but a few specific EPM2B mutations appear to correlate with a late onset and slow progressing [70,71]. In many cases, the disease shows an insidious near-simultaneous, or closely consecutive, appearance of headaches, difficulties at school, myoclonic jerks, generalized seizures, and visual hallucinations [70,71]. EEG shows a slowing background and spike-wave discharges that do not have the regularity of the JME's spike and polyspike-waves. Focal spikes localized in the occipital regions become apparent and represent an hallmark of the disease. During the final stages of the disease EEG shows long bursts of diffuse spike-waves and fast polyspikes, associated with massive positive or negative myoclonic jerks and enhanced by photic stimulation at low frequency, on a low background activity, predominantly in the occipital area. Myoclonus becomes continuous, progressive, generalized and difficult to control over time [74].Occipital seizures may present as transient blindness, simple or complex visual hallucinations, photo myoclonic, convulsive photo responses or migraine with scintillating scotoma. Not all visual hallucinations are epileptic [74].Important symptoms in the late stages of the disease are progressive dementia, refractory status epilepticus, psychosis, cerebellar ataxia, dysarthria, mutism and respiratory failure, leading to total disability or death 5–10 years after clinical onset [70,71].

Brain MRI is usually unremarkable at onset, however two reported cases FDG-PET revealed posterior hypometabolism during the early stages of the disease [75].

The primary morphological change in LD is the deposition of polyglucosans, which consists of discrete deposits of fibrillary polysaccharides composed of poorly-branched glucose polymers (LBs) [74]. They are typically found in the brain, in the periportal hepatocytes of the liver, skeletal and cardiac myocytes, and in the eccrine duct and apocrine myoepithelial cells of the sweat glands [76]. The gradual overtaking of synaptic cell processes by LB may underlie the epileptogenesis by escalating disturbance of synaptic function. It has also been suggested that there is preferential degeneration of inhibitory interneurons in LD [77].

There are presently two divergent hypotheses of polyglucosan formation in LD: one hypothesis states that the GS enzyme may have an undesirable side reaction, causing the addition to glycogen of phosphates; these phosphates leading to glycogen precipitation and mistructuring through yet to be clarified mechanisms. This hypothesis is supported by laforin's role as a glycogen phosphatase and by evidence that such a GS phosphate-adding side reaction does occur [78]. The other hypothesis considers glycogen phosphorylation as a desirable event. Every once in a while, during glycogen synthesis, a glycogen chain is overextended by GS and such a chain would be phosphorylated to prevent it from wrapping around a neighbor chain. This would attract laforin which would not only bind the phosphoglucan but via malin would ubiquitinate and inhibit GS. Laforin would then remove the phosphate [79].

15. Treatment

At present, PME treatment remains palliative, with the best current therapies having limited success in the modulation of symptoms. AED are the only options for seizures control [80]. The most used is valproic acid, that is usually effective in suppressing, momentarily, most GTCS, the symptoms associated with photic sensitivity, and some of the myoclonus. Other AEDs used are: lamotrigine (LTG) but it is not very advisable in the context of a myoclonic epilepsy; phenobarbital (PB) and primidone (PRM) are effective, but at high doses they have cognitive effects that worse those of the condition; and levetiracetam (LEV). Other helpful drugs include topiramate (TPM) and zonisamide (ZNS), which both have marked antimyoclonic effects. Additional relief can be obtained, often transiently, with ethosuximide, felbamate, and benzodiazepines (BZD). Finally, there have been two recent single case reports of rather dramatic beneficial effects of perampanel [81]. Piracetam (PIR), a more specific antimyoclonic agent, can alleviate the burden of seizures and myoclonus. Specific therapeutic approaches can be discussed in patients with a severe course: vagal nerve stimulation [82] and deep brain stimulation has also been used in PME cases; combined subthalamic and thalamic high-frequency stimulation has brought some relief, especially in the least severely affected cases [83].There is no evidence that carbamazepine (CBZ), oxcarbazepine (OXC), phenytoin (PHT), eslicarbazepine, gabapentin, pregabalin, vigabatrin, or lacosamide are of any benefit and a worsening effect may observed. However, in some cases status epilepticus responds well to phenytoin, but it should not be kept as maintenance medication. With the progression of the PME, AED treatment progresses to polytherapy, with a combination of several of the drugs quoted above. The ketogenic diet has been tried, but without success, in relatively advanced cases [84].

16. Future directions and potential targeted treatments

16.1. ULD

Recently an oligonucleotide therapeutic strategy has been used to replace the gene effect.

A specific locked nucleic acid (LNA) antisense oligonucleotide was designed to block a cryptic 5′ss in intron 1. Overall, this approach allowed the restoration of the normal splicing pattern [85].

Considering AEDs therapy Perampanel have been recent associated with a good response in seizure control in all type of seizures [86].

16.2. Sialidosis

Enzyme replacement therapy is a possible approach to treatment. This treatment has been evaluated on mouse models. In mice, restored neuraminidase activity persisted for some days and it led to a significant reduction of lysosomal storage, however the enzyme could not cross the blood-brain barrier. Furthermore, the injected recombinant protein may have caused sever anaphylactic reactions [87].

16.3. Neuronal ceroid lipofuscinosis

In the last days there have been numerous studies on animal models to develop new treatments for NCLs. The most promising approach is an enzyme replacing therapy. In fact, US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently approved an intracerebroventricularly administered enzyme replacement therapy for neuronal ceroid lipofuscinosis type 2 (CLN2).The first gene

therapy phase 1 clinical trial [88] was done in ten patients with CLN2 disease introducing a gene therapy vector designed to express TPP1 into the brain but there was no slowing of disease progression. International cooperation is now contributing to the collection of natural history data for all NCL types into the DEM-CHILD Database, which will provide data to use in future clinical trials and increase understanding of the spectrum of each type of NCLs [89].

16.4. SMA-PME

Currently, any cure for ACDase deficiency is known. Since SMA-PME is caused by a single gene defect, it is an important subject for gene therapies trials. Many active protocols on animal models are investigating, right now. Anyway, a recent proof-of-concept study using the CHO-derived rhACDase as treatment in animal models with Farber Disease, caused by the same mutation as SMA-PME, has proved promising. Further investigations are required to determine the real effect of these therapies, even in SMA-PME affected patients. [90]

16.5. MERRF

No curative therapy options are available. Fabbri et al. have identified a potential role of the bacterial protein CNF1 in the treatment of mitochondrial diseases. CNF1 is an *Escherichia* Coli protein toxin that activates the family of Rho GTPases. Fabbri et al. have demonstrated the ability of CNF1 to boost mitochondrial ATP production in cells, with an improvement in total cellular ATP content. [91]

16.6. Gaucher disease type III

Enzyme replacement therapies (ERTs) and substrate reduction therapies (SRTs) specific for GD have been used successfully in patients with GD1 since the approval of the first ERT, alglucerase, in 1991; however, these agents have no impact on the neurological symptoms of GD. No treatment is currently with this result [93]. Prospective studies report improvement of systemic manifestations in GD3 patients following treatment with ERT [92].

16.7. Lafora disease

In 2016, the European Commission granted orphan designation and permission to use metformin for the treatment of Lafora disease. Metformin as an activator of AMPK largely used as an antidiabetic disease seems to reduce LB and seizure susceptibility (ref). However, the most exciting approach will be gene therapy for the treatments of the hereditary diseases. Such therapies could be with the use of virus vector for gene replacement or reduce LB with inhibitors of GS at both the mRNA and protein levels. ASO (Antisense oligonucleotides), are emerging as an excellent therapy platform, already used with success in other neurodegenerative disease such as SMA (spinal muscular atrophy); this kind of molecules have the effect to target the mRNA encoding GYS1, PP1 subunit R5 and/or other PP1 subunits with a considerably good effect in mouse model. In particular in LD mouse models has been shown that a mere genetic 50% reduction in GS activity in the brain dramatically reduces, to near completely eliminating, LB. This is accompanied with absence of the neurological abnormalities and neurodegeneration that are otherwise present in these mice [93]. An alternative treatment may be the degradation of LBs by delivery of α amylase fused to a cell membrane penetrating monoclonal antibody.

17. Conclusion

PMEs are currently a topic of great scientific interest, considering the innovative therapeutic strategies that are being implemented in this historical period.

Precision medicine is the future for PMEs and can bring a better outcome for diseases that in the past had been considered quite untreatable.

In particular we believe it was useful for the epileptologist to understand this kind of disease which, although singularly are extremely rare, all together represent a significant percentage of the most serious epilepsies syndromes. The future effort of the research must be to identify new drugs against specific pathogenic mechanisms, or a specific action of mutated proteins, up to a gene replacement therapy.

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