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Emerging treatments for progressive myoclonus epilepsies

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Abstract

Introduction: Progressive myoclonus epilepsies (PMEs) are a group of neurodegenerative diseases, invariably leading to severe disability or fatal outcome in a few years or decades. Nowadays, PMEs treatment remains challenging with a significant burden of disability for patients. Pharmacotherapy is primarily used to treat seizures, which impact patients' quality of life. However, new approaches have emerged in the last few years, which try to curb the neurological deterioration of PMEs through a better knowledge of the pathogenetic process. This is a review on the newest therapeutic options for the treatment of PMEs.

Areas covered: Experimental and clinical results on novel therapeutic approaches for the different forms of PME are reviewed and discussed. Special attention is primarily focused on the efficacy and tolerability outcomes, trying to infer the role novel approaches may have in the future.

Expert opinion: The large heterogeneity of disease-causing mechanisms prevents researchers from identifying a single approach to treat PMEs. Understanding of pathophysiologic processes is leading the way to targeted therapies, which, through enzyme replacement or underlying gene defect correction have already proved to potentially strike on neurodegeneration.

Keywords

Epilepsy; progressive myoclonus; genetics; treatments; neurodegeneration; precision medicine

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1. Introduction

Progressive myoclonus epilepsies (PMEs) are a group of genetically determined neurodegenerative diseases with debilitating evolution, resistance to treatment, and poor prognosis. Despite their broad spectrum of manifestations, PMEs share some clinical findings, such as action myoclonus, epileptic seizures, delay or regression of psychomotor development (especially cognitive), and cerebellar signs [1].

PMEs usually begin in childhood and adolescence and their evolution may be variable, with slow progression in some forms and fatal outcome in others within few years [2]. However, age of onset, the onset symptoms, and the occurrence of epileptic seizures, myoclonus, cerebellar signs, and dementia may vary according to the etiology [1].

Overall, it is estimated that these diseases are responsible for up to 1% of epileptic syndromes in children and adolescents around the world [2]. Unverricht-Lundborg disease (ULD), Lafora disease (LD), myoclonus epilepsy with ragged-red fibers (MERRF), and neuronal ceroid lipofuscinosis (NCL) are prototypes of PMEs, but the diagnosis of specific forms remains challenging because of genetic heterogeneity, phenotypic similarities, and an overlap of symptoms with other epileptic and neurodegenerative diseases [3,4]. Nowadays, advances in molecular genetics have enabled a better understanding of the pathogenesis of these diseases, bringing hope for improved treatment options in the future.

Here, we review the therapeutic strategies in use for various PME and future perspectives in targeted therapy.

2. Search strategy

We performed a systematic search on PubMed using the terms ‘treatment’ or ‘therapeutics’ and ‘myoclonic epilepsies, progressive.’ We included ‘in vitro’ or ‘in vivo’ experimental studies, and clinical trials. Searches cover the period up to December 2019. Only studies published in English were reviewed.

3. Pharmacotherapy

Traditional anti-epileptic drugs (AEDs), such as valproate (VPA), levetiracetam (LEV), and benzodiazepines (BDZs), are widely used as first line to treat myoclonic seizures [5].

Sodium VPA is the most widely used antiseizure drug on the market and exhibits its effects in different ways: it acts on gamma-aminobutyric acid (GABA) levels in the brain, blocks voltage-gated ion channels, and also acts as a histone deacetylase (HDAC) inhibitor [6]. A mean daily dose of 250–1500 mg is usually effective as a first-line in treating myoclonic seizures in both pediatric and adult populations [5]. VPA has been associated with several metabolic and endocrine disorders, thus potentially contributing to increased cardiovascular risk in patients with epilepsy [7].

BDZs, primarily clonazepam (CZP) and clobazam (CLB), are well-established drugs for the treatment of myoclonic seizures in both children and adults. This drug class binds to the

gamma subunit of $GABA_A$ receptors, potentiating GABAergic inhibition [8]. CZP and CLB at a mean dose of 3–6 mg/day and 10 mg/day, respectively, prove effective in reducing seizures [5]; potential shortcomings include tolerance, and adverse events, such as cognitive impairment and sedation [5,9].

Levetiracetam (LEV) has long been used in the treatment of PMEs [10] and 1000–3000 mg/day is a common and effective first-line treatment [5]. LEV binds to pre-synaptic vesicular protein SV2A, inhibiting the release of the neurotransmitter stored within the vesicle; moreover, it inhibits potassium and N-type calcium channels [11,12]. Mood and behavioral problems were reported as treatment-emergent adverse events [13].

4. Dietary treatments

Since the Hippocratic era, fasting has been recognized as a therapeutic treatment for epilepsy. As ketone bodies are molecules produced by the liver during gluconeogenesis, they have been pointed out as the key mediators involved in the anticonvulsant effect of fasting; leading the way to ketogenic diet (KD) as a therapeutic diet in drug-resistant epilepsies [14]. Potential mechanisms of the effectiveness of KD are generally centered around the roles of brain energy metabolism, neurotransmitters, ion channels, neuropeptides, and oxidative stress [15–17]. KD increases the ability of neurons to manage metabolic challenges in the brain, improving neuronal function under stressful conditions and enhancing seizure threshold. Increased ketone bodies may then regulate neuron membrane excitability by activating K2P channels (two-pore domain potassium ion channels) which can seta hyperpolarized resting potential of the cell membrane. Moreover, it has been observed that KD can lead to glutamic acid decarboxylase upregulation which induces GABA synthesis and could alter GABA transaminase activity that inhibits GABA degradation [18,19]. Furthermore, KD increases norepinephrine, which has been shown to have potent anticonvulsant properties [15]. Starting from mouse models, recent studies have also identified the role of gut microbiota as a mediator of the anti-seizure effects of the KD. Germ-free or antibiotics-treated mice took no advantages in seizures threshold from the KD, leading to distort the previous concept that ketosis alone may be sufficient for the KD-mediated seizure control [20]. Nowadays, a > 50% reduction in the seizures is obtained in up to 56% of drug-resistant epilepsy children under classic KD [21,22]. Research, together with the expansion of ‘-Omics’ studies [23], will probably increase our understanding of KD-associate anti-seizure effects, improving patients’ clinical outcomes in the next few years.

4.1. Ketogenic diet in Lafora body disease

LD is a rare, autosomal recessive PME usually occurring during early adolescence and invariably leading to death in a decade. LD is caused by mutations in EPM2A or EPM2B genes, both located on chromosome 6 and encoding laforin and malm, which are involved in glycogen metabolism. Hypotheses suggest that laforin–malin complex could downregulate glycogen chain elongation by targeting glycogen synthase. Furthermore, the interaction of malin-laforin with enzymes is involved in glycogen metabolism by modulation in glycogen phosphorylase. Loss of function of either turns glycogen into an abnormal structure, which becomes insoluble and accumulates as Lafora bodies, which are composed of a dense

aggregate of polyglucosans that differ from glycogen molecules by lack of a regular branching pattern. Lafora bodies accumulate in multiple tissues but are pathogenic only in the brain [24,25]. As the disease is characterized by the accumulated polyglucosan Lafora bodies, it is reasonable that a ketogenic dietary regimen may be capable of reducing glycogen synthesis, decreasing polyglucosan accumulation, and slowing down the disease progression. A pilot study in patients with Lafora body disease showed KD was unable to stop the disease progression. However, the application of this nutritional approach should be further evaluated in larger case series [26].

4.2. Modified Atkins diet in North Sea progressive myoclonus epilepsy

North Sea Progressive Myoclonus Epilepsy (NSPME) is a rare and severe disorder, mostly caused by homozygous mutations in the GOSR2 gene, a Golgi vesicle transport gene, encoding the Golgi SNAP Receptor Complex Member 2 protein. Clinically, NSPME is characterized by progressive myoclonus, early-onset ataxia, areflexia, and seizures, which are relatively mild compared to myoclonic jerks [3]. Anti-epileptic drugs are used to treat both myoclonic jerks and seizures, but the benefits are disappointingly limited [27].

The modified Atkins diet (MAD) is a less restrictive variant of the classical KD and has shown similar benefits in seizure disorders [28]. In an observational prospective study, Egmond et al. (2017) studied the efficacy of the MAD in four NSPME patients, with health-related quality of life (HRQL) as a primary outcome measure. Choosing HRQL as the main outcome measure was the best criteria to evaluate the global effect on the patient, as seizure frequency or blinded rating of myoclonus was considered too limited to evaluate the effectiveness of the diet. One patient reported a significant (40%) improvement in his HRQL after 3 months on MAD. This patient, who was 12 years old at inclusion, then continued the diet for more than 3 years reaching a stable HRQL, despite the invariably progressive nature of his disease.

Therefore, although a larger casuistry is needed, the MAD might be considered in patients with NSPME, as it improves or stabilizes HRQL in this devastating disorder [27].

5. Neuromodulation

Neuromodulation, or neurostimulation, is a palliative treatment option for many patients who have persistent, medically intractable seizures and are not eligible for resective surgery.

Treatment can take the form of peripheral nerve stimulation, such as vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), or deep brain stimulation (DBS) [29,30]. Efficacy outcomes are variable between different techniques, reaching an overall 30–40% reduction in seizure frequency in 3 months. Even better results (up to 50–60% in seizure reduction) can be obtained by a durable, time-continuing, neurostimulation [31].

5.1. Vagus nerve stimulation

Vagus nerve stimulation (VNS) therapy is approved for the treatment of epilepsy and treatment-resistant depression in most countries [32]. Mechanisms of action of VNS are not yet clearly known but acknowledged as multifaceted. Evidence suggests the vagus may play

a role by turning-off the arising of seizures in regions susceptible to heightened excitability. These regions include the limbic system, thalamus, and thalamocortical projections. VNS also increases activity in the locus coeruleus and the raphe nuclei, and moderates the downstream release of norepinephrine and serotonin, both of which have been shown to have antiepileptic effects [33–35].

The current implantable treatment device consists of a small battery-powered stimulator that requires battery removal and replacement approximately every 6 years. A fine wire electrode extends from the device and is wrapped around the cervical vagus (usually the left vagus, because the right innervates the sino-atrial node, and this should require ECG monitoring during implantation and stimulation). Once the device is implanted, it is programmed using a microcomputer, but patients can alter the stimulus program as needed when they feel the onset of a seizure. Stimulation parameters vary widely, but typical treatment for epilepsy and depression uses a range of stimulation of 20–30 Hz, a pulse duration of up to 500 microseconds, and stimulation on-time of 30–90 s followed by 5 min off-time [36,37].

Since PMEs are usually refractory to AEDs, VNS may be an adjunctive treatment option. Some case report studies on VNS in PME patients showed a reduction close to 100% in generalized tonic-clonic seizures and status epilepticus (SE) frequency, as well as a minimal improve in cerebellar signs during a minimum of 12 months follow-up. Moreover, in their 19-year-old patient Hajnsek et al. were able to reduce the myoclonus by changing the duty cycle of VNS (7 s of on-time and 0.3 min of off-time).

In conclusion, even if larger series are needed, VNS may be considered an effective adjunctive treatment in PMEs, acting on symptoms and improving patients' quality of life (QoL) [38–42].

5.2. Deep brain stimulation

Deep brain stimulation (DBS) is a minimally invasive neurosurgical technique, involving implanting electrodes connected to a pulse generator to deliver electrical stimulation to deep brain structures.

Patient candidates to DBS are those with refractory epilepsy who are not eligible for open resective surgery. Furthermore, DBS is indicated in movement disorders such as Parkinson's disease, essential tremor, and dystonia, and has shown potential in treating neuropsychiatric disorders such as depression and obsessive-compulsive disorder [43,44].

DBS targets may vary widely according to the epileptic syndrome to treat [44,45]. In PMEs, inhibition of the subthalamic nucleus (STN) may potentially release the inhibitory effect of the substantia nigra pars reticulata (SNr) on the dorsal midbrain anticonvulsant zone, thus raising the seizure threshold. As a matter of fact, STN/SNr stimulation proved its effectiveness on generalized seizures over a 12 months follow-up period in a PME case report [46]. Once identified the target, how it should be stimulated remains an object of study. Recently, di Giacopo A. et al. showed how monopolar selective stimulation of the SNr was more effective than DBS of either the STN or both targets (STN/SNr) in reducing myoclonus in a patient suffering from PME [47].

DBS is proposed as an effective adjunctive treatment option for PME patients, alternative to VNS. Further case reports and randomized controlled trials will improve understanding of deep brain structure interactions, but STN/SNr looks like the major target, improving patient's QoL either through selective or combined stimulation of its nuclei.

5.3. Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive, magnetic fields-based technique used to induce changes in brain activity [48].

Over the last few decades, studies have focused on the therapeutic potential of rTMS in treating drug-resistant epilepsies. The assumption is that repeated pulses of TMS could either excite or suppress neural activity for a prolonged period of time, thus modulating neuronal activity [49].

The right discharge-frequency to use is still a topic of active investigation; however, studies show higher frequencies (>5 Hz) to have an overall excitatory effect and, conversely, low-frequencies (0.5 Hz) to exert an inhibitory effect on neurons reducing the occurrence of status epilepticus and increasing the onset latency of seizures [49,50].

In 2017 Rossi Sebastiano D. et al. conducted a study involving nine patients with Unverricht-Lundborg (EPM1) to explore the short-term effects of rTMS on action myoclonus. This study proved inhibitory rTMS as a safe and well-tolerated therapeutic approach to reduce the severity of myoclonus [51].

Thus, although pieces of evidence are still limited, rTMS may be considered as an adjunctive therapeutic approach in those epilepsies (such as PMEs) where treatment options repetitively prove ineffective.

6. Immunomodulation

Evidence suggests inflammation and epilepsy are linked to each other in a self-sustaining circle: inflammation increases seizures and seizures themselves cause a positive feedback cycle of inflammation [52].

This complex interplay is much more evident for severe, refractory epilepsies and PMEs are not an exception.

In 2016, Okuneva O. et al. demonstrated how cystatin B (CSTB)-deficient ($Cstb^{-/-}$) mouse model for EPM1 showed a systemic activation of pro-inflammatory pathways [53]. Moreover, neuronal ceroid lipofuscinoses (NCLs) are known as a heterogeneous group of neurodegenerative disorders linked to lysosomal dysfunction, which is closely related to inflammation [54,55].

Traditional immune-modulating and anti-inflammatory therapies (such as ACTH) have repeatedly proved to be effective in drug-resistant epilepsies [52] and new therapeutic strategies have been tested over time.

As a matter of fact, in 2016 Aldrich A. et al. first demonstrated the utility of phosphodiesterase 4 (PDE4) inhibitors in limiting disease-associated attributes of Juvenile neuronal ceroid lipofuscinosis (JNCL) in mice.

PDE4 is an enzyme prominently expressed in the central nervous system (CNS), where it acts by promoting cyclic adenosine monophosphate (cAMP) degradation. Hence, cAMP levels are usually reduced in JNCL, PDE4 inhibitors might augment cAMP levels preventing microglial inflammation and promoting a more stable neuronal homeostasis, with a good safety profile [56].

Simultaneously, Palmieri et al. showed the therapeutic possibilities opened by targeting serine/threonine kinase Akt (protein kinase B) through Trehalose (a disaccharide) in JNCL.

Akt inhibition consequently promotes translocation of the transcription factor EB (TFEB) to the nucleus, where it acts as enhancing pathways linked to cellular clearance and overcoming lysosomal defects [57].

Given the inflammatory phenotype of NCLs, Groh et al. (2017) treated mouse models of NCLs with two pharmacological compounds, already approved for the treatment of much more frequent neuroinflammatory diseases (such as multiple sclerosis).

Fingolimod was administered at a dosage of 0.5 mg/Kg/day, whereas Teriflunomide reached a dose of 10 mg/Kg/day; both compounds were supplied in the drinking water for 5 months. Treatments were well tolerated and reduced neuroinflammation in the CNS, attenuating alterations of the retinotectal system, progression of brain atrophy, and invalidating clinical features such as myoclonic jerks [58].

Therefore, even if pieces of evidence are limited to mouse models and further clinical trials are needed, PDE4 inhibitors, Trehalose, and approved immune modulators such as Fingolimod and Teriflunomide may be an effective therapeutic strategy for NCL patients, improving motor function and disease progression, with potentially inconsistent side effects.

7. Enzyme replacement therapies (ERTs)

NCLs are inherited neurodegenerative lysosomal storage diseases (LSDs). However, causative mutations may vary widely and could affect different genes functionally related to the lysosome [55]. The infantile and late-infantile forms of NCL (INCL and LINCL) are associated with mutations in CLN1 and CLN2 genes, encoding the lysosomal enzymes palmitoyl protein thioesterase-1 (PPT1) and tripeptidyl peptidase 1 (TPP1) [59,60].

Knowing the pathogenesis of INCL and LINCL, enzyme replacement therapies (ERTs) represent the most straightforward cytological approach. Initially, enzymes proved to be effective for non-CNS symptoms but not for neurodegeneration, because when intravenously administered they were unable to cross the blood-brain barrier (BBB); hence, in 2009 Tamaki SJ. et al. tried a novel approach. They transplanted purified human central nervous system stem cells, grown as neurospheres (hCNS-SCns), into the brains of immunodeficient $Ppt^{-/-}$ mouse. The rationale is to provide the deficient enzyme directly into the CNS through

secretion of PPT1 by the grafted cells. As a result, the authors observed reduction of stored materials in the lysosomes, delayed loss of motor coordination and broad neuroprotection of host cells in the hippocampus and cortex. Hence, as hCNS-SCns could appropriately integrate into the brain, they could be considered as a safe, early-to-administer, therapeutic option for INCL [61].

The first-in-human clinical trial of allogenic hCNS-SCns transplantation was conducted in 2013 on six patients (4 males and 2 females). By protocol, eligible patients were 18 months to 12 years of age with mutations in either the CLN1 or CLN2 genes, clinical manifestations consistent with INCL or LINCL, lysosomal enzymes PPT1 or TPP1 deficiency, cerebral mantle thickness greater than 20 mm, and significant cognitive and developmental dysfunction as measured by the Bayley Scales of Infant Development (BSID-II) and the cognitive assessment system (CAS).

The trial design was impacted by ethical considerations requiring testing in the setting of a fatal disease and enrollment of patients with an advanced cognitive disability. In this context, demonstrating safety was the primary objective, as the severe neurological impairment of the patient population was expected to limit the measurement of clinical activity.

Patients were assigned sequentially in groups of three to low- and high-dose HuCNS-SC cohorts. Cell doses were based on allometric scaling (by brain weight) and safety margin from cell doses tested in mice and non-human primates. Frameless stereotactic navigation was used to target eight injection sites: medial frontal, lateral frontal, and central parietal for the subcortical sites, and immediately precoronal for ventricular puncture. This pattern of transplant sites covered a large geographic region of each cerebral hemisphere while avoiding eloquent cortical structures. Intracortical injections were not possible due to the presence of severe cortical atrophy. During follow-up, neurological and neuropsychological deterioration resulted in line with the expected natural course of the disease. Moreover, evidence of donor cells engraftment in 2 of 3 postmortem brains at 357 and 918 days post-transplantation demonstrated durable persistence of hCNS-SCns, recapitulating results of preclinical in vivo investigations.

In summary, as the surveillance protocol revealed no apparent transplantation-related serious adverse events and the discovery of transplanted cells in postmortem host brain years after implantation suggests a durable effect based on a single intervention, hCNS-SCns transplantation may be considered as a safe and potential treatment for selected subtypes of NCLs [62].

In 2018, Schulz A. et al. overcame the limit of the BBB by directly instilling Cerliponase Alfa, a recombinant form of TPP1, into the cerebral ventricles. Twenty-four CLN2 patients, aged between 3 and 16 years (mean 60 ± 15 months), were enrolled in the study and underwent surgical implantation of a ventricular reservoir. After 96 weeks of treatment, patients showed a slowing-down of the motor-language deterioration (assessed through the Clinical Rating Scale), together with convulsions, pyrexia, and vomiting as concomitant mild adverse events (ADEs). Serious ADEs included implanted device infections, and hypersensitivity adverse events (HAEs). As infections could be treated with antibiotics and

device replacement, and HAEs were less severe with antihistaminic premedication, intraventricular instilled Cerliponase Alfa proved potentially effective in restoring symptoms. Further studies will subscribe its efficacy in preventing the onset of symptoms in early-treated patients [63,64].

8. Gene therapies

Gene therapy is designed to introduce genetic material into cells. Thus, if a mutated gene causes a necessary protein to be faulty or missing, a carrier (called vector) will deliver a normal gene copy, restoring the function of the protein. In treating epilepsy, gene therapy has to deal with the BBB, which prevents genetic vectors from entering the brain from the bloodstream. Consequently, CNS gene therapy may be sorted by the characteristics of gene delivery vehicles, but an invasive approach is often needed.

The ultimate goal remains long-term expression of the transferred genes, achieving not only a sustained anticonvulsant but also an antiepileptogenic effect [65,66].

8.1. Viral vectors

Adeno-associated viruses (AAVs) belong to the Parvoviridae family and were initially discovered as a contaminant of adenovirus preparations, hence their name. AAV biology proved to be outstanding for creation of the ideal recombinant genetic vector. This is why, today, recombinant AAVs (rAAVs) are the leading platform for in vivo gene therapies [67].

A phase I study of LINCL using an AAV was firstly conducted in 2010. Selection criteria allowed 10 children to be included in the study and neurosurgical target sites were selected based on preoperative MR imaging studies. As the major goal was to achieve a diffuse distribution of the injected virus, the authors identified three main entry sites over the frontal, midfrontal, and parieto-occipital regions of each cerebral hemisphere. Postoperative FLAIR MR imaging was then performed to assess the targeting of infusion sites. Within 24 hours after surgery, ‘positive’ target sites demonstrated an increased FLAIR signal. Success was achieved in 65% of sites (39 out of 60, considering 6 sites for each patient). However, it is likely that the absence of signal at some sites may not reflect fail but indicates more widespread delivery with a concomitant reduction in the focal concentration necessary for a change in imaging signal. At present, there is no method to distinguish between these different possibilities; neither there is an in vivo methodology for monitoring the distribution of therapeutic compounds. No patient experienced peri-operative subdural hemorrhage, despite the risk connected to cerebral atrophy. Moreover, rAAVs vectors contained no viral genes, evoking a minimal inflammatory response.

In summary, the neurosurgically delivered gene therapy used in this limited clinical study was practical and safe, supporting the potentialities of this kind of approach in treating NCLs [68]. Recently, further efforts led to test less invasive administration ways of rAVVs vectors. In 2019 Kleine Holthaus SM et al. showed neonatal bilateral intra-cerebro-ventricular injections of rAAVs vectors to increase lifespan and reduce neurodegeneration in mouse models of NCLs [69]. These results are encouraging and confirmed by a previous study on canine models of NCLs [70]. However, this approach has no impact on the

systemic co-morbidities of such diseases, indicating that systemic administration ways of rAAVs will be needed [71].

8.2. Non-viral gene therapy

Viral vector-based gene therapy clinical trials are limited by the slight inflammatory response induced in the CNS. Moreover, additional concern derives from insertional mutagenesis, because integrating viral DNA might disrupt the expression of tumor suppressor genes or activate oncogenes leading to malignant transformation of cells. Some of these issues may be overcome by non-viral gene therapy. Firstly, non-viral vectors tend to have low or null immunogenicity, due to the absence of adaptive immune system activation as is the case with some viral systems. In addition, non-viral gene therapy routinely uses expression vectors that do not integrate within the DNA, reducing the risk of insertional mutagenesis.

Among non-viral approaches, lipid-based vectors to transport pDNA or RNAs are the most widely used. Non-viral vectors carrying genome editing systems are feasible platforms to permanently correct disease mutations. Therefore, considering their demonstrated bio-safety, low cost, and ease of production, non-viral vectors have important advantages over viral approaches and are a promising tool for both precise and permanent correction of disease genes [72,73].

8.3. Antisense oligonucleotides (ASOs) therapies

Antisense technology is based upon the conceptual use of single-stranded DNA sequences to hybridize specific complementary mRNA, and thus inhibiting the process leading to protein formation. However, this theoretical simplicity is matched with difficulties in the laboratory and clinical use of ASOs. Firstly, synthetized oligonucleotides have to face rapid degradation provided by endo- and exonucleases; secondly and more importantly, ASOs must have a structure, comprising residues and electric charges, suitable for a stable and selective oligonucleotide/mRNA complex.

Once bound to targeted mRNAs, oligonucleotides can either promote RNA degradation or prevent the translational machinery through occupancy-only mechanism, referred to as steric blocking [74].

As abnormalities of CSTB mRNA are common effects of various mutations in EPM1, Matos L. et al. (2018) developed an ASOs approach to investigate the possible mitigation of the splice defect present in a Portuguese patient.

The EPM1 patient addressed was homozygous for the c.66 G > A CSTB mutation, which does not alter the coding amino acid sequence (p. Q22Q) but activates a cryptic splice site downstream in CSTB intron 1. As a consequence, patient-derived fibroblasts showed both normal transcript with the synonymous G > A change at the last nucleotide of exon 1 and a mutant one partially including intron 1 due to activation of the cryptic splice site. Once the transcript is not degraded, it gives rise to a truncated protein.

Authors designed a specific locked nucleic acid (LNA) ASOs to complementary target the cryptic donor splice site in intron 1 of CSTB, and redirect splicing. As expected, patient's treated fibroblast expressed only the normal spliced transcript, with normal CSTB protein levels. Moreover, the recovery was LNA dose-specific, without evidences of increased cell death [75].

Recently, the feasibility of ASOs-based approaches was definitively proved by Kim J. et al. Identification of missplicing of exon 6 (i6) in the CLN7 gene causing NCL in their 6-year-old patient allowed researches to design a specific ASO to directly correct the splicing defect. Results proved encouraging showing a remarkable (>50%) reduction in seizure frequency and duration, combined with an excellent safety profile. Therefore, although evaluation of the neurodegenerative profile is limited by the advanced stage of the patient's disease [76], and further assessments will be needed in the next few years, the possibility to translate this technology into the clinical practice is becoming real.

8.4. Mitochondrial tRNA modification

Human mitochondrial disorders are generally caused by mutations in mitochondrially encoded tRNAs, responsible for the synthesis of proteins from mitochondrial DNA (mtDNA), thus participating in the processes of oxidative phosphorylation (cells' energy metabolism). These mutations may induce cell-specific stress responses, partly explaining the wide clinical heterogeneity of these disorders [77–79].

A prototype of mitochondrial disease is myoclonus epilepsy with ragged-red fibers (MERRF).

Clinically characterized by a variable mixture of myoclonus, ataxia, generalized seizures, and the hallmark presence of RRFs in muscles, MERRF is known since '90s to be mainly caused by the transition mutation m.8344A>G in the mitochondrial tRNA Lysine (Lys) gene [80].

About twenty years later, Richter at al. used a quantitative RNA sequencing approach to finally try to investigate and understand the basis of tRNA modification in-human mitochondrial disorders. The study revealed mutant $tRNA^{Lys}$ to lack N1-methyladenosine at position 58 (m^1A58) which is fundamental to introduce a positive charge in the tertiary structure of the protein and thus compromising translation, elongation, and stability of nascent chains. The restoration of the m^1A58 in the $tRNA^{Lys}$ of patients' myoblasts, through overexpression of the m^1A58 methyltransferase (retroviral transduction of TRMT61B cDNA), proved to be effective in increasing the synthesis of mitochondrial nascent chains and preventing the formation of aberrant proteins. Therefore, although understanding of mitochondrial tRNAs' functions understanding is still at its beginning, this work may be considered as the first proof of principles, demonstrating the possibility to concretely act on mitochondrial diseases in the future [79].

8.5. Protein therapy

BBB is the ultimate great drawback to the treatment of neurological disorders. In 1999, Schwarze and collaborators from the Washington University School of Medicine

demonstrated the protein transduction domain (PTD) of HIV-1 TAT protein to be able to transfer linked proteins through biological structures, including BBB, in living animals [81]. Following this direction, further studies have deepened our understanding of PTD-tat-linked proteins delivery through membranes, identifying in the heparin-binding properties of PTD-tat the goal for in vivo material translocation [82–84]. However, it was only in 2006 that a PTD-tat approach was tested in PME. The authors used PTD-tat-linked CSTB to eventually prove the potential of protein therapy in cultured cell models of EPM1. The choice of using CSTB and EPM1 was not casual. CSTB is a small cytoplasmic protein, not requiring organellar passaging or modifications; moreover, EPM1 patients express small amounts of CSTB; thus, no immune response is expected against the supplemented protein. Despite initial positive results, PTD-tat-CSTB proved not to localize at the nucleus. False-positive results are a risk while working with PTD-tat, but it is also possible that the true limiting barrier is not the BBB but the cell membrane. PTD-tat-fusion proteins could be able to pass through the gaps between the endothelial cells of the BBB and, once on the brain side of the barrier, they could not enter neurons. In conclusion, PTD-tat for protein therapy remains a possible treatment option, but further studies are needed, and it will not likely be used for the treatment of diseases like EPM1 [85].

9. Conclusions

PMEs group different neurological disorders displaying clinical flags of an underlying neurodegenerative process. Despite efforts in fasting the diagnostic process, treatment of PMEs remains primarily palliative, trying to abate seizures and myoclonus which severely affects patients' QoL beyond the underlying disease process. Traditional AEDs, such as VPA, LEV, and BDZs are invariably the initial therapeutic approach for action myoclonus and seizures [4]. However, both monotherapy and combination of different drugs usually fail in managing all the disabling clinical symptoms; hence, the need for adjunctive treatment options. Whereas traditional treatments such as the Ketogenic Diet prove relatively unsuccessful for PMEs, promising therapeutic approaches, seem to come from the Neuromodulation field. Both VNS and DBS proved effective, reducing seizures and/or myoclonus in patients not fully managed with pharmacotherapy. Great expectations primarily come from those therapies addressing the etiology, which are meant to impact on disease progression, such as enzyme replacement and gene therapy. Clinical studies are still limited, but open perspectives of a multidisciplinary approach for a patient-based therapeutic treatment, which could be the real answer for these disabling diseases.

10. Expert opinion

PMEs are clinically and pathogenetically heterogeneous disorders; however, if some shared clinical symptoms can be recognized and are mandatory to allow classification, no single pathogenetic mechanism can be identified. Pathophysiology proves essential to eventually treat diseases and this wide heterogeneity leads to a broad range of treatment options (Figure 1). Going beyond a palliative treatment approach of PMEs requires a fine understanding of biological processes. Thus, if a categorical diagnosis was previously accepted, nowadays gene hunting and identification of causative mutations prove essential to identify the most targeted therapy. Substitutive enzyme and gene therapy proved to be the first effective

precision therapies to potentially modify the course of the disease. In the last years, translational research provided clinics with a toolbox of methods to intervene on genetic defects of different types. These methods urge a change in our treatment paradigm. Target not the symptoms but the etiology, and not the gene but the specific genetic defect, with the appropriate tool. To this aim, functional studies on the role of physiologic protein and the consequences of its mutations are crucial to identify the correct intervention strategy. Similarly, the earliest diagnosis can allow to anticipate treatment at a pre-symptomatic stage.

Actual limitations, provided by our little understanding of exogenous DNA integration and cross-relation with native DNA, will be undoubtedly overcome in the next few years by increasing knowledge. Concerns of in-human application may also derive from the invasive, neurosurgical approach mostly needed to deliver genetic material into the brain; a cost–benefit ratio could be undertaken, highlighting potential results in contrast with the invariable progressive nature of PMEs. On the other hand, less invasive and more feasible delivery system techniques will be needed if we think of a much more wide application of gene therapy, also in non-progressive disorders.

Currently, target approaches carry high economical costs and are hardly affordable for public health providers or private patients. These costs can be eventually cut by standardized drug development platforms; by implementing the scalability of these tools, so that they can be more quickly redirected toward different targets; by standardizing the delivery systems, to facilitate the approval by regulatory agencies. On the other hand, potential novel treatments for various PMEs can derive from a re-targeting of existent approved pharmaceutical compounds. High-throughput screening (HTS) systems of extensive libraries of drugs represent a cheaper and faster way to identify novel-specific purposes for already known drugs, given a proper outcome measurement (e.g. stimulate or inhibit a gene expression, a metabolic pathway, etc.).

Further clinical and experimental data will be provided in the next few years, widening our perspective and possibilities of a routinely clinical administration of currently straightforward approaches. The challenge to heal neurodegenerative disorders will continue, together with the hope for the earliest approach, potentially able to even cut the onset of symptoms. In this way, a collaborative strategy between clinicians and research laboratories will become a common way to relate to these diseases, with early diagnosis and treatment specifically designed for patients.

In the next few years, promising ‘in vivo’ tested approaches will undoubtedly be a subject of further research and clinical trials. Larger studies will provide even stronger evidence on the feasibility of targeted, patient-based, therapeutic approaches. Expansion of genetics, biology, and understanding of diseases’ pathophysiology are necessary steps toward a wide application of innovative therapeutic strategies into the every-day clinical practice. Furthermore, if striking on neurodegeneration will always remain the major goal of newest therapeutic strategies, the common underlying mechanism of disease (e.g. inflammation) may gain rise in the next 5 years, allowing treatments able if not to heal but to relief symptoms of pathogenetically heterogeneous diseases. Therefore, future studies will impact

on patients' QoL, invariably leading to a less burden of disease for those patients already affected and bringing hope for therapeutic possibilities in affected newborns.

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Article highlights

- Progressive myoclonus epilepsies (PMEs) are a heterogeneous group of disabling, neurodegenerative disorders, affecting children and adults.
- Palliative treatments, mainly directed towards symptoms control, remain essential to improve patients' quality of life.
- Target therapies have the potential to curb neurological deterioration through a better understanding of PMEs' finest pathogenetic processes.

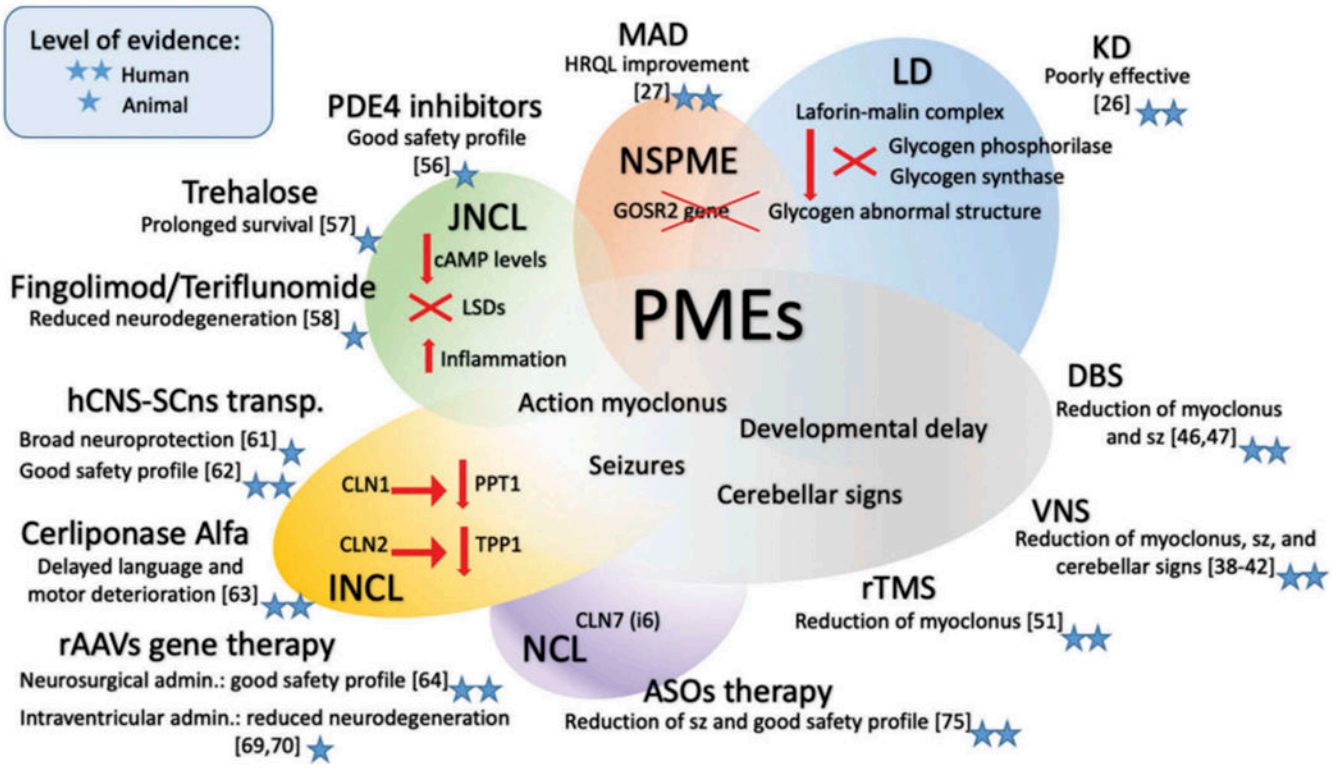

Figure 1.

PMEs = Progressive myoclonus epilepsies; LD = Lafora disease; KD = Ketogenic diet; NSPME = North Sea Progressive Myoclonus Epilepsy; GOSR2 = Golgi vesicle transport gene; MAD = Modified Atkins diet; HRQL = Health-related quality of life; JNCL: Juvenile Neuronal Ceroid Lipofuscinosis; cAMP = Cyclic adenosine monophosphate; LSDs = Lysosomal Storage diseases; PDE4 = Phosphodiesterase 4; INCL = Infantile Neuronal Ceroid Lipofuscinosis; PPT1 = Palmitoyl protein thioesterase-1; TPP1 = Tripeptidyl peptidase 1; hCNS-SCns = Human Central Nervous System Stem Cells, grown as neurospheres; transport. = transplantation; rAAVs = Recombinant Adeno-associated viruses; admin. = administration; NCL = Neuronal Ceroid Lipofuscinosis; CLN7 (i6) = missplicing of exon 6 in the CLN7 gene; ASOs = Antisense oligonucleotides; sz = seizures; rTMS = Repetitive Transcranial Magnetic Stimulation; VNS = Vagus Nerve Stimulation; DBS = Deep Brain Stimulation.