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Update on Pharmacological Treatment of Progressive Myoclonus Epilepsies

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Abstract

Background—Progressive myoclonus epilepsies (PMEs) are a group of rare inherited diseases featuring a combination of myoclonus, seizures and variable degree of cognitive impairment. Despite extensive investigations, a large number of PMEs remain undiagnosed. In this review, we focus on the current pharmacological approach to PMEs.

Methods—References were mainly identified through PubMed search until February 2017 and backtracking of references in pertinent studies.

Results—The majority of available data on the efficacy of antiepileptic medications in PMEs are primarily anecdotal or observational, based on individual responses in small series. Valproic acid is the drug of choice, except for PMEs due to mitochondrial diseases. Levetiracetam and clonazepam should be considered as the first add-on treatment. Zonisamide and perampanel represent promising alternatives. Phenobarbital and primidone should be reserved to patients with resistant disabling myoclonus or seizures. Lamotrigine should be used with caution due to its unpredictable effect on myoclonus. Avoidance of drugs known to aggravate myoclonus and seizures, such as carbamazepine and phenytoin, is paramount. Psychiatric (in particular depression) and other comorbidities need to be adequately managed. Although a 3- to 4-drug regimen is often necessary to control seizures and myoclonus, particular care should be paid to avoid excessive pharmacological load and neurotoxic side effects. Target therapy is possible only for a minority of PMEs.

Conclusions—Overall, the treatment of PMEs remains symptomatic (i.e. pharmacological treatment of seizures and myoclonus). Further dissection of the genetic background of the different PMEs might hopefully help in the future with individualised treatment options.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or other-wise.

Keywords

seizures; epilepsy; antiepileptic drugs; myoclonic jerks; therapy; photoparoxysmal response

1. INTRODUCTION

Progressive myoclonus epilepsies (PMEs) are a group of rare conditions accounting for < 1% of all epilepsies [1,2]. PMEs feature a combination of myoclonus, seizures, variable degree of cognitive impairment and other/focal neurological deficits [3]. Age at onset varies from infancy to adulthood among different diseases and the course is progressive [2]. The leading symptom is represented by myoclonus, a sudden, brief (shock-like), involuntary muscle jerk resulting from a burst of muscular activity (positive myoclonus) or from brief cessation of ongoing muscular activity (negative myoclonus) [4]. Myoclonic jerks may manifest at rest, when maintaining a posture or, more commonly, during action; moreover, they can be either spontaneous or provoked by specific stimuli such as intermittent light stimulation [5,6]. Many seizure types may occur in PMEs, the most common being generalized (especially tonicclonic and absence) seizures, although focal seizures may occur in some PMEs (i.e.: visual seizures in Lafora disease: LD) [7,8]. Photosensitivity occurs in nearly all PMEs (including Gaucher's disease and myoclonic epilepsy with ragged red fibers: MERFF) [9] and may be quite severe and disabling in some PMEs. At the onset of disease, photosensitivity can be very prominent, leading to misdiagnosis of idiopathic generalized epilepsy or occipital epilepsy. Seizure frequency is extremely variable (ranging from occasional to daily) among PMEs and epilepsy may be intractable [7]. Several pathologies with different patterns of transmission can cause PMEs, the most common being Unverricht-Lundborg disease (ULD) and LD, followed by neuronal ceroid lipofuscinoses (NCL), MERRF and sialidosis [7,10]. Despite extensive investigations, a number of PMEs remain undiagnosed [10]; nonetheless, recent genetic advanced techniques such exome-sequencing lead to a reduction of unsolved cases [11].

Of note, clinical trials are difficult to perform in PMEs due to the rarity of these conditions and to the lack of specific instruments for the evaluation of disease severity and evolution [12,13]. Moreover, the progression of symptoms makes challenging to assess patients initially responding to AEDs.

In this review, we will focus on the current pharmacological approach to PMEs. Alternative treatments (such as vagus nerve stimulation, deep brain stimulation, ketogenic diet) have been reviewed elsewhere [13] and will not be treated herein.

2. REVIEW OF THE LITERATURE

Medical publications concerning pharmacological treatment of PMEs were reviewed. References were identified by searches of PubMed until February 9, 2017 with the terms "progressive myoclonus epilepsy", "myoclonic epilepsy", "myoclonus", alone or in combination with "treatment", "management", "antiepileptic drugs" (AEDs), "valproic acid or valproate" (VPA), "zonisamide" (ZNS), "benzodiazepines" (BDZ), "clonazepam" (CNZ), "clobazam" (CLB), "piracetam" (PIR), "levetiracetam" (LEV), "brivaracetam" (BRV),

"phenobarbital" (PB), "primidone" (PRM), "phenytoin" (PHT), "topiramate" (TPM), "lamotrigine" (LTG), "perampanel" (PER), "carbamazepine" (CBZ), "gabapentin" (GBP), "tiagabine" (TGB) and "vigabatrin" (VGB). Articles were also identified through searches of the authors' own files. Selection criteria were newness, importance, originality, quality, and relevance to the scope of this review.

3. RESULTS

The majority of available data on the efficacy of antiepileptic medications in PMEs are primarily anecdotal or observational, based on individual responses in very small series. Of course, polytherapy might conceal positive effects of individual drugs. Most literature evidence comes from studies on ULD, which represents the most common and less severe form of PMEs [14 -16]. So far, the treatment of PMEs remains symptomatic (i.e. pharmacological treatment of myoclonus and seizures), since there is no etiologic treatment for most PMEs. Pharmacological treatment of PMEs usually relies on a combination of ≥ 2 AEDs [2]. Evidence from many PMEs series [14, 17–20] shows that the drug of choice is usually VPA, due to its high effectiveness on myoclonus, seizures, and photosensitivity [21,22]. One exception is represented by mitochondrial disorders such as MERFF, due to the known interaction of VPA with mitochondrial respiration and metabolism [23]; however, if administration of VPA is considered for patients with these disorders (e.g.: subjects with severe, intractable myoclonus) supplementation with L-carnitine should be recommended [23]. VPA (20-40 mg/kg/day) tolerability is usually good, and common side effects may include drowsiness, nausea, weight increase, postural tremor. Evidence for the usefulness of VPA in PMEs was given by Iivanainen and Himberg [24] in an open-label prospective study on 26 Finnish patients, most of whom probably affected by ULD (study conducted in pre-molecular era). All these patients were first receiving AEDs polytherapy that could include some drugs potentially aggravating myoclonus such as PHT and CBZ. At study onset, all the drugs were stopped and a combination of VPA and CNZ was started; PB was added if generalized tonic-clonic seizures (GTCS) persisted. Patients showed a dramatic improvement in myoclonus severity and GTCS frequency, and benefit persisted in 73% of patients at 6-year follow-up; of course, the striking improvement could also be due to the withdrawal of potentially aggravating drugs, or to a synergic action of VPA with CNZ.

BDZs, especially CNZ (0.5-10 mg/day), are frequently administered as add-on treatment for their efficacy on myoclonus. Evidences on their efficacy were firstly provided by the abovementioned trial [24]. Due to the possible development of tolerance, some patients may need dose adjustments after a few weeks or months. Alternatively, in case of reduced efficacy, a shift with other BDZ, such as CLB or nitrazepam, can be attempted [13]. Of note, ULD patients who abruptly withdraw a long-lasting treatment with CNZ may experience myoclonic status epilepticus (personal observation by one of the authors, EF). The most common side effects include drowsiness and detrimental influence on cognitive function. This latter aspect may compromise patients' quality of life.

Pyrrolidone derivatives (the ancestor of which is PIR), have long been used for the treatment of PMEs due to their effectiveness, good tolerability profile, and low drug-drug interactions. PIR (2–40 g/day) represents a very useful antimyoclonic agent. In a placebo-controlled

double-blind crossover trial on 21 patients, Brown et al. [25] demonstrated the usefulness of PIR at the dose of 2.4-16.8 g daily in cortical myoclonus due to various causes. A multicenter, randomized, double-blind, placebo-controlled trial showed that PIR, significantly reduced myoclonus and improved gait with a dose-dependent effect [26]. In an open-label study on 12 PME patients [27], add-on PIR at high doses (up to 45 g/day) caused marked and sometimes spectacular improvement that maintained in some patients for up to 7 years, without significant adverse effects. Nevertheless, some patients experienced efficacy reduction after some weeks. Fedi et al. [28] evaluated long-term (up to 18 months) efficacy and tolerability of add-on PIR in 11 patients with advanced PMEs (ULD in 2, LD in 3, MERFF in 3, sialidosis in 1, undetermined in 2). A statistically significant improvement in myoclonus severity was observed mainly during the first 12 months; side effects were rare, mild, and transitory. Of note GTCS frequency and severity did not modify. Currently, PIR is almost discarded for different reasons. Firstly, newer available pyrrolidone derivatives such as LEV are effective not only on myoclonus but also on different seizure types and photosensitivity [29,30]. Secondly, some patients are poorly compliant with PIR treatment, due to the high number of daily administrations required and for the elevated cost, usually not reimbursed by National Health Services (as an example, in Italy the monthly cost for PIR 30 g/day is around 300 €).

LEV (1000-3000 mg/day), the s-enantiomer of PIR, has shown to be effective in different PME series [31–38]. Good tolerability and low interactions are important advantages of LEV pharmacological profile. In the widest of these series [34], efficacy and tolerability of add-on LEV were retrospectively evaluated on 13 ULD subjects. The study demonstrated the good efficacy and safety of LEV, since 8 patients had a significant improvement of myoclonus, and only 1 patient dropped-out (due to drowsiness and restlessness). Of note, in patients shifting from high-doses PIR to LEV, myoclonus worsening could occur. In these subjects, a combination of moderate doses PIR (6-15 gr/day) with LEV (2-3 gr/day) represented a useful strategy [34]. Finally, LEV should be considered in PMEs with myoclonic status epilepticus [39]. Brivaracetam (BRV) is a selective, high-affinity synaptic vesicle protein 2A ligand reported to be 10- to 30- fold more potent than its n-propyl analog LEV [40,41], has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2016 as an add-on treatment for adult patients with partial seizures. BRV may be potentially useful in the management of PMEs. However, two randomized, double-blind, placebo-controlled trials assessing the efficacy and tolerability of adjunctive BRV (5-150 mg/day) as an add-on treatment in 101 ULD patients did not report a significant improvement of myoclonus [12]. Of note, these trials had some limitations, consisting in the small sample size, the variability of disease duration (ranging from 2 to 50 years), and, therefore, a potentially reduced treatment response in subjects with longer disease duration; finally, the majority of patients were on PIR or LEV (both acting as SV2A ligands like BRV) immediately before or during the trial, with probable saturation of these binding sites able to prevent additional effect. Of note, BRV is very effective in suppressing photosensitivity [42].

Different studies suggest that ZNS (100-500 mg/day), a Na+ and T-type Ca++ channel blocker, should be considered a useful agent in the treatment of PME [19, 43–45]. In the series by Kyllerman & Ben-Menachem [43], 7 PMEs patients (6 with ULD, 1 LD), mostly

receiving VPA+CNZ, were treated with add-on ZNS. Five out of 7 experienced a striking long-lasting improvement of myoclonus and decreased frequency of GTCs. Unfortunately, in 3 of these subjects (including the only 1 with LD), disease progression lead to further deterioration of these abilities after a few years. An open-label trial by Vossler et al. [19] evaluating a 16-week add-on treatment with ZNS (6 mg/kg/day) in 30 patients with PMEs (mostly ULD, MERFF and NCL), showed >50% reduction of “myoclonic seizures” in about half of the subjects; 5 patients discontinued ZNS for side effects (anorexia, drowsiness, asthenia). In a short-term (6-8 weeks) multicentre, open-label trial by Italiano et al. [45] evaluating add-on ZNS (6 mg/kg/day) in 12 ULD subjects, a significant reduction of myoclonus severity (evaluated by mean of UMRS scale) was observed. Only two patients showed reduction of ZNS efficacy a few days after the end of the trial. Moreover, ZNS was generally well-tolerated and only 2 patients dropped-out due to mild adverse effects. Finally, a complete suppression of photoparoxysmal response in a patient with ULD has been reported [44].

PB (and its structural analogue primidone) (up to 300 mg/day) is usually reserved to patients with resistant disabling myoclonus [24]. Efficacy on GTCS has been suggested by some studies [24, 46]. Particular attention should be paid to the inhibitory effect of VPA on PB elimination, resulting in PB accumulation and in- creased somnolence.

A small series [47] and 1 individual case report [48] suggested TPM (at 3-6 mg/kg/day, 200-400 mg/day) as a therapeutic option in PMEs. Mechanisms of action of TPM include Na^+ - channel and AMPA-receptor blocking activity as well as GABA-ergic effects. In the open-label trial by Aykutlu et al. [47] 5 out of 8 PME patients (5 with LD; 3 unknown) experienced improvement of myoclonus and seizures. However, drug was discontinued in 2 out of these 5 pa-tients because of intolerable side effects (cognitive decline and vomiting).

PER (4-12 mg/day) is a new antiepileptic drug. Its mechanism of action consists in the selective blockade of AMPA receptors. It has been approved by FDA and EMA as an add-on treatment of partial seizures and of primary GTCS (in the setting of idiopathic generalized epilepsies) in patients older than 12 years. Two single case reports [49,50] and 2 open-label studies [51, 52] suggest its potential use in PMEs. Schorlemmer et al. [49] described a 21-year- old bedridden patient with LD on VPA LEV, ZNS, CNZ, PIR, and ketogenic diet, who experienced a drastic improvement of myoclonus and seizures with PER at 3-month-follow-up. Dirani et al. [50] prescribed PER to a 15-year-old LD girl in whom previous treatment with VPA, LTG, TPM, LEV and CNZ were abruptly stopped a few days before. PER at 10 mg/day was started with improvement of myoclonus and seizures at 1-month-follow-up. In the series by Goldsmith and Minassian [51], 10 LD subjects (disease duration 2-27 years) were given adjunctive PER (4 to 10 mg/day, mean dose 4.7mg/day): myoclonus drastically improved in 7 patients (follow-up duration: 9 months), seizure-frequency reduced in 4, while disability and cognitive functions did not improve in any patient. Three subjects dropped-out for side effects (irritability, cognitive slowing, weakness, headache) or inefficacy. PER was quite effective in suppressing photoparoxysmal response in these patients. Crespel et al. [52] evaluated adjunctive PER (dose at last follow-up: 2-8 mg/day; median follow-up: 16 months) in 11 patients with ULD and 1 patient with KCNC1 mutation. All subjects had disabling disease related to severe action myoclonus (12 patients) or frequent seizures

(generalized clonic or tonic-clonic) (6 patients). Ten patients (83%) had a clear-cut reduction of myoclonus severity evident as soon as with 2 mg/day, while 6 patients (100%) experienced seizure disappearance. However, psychological or behavioural side-effects (irritability, anxiety, depression) occurred in 50% of subjects leading to PER withdrawal in 3 patients. This observation suggest that PER may be useful in PMEs; nonetheless, a very close monitoring of psychiatric side effects is necessary. Of note, another AMPA receptor antagonist, BGG492, was tested and proved to be highly effective in suppressing photoparoxysmal response [53].

Literature on the efficacy of LTG on myoclonus in patients with PMEs is controversial. LTG was found to be particularly effective on seizures in infantile and juvenile NCL (maintenance dose 1.25–15 mg/kg/day) [17]. More recently, LTG was also reported to improve disabling myoclonus in a patient with a mtDNA A3243G mutation [54]. On the contrary, in the retrospective analysis by Genton *et al.* [55], add-on treatment with LTG in 5 patients with ULD was ineffective or even determined an aggravation of myoclonic jerks; the authors concluded that LTG is not a reasonable treatment option for ULD.

PHT has been widely used to treat seizures in PMEs in the past. However, this drug has been found to aggravate cognitive function and cerebellar ataxia in ULD. Indeed, the use of PHT has been proposed as an explanation for the poor prognosis of ULD described in the early series reports from Baltic region [56]. Conversely, PHT has proven to be useful in selected cases of status epilepticus, particularly when this occurs in the late stages of a variety of PMEs [57–59].

Sodium channel blockers (carbamazepine, oxcarbazepine, and phenytoin; lacosamide probably as well, being a Na-channel blocker) and GABAergic drugs (vigabatrin and tiagabine), as well as gabapentin and pregabalin, should be avoided, as they may aggravate myoclonus and myoclonic seizures [60].

The strong antimyoclonic effect of alcohol has been highlighted by Genton and Guerrini [61] and a limited use of this substance may be useful in social occasion. Two individual case reports [62,63] suggested that other medications, such as baclofen and ropirinole, might have potential benefit in PMEs. These isolated observations were never replicated.

Trials with other agents such as hydroxy-L-tryptophan [64–67] provided inconsistent results.

The administration of coenzyme Q10 (CoQ10) (50-100 mg 3x/day) and L-carnitine (1000 mg 3x/day) has been reported of some benefit in patients with MERRF [68]. A randomized, double-blind, placebo-controlled trial on 16 individuals with heterogeneous mitochondrial diseases (including MERRF) suggested a favorable influence of the combination of CoQ10 with creatine and lipoic acid on surrogate markers of cellular energy dysfunction [69] but their effect on myoclonus or seizures is unknown.

TARGET THERAPIES FOR PMES

Currently, target therapy is possible only for a minority of PMEs. Enzyme replacement therapy (ERT) with recombinant glucocerebrosidases is available for patients with non-

neuronopathic Gaucher disease (GD), but its use in patients with neuronopathic GD is still controversial, since the recombinant enzyme does not cross the blood-brain barrier [70]. Moreover, ERT shows limited or no efficacy on stabilizing the progression of neurologic manifestations of GD [71–73]. Additional therapeutic strategies include substrate-reduction therapies, such as miglustat (N-butyldeoxynojirimycin), an inhibitor of glucosylceramide synthesis [74], which is able to cross the blood-brain barrier. Nevertheless, an open-label trial did not show any significant benefit of combination therapy of ERT with miglustat on seizures and other neurologic manifestations of GD [75].

Gene therapy and ERT clinical trials for CNL are currently ongoing [76]. Preliminary data from NCT00151216 trial showed promising results of viral vector-mediated gene therapy in reducing the rate of late-infantile neuronal ceroid lipofuscinosis progression [77].

Target therapies for the two commonest forms of EPM, ULD and LD, are not available at present time. However, this is fast approaching at least in LD, where it was shown that a simple reduction of glycogen synthesis by 50% abolishes the disease in the mouse models [78,79].

CONCLUSION

VPA is the drug of choice for PMEs, except for MERFF. LEV or, alternatively, CNZ should be considered as first add-on treatments. ZNS and PER represent promising alternatives. PIR should be reserved to patients with disabling myoclonus not responding to previously mentioned AEDs. PB and PRM could be useful in patients with resistant disabling myoclonus or seizures. LTG should be used with caution, due to its unpredictable effect on myoclonus. Avoidance of drugs known to aggravate myoclonus and seizures, such as CBZ, PHT or VGB, is paramount. Withdrawal of the aggravating agents and adjustment of medication may provide some relief. Alcoholic drinks can be beneficial in small quantities, especially on social occasions. If photosensitivity persists despite AEDs, avoidance of bright lights and striped patterns as well as use of dark glasses can be helpful [80]. Supportive and rehabilitative measures towards specific disabilities of PMEs, as well as social and psychological support, are paramount. Psychiatric (in particular depression) and other comorbidities need to be adequately managed, paying attention to pharmacological interaction with AEDs. Although a 3- to 4-drug combination is quite usual, particular care should be paid to avoid excessive pharmacological load and neurotoxic side effects. Some patients (especially those with ULD) will fare reasonably well with a limited drug regimen, usually a combination of VPA and another above-mentioned AEDs with additional short courses of BZDs, when needed. On the contrary, other subjects will remain severely disabled and will need much heavier pharmacological regimens. Further dissection of the genetic background of the different PMEs might hopefully help in the future with individualised treatment options.

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