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Is adjunctive perampanel beneficial for Lafora disease?

Da li je primena perampanela korisna u lečenju Laforine bolesti?

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Abstract

Background/Aim. Lafora disease (LD) is progressive myoclonus epilepsy, characterized by intractable myoclonus and seizures, inevitable neurological deterioration, brutal cognitive decline and poor prognosis. The treatment still remains purely symptomatic. Recently, two single-case studies and one case series study reported the favourable effects of perampanel in LD. Our study aimed to test the benefits reported in three separate case studies. **Methods.** We performed an open label, prospective study of 4 patients aged between 22 and 34 years with mutation in NHLRC1 (EPM2B) gene, treated with perampanel (6–8 mg/day) as add-on therapy. Follow-up period comprised 14–26 months. Seizure frequency, myoclonus, functional disability and cognitive performance were analysed. **Results.** In 3 patients, both, seizures and myoclonus, showed remarkable improvement after the drug introduction (> 50% reduction). No significant effect was seen in one case. The functional and cognitive impairment maintained at the same level, though all patients were at the later stage of the disease. Psychiatric side effects were dose related. **Conclusion.** Our study supports the rare, previously reported observations that perampanel is beneficial in treating LD patients.

Key words:
lafora disease; diagnosis; anticolvusants; perampanel; treatment outcome.

Apstrakt

Uvod/Cilj. Laforina bolest (LB) je progresivna mioklonička epilepsija koja se odlikuje tvrdokornim mioklonusom i napadima, neumoljivim neurološkim i brutalnim kognitivnim propadanjem i lošom prognozom. Terapija je, za sada, isključivo simptomska. Nedavno su dve studije pojedinačnih slučajeva i jedna sa prikazom serije bolesnika pokazale povoljan efekat perampanela na LB. Cilj rada je bio da se istraži povoljan uticaj primene perampanela u terapiji LB, kako je to prikazano u malom broju studija u dostupnoj literaturi. **Metode.** Sprovedena je otvorena, prospektivna studija na 4 bolesnika, uzrasta 22–34 godine, sa mutacijom u NHLRC1 (EPM2B) genu, koji su lečeni perampanelom 6–8 mg/dnevno, kao dodatnom terapijom. Period praćenja je bio 14–26 meseci. Procenjivani su učestalost napada, mioklonus, funkcionalna onesposobljenost i kognitivno funkcionisanje. **Rezultati.** Nakon uvođenja terapije postignuta je značajno bolja kontrola napada i došlo je do smanjenja (> 50%) mioklonusa kod 3 bolesnika. Kod jednog bolesnika nije zapažen povoljan terapijski odgovor. Funkcionalno i kognitivno poboljšanje nije uočeno, iako su svi bolesnici bili u kasnijim stadijumima bolesti. Psihijatrijska neželjena dejstva su bila dozno zavisna. **Zaključak.** Našom studijom podržana su retka iskustva da je perampanel koristan u lečenju bolesnika sa LB.

Ključne reči:
laforina bolest; dijagnoza; antiepileptici; perampanel; lečenje, ishod.

Introduction

Lafora disease (LD) is very rare, an autosomal recessive, progressive metabolic disorder characterized by intractable myoclonus and seizures, inevitable neurological deterioration, brutal cognitive decline, unfavourable clinical course, and poor prognosis [1].

LD in majority of patients is caused by mutations in either the EPM2A or EPM2B gene, which encode the laforin glycogen phosphatase and the malin ubiquitin E3 ligase, respectively. These proteins have important role in glycogen metabolism due to not yet fully understood pathophysiological mode of action. Hallmark of pathological examination is accumulation of polyglucason inclusion bodies, called Lafora bodies, in the cytoplasm of various cells, the most striking in neuronal cell bodies and dendrites [2, 3].

Clinical presentation appears during late childhood or adolescence (usually between 8 and 18 years of age), with an in-

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sidious appearance of headaches, learning disability, focal occipital seizures, pharmacoresistant generalized tonic-clonic seizures (GTCS) and intractable myoclonus. Myoclonus can be fragmentary, symmetric, or massive and could be the primary reason for early wheelchair dependency. During the course of the disease, severe neurological and cognitive deterioration, dementia, intractable epilepsy and vegetative state led to early death, usually within the first decade from the disease onset.

The treatment of patients with LD still remains purely symptomatic, with antiepileptic and antimyoclonic drugs. Usually, they continue to experience disabling seizures and myoclonus. Two recent single-case studies [4, 5] and one case series study [6] reported the beneficial effects of the relatively new antiepileptic drug (AED), selective alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist perampanel (PER) in the treatment of LD. The drug appeares to lead to sustained remission in myoclonus and GTCS.

Perampanel is highly selective, non-competitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid postsynaptic glutamate receptor antagonist. Activation of AMPA receptors by glutamate is thought to be responsible for excitatory synaptic transmission in the brain. Thus PER reduces neuronal hyperexcitation associated with seizures by targeting glutamate activity.

The efficacy and tolerability of PER has been demonstrated in well designed studies and it was approved as adjunctive therapy for drug-resistant partial seizures with or without secondary generalisation in patients with epilepsy [7, 8]. Recommended dosage is 4-8 mg/day up to 12 mg/day [9, 10].

Here we report an open label, prospective study of 4 patients with genetically proved LD, treated with PER as add-on therapy.

Methods

We studied 4 patients (2 males and 2 females), aged between 22 and 34 years (mean age 27.375 years). The diagnosis was confirmed by genetic analysis, all with mutation in NHLRC1 (EPM2B) gene.

These patients were previously included and reported in a clinical and genetic study of 14 LD patients from 10 families of Serbian/Montenegrin origin with more detailed clinical data presented in this paper [11]. The onset of the disease was between 11.5 and 14 years (mean age 12.75 years). The mean duration of the disease was 14.5 years (in the range of 8 and 21 years).

Patients with genetically confirmed LD were enrolled in our open label study after informed consent was obtained from patients and/or parents. The first patient was entered into the study in January 2015. Patients were assessed by both their treating physicians and parents prior to introduction of PER in order to obtain a comparative data.

Therapy with PER started at the dose of 2 mg/day and was increased by 2 mg/day every 1–2 weeks. PER was titrated to an individual therapeutic dose depending on tolerability and clinical response, up to 12 mg/day. All concomitant AEDs, sodium valproate (4 patients), clonazepam (2 patients), levetiracetam (2 patients), phenobarbital and lorazepam (each in one patient) remained unchanged. Some adjustments of the AEDs dose regimen were made by the patient's treating physician when clinically indicated. After starting treatment with PER, its clinical efficacy was evaluated by comparing the seizure frequency and effect on myoclonus at the end of follow-up with those at the baseline. Parents were asked about the number of GTCS, experienced by the patients during the previous one-month period prior to evaluation time points. The averages and percentages of changes in GTCS frequency from the baseline period were calculated.

Follow-up period comprised 14–26 months with early termination in one patient due to the lack of efficacy.

Apart from recording the frequency of GTCS, parents were asked to assess: (a) myoclonus frequency, severity, amplitude, and intensity, and (b) the level of functional disability and cognitive performance.

We defined myoclonus as sudden jerks or twitches that occur in groups of muscles.

Myoclonus was assessed using numerical scales based on a modified version of the Unified Myoclonus Rating Scale (UMRS) (Table 1) [12]. Levels of ability across functional domains were assessed separately from myoclonus to determine the effects of PER on daily living tasks and to get a better picture of the disease stage for each patient.

Table 1

Unified Myoclonus Rating Scale (UMRS) [12]

	Intensity of myoclonus
A.	Myoclonus frequency (0–5)
1.	no myoclonus
2.	only part of the day
3.	less than every 5 min
4.	once every 3–5min
5.	once every 1–2 min
6.	more than once a minute
B.	Myoclonus severity (0–4)
C.	Amplitude of myoclonus (0–3)
D.	Global assessment of intensity of myoclonus by patient caregiver (0–4)
Adjusted sum score: [(A + B + C + D) / 16 * 10]	

Adverse events (AEs) were reported throughout the study.

To assess the progression of the disease at PER introduction, we used Franceschetti's disability scale based on the residual motor and mental functions, daily living and social abilities (Table 2) [13].

Table 2

Disability scale based on the residual motor and mental functions, daily living and social abilities [13]

1. Mild cognitive and motor impairment, preserved daily living activities and social interaction
2. Moderate mental decline, limitations in motor activities and limited social interaction
3. Severe mental and motor impairment, needing help in walking and regular assistance in daily living activity and poor social interaction
4. Patient wheelchair - bound or bedridden, and no significant daily living activities or social interaction

Results

Molecular-genetic and clinical characteristics of patients are shown in Tables 3 and 4.

In all patients the previous antiepileptic therapy (sodium valproate, benzodiazepines, ethosuximide, levetiracetam, topiramate, zonisamide, primidone, piracetam and phenobarbital) was not effective. PER was gradually titrated and administered as add-on therapy at the doses of 6–8 mg once daily.

Four patients were enrolled with a mean age of 26.5 years. Two of the patients were females, and two were males. The mean dose maintained by patients at final evaluation was 8 mg/day. Two patients reduced their daily dose by 2 and 4 mg after reaching their maximum titrated dose of 10 mg daily, because of side effects (mood changes, agitation, increased hallucinations). By the end of the therapeutic response follow-up, three patients (pts. 1, 2, 3) had a greater-than-12-month exposure to PER treatment. One patient (pt. 4) discontinued treatment after 3 months of the treatment because of lack of efficacy for myoclonus. Patients were taken off the treatment at dosages of 6 mg (pt. 2), 8 mg (pts. 1 and. 3), and 10 mg (pt. 4).

Compared to baseline, totally 3 patients of 4, showed improvement with introduction of PER. They had sustained reduction of myoclonus and almost complete disappearance in two patients (pts. 1 and 2) for shorter period of time (1-3 months). One patient (pt. 2), who was good responder initially, developed sleep disturbances, irritability and violent behavior on 8 mg/day. With dose reduction to 4 mg/day, side effect disappeared, but myoclonus was more pronounced. With dosage adjunction at 6 mg/day, the patient had no massive, erratic myoclounus, and only rarely was irritated. In one patient (pt. 3) PER was reduced after 2 months because of adverse effects, irritability and visual hallucinations. In one patient (pt. 4) PER was discontinued after 3 month of 10 mg/daily use, due to the lack of efficacy in myoclonus control.

Generalized tonic-clonic seizures were better controlled in all patients, two of them (pts. 1 and 2) had no GTCS for longer period of time, and other 2 had rare GTCS, with reduction for more than 50%. No aggravation of seizures was reported. The average number of GTCS per 28 days reported at baseline was 5 (range: 2–8). At the final evaluation the average number of GTCS was reduced to 1.0 (range 0–2).

Three patients (pts. 1, 2 and 3) had improvement in myoclonus. The average group adjusted score of myoclonus intensity at baseline was 6.56 compared with 2.97 and 2.5 at 3 months and 12 months, respectively (Table 5). There was no significant change in functional or cognitive measures. The mean adjusted score of functional disability at baseline was 3.5 and remained the same at the final scoring.

Table 3

Molecular-genetic findings in patients with Lafora disease (LD)

Patient sex	Genetic mutation
1. Male	EPM2B (heterozygous, c.1048-1049delGA, deletion of the EPM2B gene)
2. Female	EPM2B (heterozygous, c.1048-1049delGA, deletion of the EPM2B gene)
3. Female	EPM2B (homozygous c.1048-1049delGA)
4. Male	EPM2B (homozygous c.1048-1049delGA)

Table 4

Clinical characteristics of our patients with Lafora disaese treated with adjunctive perampanel (PER)

Patient	Disease onset (years)	Disease duration (years)	Congitive functioning	Disability level	Previous AEDs	Co-medication with PER	Age at PER introduction (years)	PER dosage (mg/day)	PER efficacy
1	13	21	severe decline	4	VPA, PRM, ZNS ketogenic diet, TPM LEV, CLZ, PB	VPA, LZP, PB	30	8	GTCS free, myoclonus reduced
2	12.5	17.5	severe decline	4	VPA, TPM kategenic diet, LEV PB, CLZ	VPA, LEV	26.5		GTCA free, nearly stopped myoclonus
3	11.5	12	moderate decline	2/3	VPA, LEV, CLZ CLB, TPM	VPA, CLZ	20	8	GTCS decreased, myoclonus reduced
4	12.5	8	IQ 65	3	VPA, LEV, CLZ CLB, TPM	VPA, LEV, CLZ	20.5	10	non-responder

IQ – intelligence quotient; AED – antiepileptic drug; VPA – valproic acid; LEV – levetiracetam; CLZ – clonazepam; CLB – clobazam; TPM – topiramate; PRM – primidone; ZNS – zonisamide; PB – phenobarbital; LZP – lorazepam.

Table 5
Perampanel efficacy on seizures and myoclonus in Lafora disease (LD) patients

Patient	No. of seizures/ 28 days[b] (Adjusted myoclonus score)	No. of seizures/ 28 days [3] (Adjusted myoclonus score)	No. of seizures/ 28 days [12] (Adjusted myoclonus score)
1	8 (3.75)	0 (0.625)	2 (1.25)
2	6 (7.5)	0 (0)	0 (2.5)
3	2 (6.25)	1 (3.75)	1 (3.75)
4	4 (8.75)	2 (7.5)	–
Average	5 (6.56)	0.75 (2.97)	1 (2.5)

[b] – baseline; [3] – 3 months after the drug introduction; [12] – 12 months after the drug introduction.

There were no differences between baseline and final functional abilities scoring (3.5). All of our patients had severe cognitive deterioration, with the average disease duration of 26 years. Two patients (pt 1 and 2) were bed-ridden (score 4 on disability scale, after average 9.5 years from the first symptoms) and had gastrostomy (after average 13.5 years from the first symptoms). Remaining two patients could walk only with assistance and had very reduced social life (score 3, after average 9.5 years from the first symptoms).

Adverse effects associated with PER treatment were reported in 3 of 4 patients. They included: sleep trouble, irritability, aggression, somnolence, impairment of vision, increased hallucinations, and headaches. No serious adverse effects were reported. They were rated mild to moderate and decreased or disappeared after the dose adjustment.

Discussion

There is no effective therapy for LD. The inexorable progression and protracted suffering are agonizing to both patients and families. As Goldsmith and Minassian [6] stated, any extent of symptom relief is therefore highly desirable. Our study aimed to test the benefits reported in three separate case studies [4–6].

Our patients had EPM2B mutation. As previously described, patients of Serbian/Montenegrin origin mainly have EPM2B mutation. This study suggests that mutations in the NHLRC1 gene may be a common cause of LD in the Serbian/Montenegrin population, primarily because of a founder effect [9]. We were encouraged by the publication of two case studies showing efficacy of PER [4, 5] to use this medication in some of our patients. Our LD patients had limitations due to the high price and non-availability of the drug in Serbia. So, only small group of patients were able to use adjunctive PER.

In the meantime, new case series with 10 LD patients treated with PER was published [6].

Our results are in general accord with the both single case and case series reports. A sustained and reproducible remission of myoclonus and GTCS was achieved with 8 and 10 mg of PER for a follow-up of six months in a 21-year-old woman with LD due to the homozygous missense mutation in exon 3 of the EPM2A gene (c.538CNG; p.L180V) [4]. In our 3 of 4 patients, both, seizures and myoclonus, improved after the drug introduction. No favourable therapeutic effect of PER was seen in one case. Differently from previously published case studies except in one case, the response was impressive with near complete seizure reduction. Prevalence of the EPM2A patients were reported by Goldsmith and Minassian [6]. In another French-Serbian group of 8 LD patients with both, EPM2A (3 pts) and EPM2B (5pts) mutations, despite poorer cognitive and functional condition in EPM2B subgroup, no clear difference in the therapeutic response to adjunctive PER was noted [14].

The (sub)continuous positive and negative myoclonus is especially disabling symptom in LD. According to evaluations and caregiver interviews, it appears that myoclonus did improve substantially in 3 of 4 of our patients.

Our case study was open-label and thus susceptible to biases.

Psychiatric and behavioural disturbances could be seen as adverse effects of PER. Patients with a history of psychiatric disorders may be at greater risk of developing anger, aggression, hostility, threatening behavior, homicidal ideation and irritability. LD patients with cognitive problems could be considered to be at greater risk for both, psychiatric and behavioral side effects.

Clinical recommendations were directed toward medications with broad spectrum efficacy in epilepsy, such as valproic acid, zonisamide and levetiracetam, and most clinicians refrain from using medications with activity restricted to focal seizures. PER was originally developed for focal-onset epilepsy, but recent studies have shown its spectrum strongly extended to generalized epilepsy [15] and our study appears to support this extension to progressive myoclonus epilepsy (PME), at least to LD.

The previous case studies reported improvements in functional abilities in LD patients treated by PER. In a case reported by Schorlemmer et al [4]. given daily dose of 10 mg, seizures stopped and the patient also regained her ability to walk with help and the aid of a walker. Dirani et al. [5] found striking improvement not only in myoclonus and seizure control but also in neurological functioning. Case series by Goldsmith and Minassian [6] showed no functional improvement. Observed adverse effects by caregivers were relatively mild and tolerable. No serious adverse effects were reported. However, side effects were severe enough for three patients

to withdraw from the treatment [4]. In our study, the functional and cognitive impairment maintained with no improvement, although the drug was introduced in later stages of the disease (3 and 4), after 9.5 years from the first symptoms.

A randomized study evaluating behavior, efficacy and safety of PER in adolescents with intractable focal seizures showed that most frequently reported adverse effects were dizziness [26 patients (30.6%) vs. placebo (14.6%)], somnolence [13 patients (15.3%) vs. placebo (4.2%)], and headache [nine patients (10.6%) vs. placebo (14.6%)]. Aggression was reported in seven patients receiving PER (8.2%) vs. 2.1% receiving placebo [16, 17].

Ultra-structural studies showed that the cytoplasm of dendrites at synapses are occupied or replaced by Lafora bodies (insoluble, malformed glycogen) suggesting a possible impact on synaptic function [18]. Perampanel was introduced as antiepileptic drug for partial-onset seizures. Its specific modulation of AMPA receptor, with noncompetitive binding at glutamate subreceptor, relatively independent of presynaptic transmitter release, is reducing neuronal excitability. It was shown that in LD, gamma-aminobutyric acid (GABA)ergic cortical neurons are reduced, due to neuronal loss and a specific damage in neurodevelopment of GABAergic neurons in the cerebral cortex as well [19]. Neurophysiology studies showed that hyperexcitability in LD is connected with severe impairment of inhibitory mechanisms [20], though impairment of astrocytic glutamate clearance was also suggested. Disrupted glycogen metabolism could explain important role of glutamate in LD hyperexcitability, since normal glycogen synthesis and breakdown are critical to the homeostasis of glutamate [21, 22]. Perampanel would likely confer benefit by diminishing neuronal network hyperexcitability, through its known AMPA antagonism and the balance of inhibitory to excitatory neurotransmitters [5], not only for GTCS but also for cortical reflex myoclonus, commonly present in LD [23].

Today we are step away from the curative therapy. Researchers are screening for small molecule inhibitors of glycogen synthase, they are using antisense oligonucleotides and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technics, developing gene and protein therapy [24, 25].

Conclusion

Perampanel introduced as add-on therapy in LD patients with advanced form of the disease, showed sustained remission in myoclonus and GTCS. Psychiatric side effects were dose related. In the close future the curative therapy will be available, but until then our small case series study supports previously published very rare observations that perampanel is beneficial new tool in the treatment of this severe epilepsy.

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