Case Report

Seizure control and improvement of neurological dysfunction in Lafora disease with perampanel

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Lafora disease is a rare and fatal disease characterized by seizures, progressive cognitive and behavioral deterioration, as well as cerebellar dysfunction. Currently, there is no efficacious treatment that will control the seizures and improve the cognitive decline in this disease. We report a patient with Lafora disease who experienced a dramatic amelioration in her seizure frequency as well as the associated neurological and cognitive dysfunction following initiation of treatment with perampanel administered as monotherapy. Perampanel is the first potentially efficacious treatment for Lafora disease. We discuss a potential mechanism for the efficacy of perampanel in this disease.

1. Introduction

Lafora disease is a rare, fatal, autosomal recessive form of progressive myoclonic epilepsy which is more common in the Middle East, southern European countries, and Southeast Asia [1]. Mutations in two genes, EPM2A encoding laforin and NHLRC1 encoding malin, account for the majority of mutations causing Lafora disease and are phenotypically indistinguishable.

The symptoms typically start between the ages of 13 and 15 years in a previously healthy and developmentally normal child with myoclonic, focal visual, and generalized tonic–clonic seizures associated with progressive cognitive and behavioral deterioration and cerebellar dysfunction. Once they appear, the myoclonic seizures, which can be spontaneous, reflexive, or action-precipitated, are inexorably progressive, resulting in falls and wheelchair dependency. The neurocognitive decline is relentless either before or within months of the onset of the seizures. The end stage of the disease is marked by severe dementia, spastic quadriaparesis, and almost constant myoclonus [2]. Most affected individuals die within ten years of onset, usually from status epilepticus or from complications related to nervous system degeneration [3]. Pathologically, inclusion bodies known as Lafora bodies are present in several organs, including the brain, heart, skin, liver, and muscle. It is, however, unclear if they are the cause or a consequence of the disease [4].

The efficacy of anticonvulsants in controlling the seizures in Lafora disease is, overall, disappointing. Usually, broad-spectrum drugs such as valproate, levetiracetam, topiramate, and benzodiazepines have been recommended with modest and transient efficacy on seizure frequency, but without effect on cognitive dysfunction. We report on a patient with Lafora disease who experienced a dramatic reduction in her seizure frequency after initiation of treatment with perampanel as monotherapy associated with a striking improvement in cognition, behavior, and cerebellar function.

2. Case presentation

The patient is a 15-year-old Bahraini girl with onset of seizures at the age of 12 years. She initially experienced a generalized tonic–clonic (GTC) seizure followed by another GTC seizure a year later. Six months later, she started to experience multifocal myoclonic jerks that gradually increased in frequency and intensity, in addition to frequent GTC seizures. Treatment with valproate failed to improve her seizure frequency, as she was experiencing near-continuous multifocal disabling spontaneous and action myoclonus in addition to GTC seizures recurring every 2 days. At around that time, the patient started to experience infrequent visual hallucinations in the form of elementary flashes of light. With the onset of the myoclonic jerks, she also developed progressively worsening dysarthria, ataxia, and cognitive regression and stopped attending school. Despite the addition of lamotrigine and topiramate, she continued to have worsening myoclonic jerks, associated with frequent falls, and eventually used a wheelchair. Subsequently, lamotrigine and topiramate were discontinued, and levetiracetam and clonazepam were introduced, but to no avail. Because of the lack of
efficacy, her parents decided to stop all anticonvulsants. On initial eval-
uation at our Medical Center, the patient was not on medication and
was experiencing continuous myoclonus and a GTC seizure every two
days. On examination, she was in a wheelchair with a blunted affect,
very slowly answering some questions with one- or two-word sentences,
with pronounced dysarthria, severe appendicular and truncal ataxia, and
was experiencing near-continuous severe multifocal spontaneous and
action myoclonus as well as distal polyminimyoclonus. Because of her ad-
vanced condition, standard neuropsychological testing was not possible.

The patient was the product of a full-term pregnancy with no prena-
tal complications, normal neurodevelopment, and no previous history
of febrile convulsions. Her parents are nonconsanguineous, and she has 3 siblings (a 20-year-old brother, an 11-year-old brother, and a
3-year-old sister) without a history of seizures so far. There is no family
history of epilepsy.

Video-EEG monitoring revealed moderate generalized slowing and
disorganization of the background, very frequent bursts of
generalized atypical spike-and-wave discharges with a biposterior
predominance frequently associated with myoclonic jerks, and a
photoparoxysmal response. An epilepsy protocol brain MRI/MRS
revealed a faint increased signal in the left temporal pole and a lac-
tate peak in the white matter bilaterally, likely postictal. There was a
decrease in the NAA/Cr and NAA/Ch in the cerebellum when com-
pared with the rest of the brain. An ophthalmologic examination
was normal. On PAS stain, an axillary skin biopsy highlighted numer-
ous diastase-resistant intracytoplasmic inclusion bodies within the
apocrine glands, findings consistent with Lafora disease. Genetic
testing for EPM2A and EPM2B revealed an NHLRC1 homozygous
mutation, consistent with the diagnosis of progressive myoclonic epilepsy type 2B (malin).

Since the girl’s parents were very reluctant to restart any of the
previously tried anticonvulsants, she was started on perampanel with
a rapid titration to 10 mg daily over a 12-day period (administered as
8 mg QHS one day alternating with 12 mg QHS the next).

Approximately two weeks following initiation of perampanel,
there was a dramatic amelioration in her myoclonus and GTC seizure
frequency, in addition to a marked improvement in her activities of
daily living. When evaluated in the clinic one month after initiation
of perampanel (and two weeks after reaching the target dose), the
patient walked unassisted to the office, had a major positive change
in her affect, and was able to carry on a conversation with a substanz-
tial improvement in her dysarthria. She was able to use her hands
appropriately, reaching for objects and transferring them with only
minimal and intermittent spontaneous and action myoclonus
noted. According to her parents, her memory improved substantial-
lly, and the patient became more sociable and was able to participate
in the activities of daily living. She was now able to eat and drink
independently, whereas she was totally dependent prior to the ini-
tiation of perampanel. In addition, the parents reported that she expe-
renced only one GTC seizure over more than a month and a striking
improvement in the frequency and severity of the myoclonus.
Because of the persistence of the intermittent myoclonic jerks, we
elected to insert a vagus nerve stimulator (VNS) with the parameters
gradually increased to an intensity of 1.25 mA, frequency of 30 Hz,
pulse width of 250 ms, 14 s on, and 0.8 min off (duty cycle of 44%).
An electroencephalogram done with the combination of perampanel
and VNS just a few days after achieving those parameters revealed
a substantial reduction in the frequency of the epileptiform
discharges.

The patient returned to Bahrain on perampanel monotherapy
(8 mg/day alternating with 12 mg/day) in conjunction with the VNS.
On her last follow-up, seven months after initiation of perampanel,
the patient continued to improve, was able to run and play with a ball,
was able to write without myoclonus, and was able to perform all ac-
ivities of daily living independently. No significant adverse events were
reported by the family.

3. Discussion

This is the first report to document the dramatic efficacy of
perampanel administered as monotherapy in Lafora disease.

The treatment of seizures in Lafora disease is mostly based on anec-
dotal evidence because of the lack of randomized, double-blind clinical
trials. A number of broad-spectrum anticonvulsants including clonaze-
pam, levetiracetam, piracetam, phenobarbitol, topiramate, valproate,
and zonisamide were tried in small series with limited and transient
success [5–8]. It is well established that narrow-spectrum drugs such as
carbamazepine, gabapentin, phenytoin, vigabatrin, and tiagabine
may aggravate myoclonus and should be avoided, although some of
those agents are used in advanced cases when the risk of recurrent
status epilepticus is increased [9]. In addition, lamotrigine should be
used with caution because of reports of aggravation of myoclonus in
other myoclonic epilepsies [10].

Our patient was initially treated with most of the recommended
anticonvulsants including valproate, levetiracetam, topiramate, and
clonazepam, with a poor initial response and subsequent worsening of
seizure frequency. Perampanel administered as monotherapy resulted
in a dramatic improvement in seizure frequency with near-total disap-
ppearance of the constant spontaneous and action myoclonus experi-
enced by our patient. Although VNS might have contributed to the
sustained seizure control, a remarkable improvement in seizure
frequency and severity preceded the insertion of the device.

Perampanel, one of the newer antiepileptic drugs, is believed to
exert its anticonvulsant effect as a selective noncompetitive antagonist
of the AMPA-type glutamate receptors. It was recently licensed as
adjunctive therapy for the treatment of refractory focal-onset seizures
[11–13]. Because of its long half-life (105 h as monotherapy), it is
administered as a once-daily dose, usually at bedtime. There is only
one previous report documenting its efficacy when used as add-on ther-
apy in the treatment of Lafora disease in a 21-year-old woman. In that
case, the addition of perampanel to a regimen that included clonaze-
pam, levetiracetam, piracetam, valproate, zonisamide, and ketogenic
diet in addition to VNS resulted in seizure remission for more than
3 months and led to a reduction in the amount of epileptiform
discharges on EEG [14].

In addition to the paucity of efficacious anticonvulsants for the
control of seizures in Lafora disease, there is no known pharmacologic
treatment that improves the cognitive, behavioral, and/or cerebellar
abnormalities associated with this disease. What was striking following
the initiation of perampanel was its impressive efficacy not only in
improving seizure frequency and severity but also in substantially ame-
liorating the neurocognitive and cerebellar dysfunction experienced by
our patient. This young woman, who was in a wheelchair, with severe
ataxia and dysarthria and with a blunted affect, was a transformed indi-
vidual just one month after initiating treatment with perampanel. She
was able to walk unassisted, had clearer speech, was socially interactive,
and was able to carry on a conversation and appropriately answer ques-
tions. The progress in her clinical condition continued to improve during
the subsequent six months.

A recent study suggesting that a loss of GABAergic cortical neu-
rons underlies the neuropathology of Lafora disease might be rele-
vant in trying to explain those observations [4]. It was shown in a
transgenic mouse model of Lafora disease that the population of
GABAergic cortical neurons is reduced, leading the authors to opine
that an imbalance in the ratio of GABAergic to glutamatergic neurons
might be pathophysiologically related to the development of Lafora
disease [4]. This hypothesis could potentially explain the efficacy of
perampanel, which by blocking the AMPA receptors, might partially
normalize the imbalance of inhibitory to excitatory neurotransmit-
ters in the cortex and cerebellum.

In summary, our case suggests that perampanel might be efficacious
in controlling seizures and ameliorating the associated neurological
dysfunction in Lafora disease. Whether this effect is transient or
sustained will require observations on patients with longer follow-up periods. In view of the lack of efficacious treatment for this condition, we propose that perampanel be tested in animal models of Lafora disease [15] and encourage clinicians to evaluate its efficacy in this condition, which might serve as a basis for a subsequent randomized trial for the treatment of this dreadful disease.

Conflict of interest

There is no conflict of interest to report.

References

[1] Panayiotopoulos C. A clinical guide to epileptic syndromes and their treatment; 2002.
[2] Delgado-Escueta AV. Advances in Lafora progressive myoclonus epilepsy. Curr Neurol Neurosci Rep 2007;7:428–33.
[3] Minassian BA. Progressive myoclonus epilepsy with polyglucosan bodies: Lafora disease. Adv Neurol 2002;89:199–210.
[4] Ortolano S, Vitez R I, Agis-Rabasa RC, Spuch C. Loss of GABAergic cortical neurons underlies the neuropathology of Lafora disease. Mol Brain 2014;7:7.
[5] Shahwan A, Farrell M, Delanty N. Progressive myoclonic epilepsies: a review of genetic and therapeutic aspects. Lancet Neurol 2005;4:239–48.
[6] Boccella P, Striano P, Zara F, Barbieri F, Sarappa C, Vacca G, et al. Biopically demonstrated Lafora disease without EPM2A mutation: a clinical and neurophysiological study of two sisters. Clin Neurol Neurosurg 2003;106:55–9.
[7] Yoshimura I, Kaneko S, Yoshimura N, Murakami T. Long-term observations of two siblings with Lafora disease treated with zonisamide. Epilepsy Res 2001; 46:283–7.
[8] Fedi M, Reutens D, Dubeau F, Andermann E, D’Agostino D, Andermann F. Long-term efficacy and safety of piracetam in the treatment of progressive myoclonic epilepsy. Arch Neurol 2001;58:781–6.
[9] Miyahara A, Saito Y, Sugai K, Nakagawa E, Sakuma H, Komaki H, et al. Reassessment of phenytoin for treatment of late stage progressive myoclonus epilepsy complicated with status epilepticus. Epilepsy Res 2009;84:201–9.
[10] Genton P, Gelisse P, Crespel A. Lack of efficacy and potential aggravation of myoclonus with lamotrigine in Unverricht-Lundborg disease. Epilepsia 2006; 47:2083–5.
[11] Krauss GL, Serratosa JM, Villanueva V, Endziiiene M, Hong Z, French J, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 2012;78:1408–15.
[12] French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 2012;79:589–96.
[13] Steinhoff BJ, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, Saitlin A, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. Epilepsia 2013;54:1481–9.
[14] Schorlemmer K, Bauer S, Belke M, Hermens A, Klein KM, Reif FS, et al. Sustained seizure remission on perampanel in progressive myoclonic epilepsy (Lafora disease). Epilepsy Behav Case Rep 2013;1:118–21.
[15] Ganesh S, Delgado-Escueta AV, Sakamoto T, Avila MR, Machado-Salas J, Hoshii Y, et al. Targeted disruption of the Epm2a gene causes formation of Lafora inclusion bodies, neurodegeneration, ataxia, myoclonus epilepsy and impaired behavioral response in mice. Hum Mol Genet 2002;11:1251–62.