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Case Report

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

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ABSTRACT

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 quadriparesis, 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

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efficacy, her parents decided to stop all anticonvulsants. On initial evaluation 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 advanced condition, standard neuropsychological testing was not possible.

The patient was the product of a full-term pregnancy with no prenatal 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 lactate peak in the white matter bilaterally, likely postictal. There was a decrease in the NAA/Cr and NAA/Ch in the cerebellum when compared with the rest of the brain. An ophthalmologic examination was normal. On PAS stain, an axillary skin biopsy highlighted numerous 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 substantial 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 substantially, 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 initiation of perampanel. In addition, the parents reported that she experienced 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 μs, 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 activities 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 anecdotal evidence because of the lack of randomized, double-blind clinical trials. A number of broad-spectrum anticonvulsants including clonazepam, levetiracetam, piracetam, phenobarbital, 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 disappearance of the constant spontaneous and action myoclonus experienced 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 therapy in the treatment of Lafora disease in a 21-year-old woman. In that case, the addition of perampanel to a regimen that included clonazepam, 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 ameliorating 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 individual 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 questions. The progress in her clinical condition continued to improve during the subsequent six months.

A recent study suggesting that a loss of GABAergic cortical neurons underlies the neuropathology of Lafora disease might be relevant 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 neurotransmitters 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.

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