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Case Report

Perampanel attenuates myoclonus in a patient with neuronal ceroid lipofuscinoses type 2 disease

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Abstract

Neuronal ceroid lipofuscinoses type 2 disease (CLN2) is a very rare, autosomal recessive neurodegerative disease caused by deficient activity of the enzyme tripeptidyl peptidase 1 (TPP1). The seizures in CLN2 are polymorphic and resistant to antiepileptic drugs. In particular, myoclonus (epileptic and non-epileptic) predominant as the disease progresses. Herein, we present a child of CLN2 disease, who had near-continuous myoclonus, and was subsequently attenuated by administration of Perampanel. This girl had initially presented with language delay and generalized tonic clonic seizure at 3 years of age. The diagnosis of CLN2 was made via genetic study, which showed compound heterozygous mutation on *TPP1* gene (c.622 C > T and partial gene deletion including at least exons 1–3). Currently, at the age of 8 years, there was near-continuous myoclonus (epileptic and non-epileptic), which worsen during acute illness. Eventually, she was given Perampanel with starting dose of 1 mg/day and slowly titrated upto 6 mg/day in 4 weeks. There was significant attenuation of myoclonus (>50% seizure reduction). To our knowledge, this is the first case in the literature describing the efficacy of perampanel in treating myoclonus in CLN2 disease.

Keywords: Neuronal ceroid lipofuscinoses type 2 disease; Perampanel; Myoclonus; Antiepileptic medication

1. Introduction

Neuronal ceroid lipofuscinoses type 2 disease (CLN2) is a catastrophic progressive myoclonus epilepsy (PME) that typically onset at early childhood. The disease is characterized by language delay and seizures in an otherwise healthy toddler at about 2–4 years of age, followed by rapid neurological deterioration, epilepsy, movement disorders, blindness and ultimately early death in adolescence [1]. In addition to cognitive deterioration, epilepsy is a major feature and causes significant morbidities and burdens in these patients. The seizures are polymorphic, including generalized tonic-clonic, focal seizures, myoclonic seizure, etc. and resistant to antiepileptic drugs. In particular, myoclonus (epileptic and non-epileptic) becomes a predominant feature as the disease progresses.

CLN2 disease is a recessive neurodegenerative disease caused by deficient activity of the enzyme tripeptidyl peptidase 1 (TPP1). Although enzyme-replacement therapy with recombinant human

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tripeptidyl peptidase 1 had emerged as a promising treatment to slow down neurological decline in newly diagnosed patients recently [2], multidisciplinary care and symptomatic treatments were the mainstay treatment to date. Regarding the treatment of epilepsy in these patients, the antiepileptic drugs (AEDs) are used according to general principles, with valproate acid, levetiracetam, benzodiazepine, lamotrigine are commonly used as firsts line therapies. However, the seizures are usually refractory. In addition, the prescription of multiple AEDs is usually hindered by their side effects such as sedation.

Herein, we present a child of CLN2 disease, who had near-continuous myoclonus, and was subsequently attenuated by administration of perampanel, a new antiepileptic drug. The family provided their written informed consent for the genetic testing, and this retrospective case review was approved by the ethic committee of National Taiwan University Hospital.

2. Patient description

This female patient was born uneventfully to a non-consanguineous parents. There was no family history of neurological disease in both her parent's families. The patient was the second child of her parents. Her elder sister, who was 2 years older, was presumed to had the same disease. The elder sister had seizure onset at the age of about 2 years, followed by rapid neurological deterioration and became bed-redden at the age of 6 years. She eventually died at the age of 12 years due to infection.

This patient had language delay (she could only produce single words at the age of 3 years) but otherwise normal neurological development. She was brought to medical attention at the age of 3 years due to generalized tonic-clonic seizure. Multiple types of seizures emerged since then, including autonomic seizures and myoclonic seizures. The EEG at 3 years of age showed background activities consisted of occipitaly dominated 7–8 cps theta waves intermixed with 3-6cps slow waves and focal epileptiform discharges over bilateral occipital areas. There was no photic paroxysmal response (PPR). The brain MRI (Fig. 1) showed mild cerebellar atrophy. Ataxia and cognitive deterioration developed within one year. Under the suspicion of progressive myoclonic epilepsy, skin biopsy was performed but did not show curvilinear profiles or fingerprint-like structures. However, subsequent genetic study showed compound heterozygous mutation on *TPP1* gene (c.622 C > T and partial gene deletion including at least exons 1–3). Therefore, the diagnosis of CLN2 Disease was made.

She had rapid clinical deterioration since then. At the age of 5 years, she became total blindness, could not communicate, and progressively lost voluntary movements. She became bed-ridden at the age of 6 years and depended on nasogastric tube feeding. Regarding the epilepsy, the seizures were refractory despite multiple antiepileptic drugs (valproate, levetiracetam, topiramate, clobazam, piracetam and phenobarbital), as well as ketogenic diet. At the age of 8 years, there was near-continuous erratic myoclonus. We used the video EEG to evaluate the myoclonus of this patient. In most myoclonus of the patient, there was no concomitant epileptiform discharge, indicating non-epileptic myoclonus. Only rarely the myoclonus was associated with generalized epileptiform discharges, which was worsen during acute illness. Eventually, she was given perampanel with starting dose of 1 mg/day and slowly titrated upto 6 mg/day in 4 weeks. There was significant attenuation of myoclonus according to the recording during admission and the description of major care giver at outpatient clinic. During 6-months follow up, although there was still daily myoclonus, there were >50%

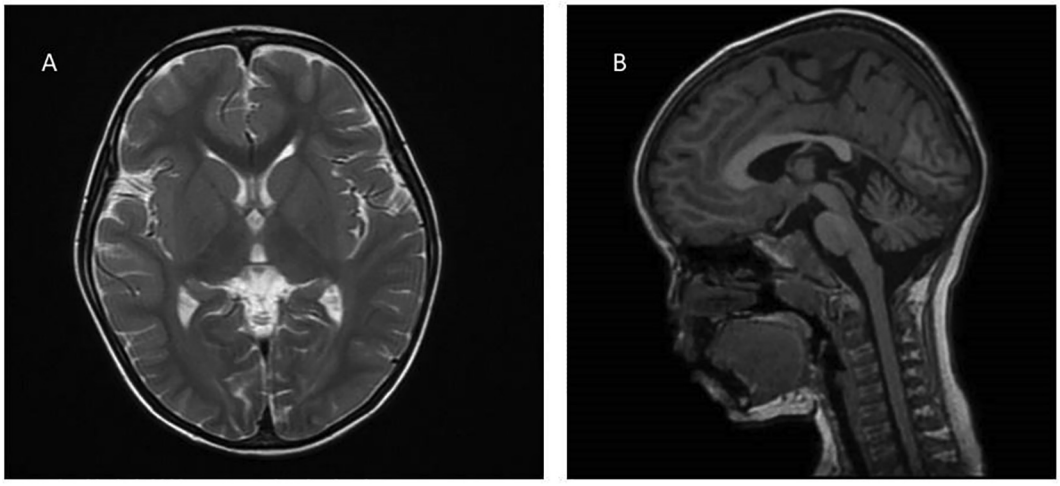

Fig. 1. T2 MRI images of our case at the age of 3 years, showing cerebellar atrophy.

decreases of myoclonus, and there was no obvious side effect. The neurological status remained stationary. Nonetheless, the family is satisfied with the improvement of myoclonus because the myoclonus occasionally interrupted the sleep of the patient. The sleep quality of the patient had improved significantly.

3. Discussion

To the best of our knowledge, this is the first reported case describing the efficacy of perampanel in reducing myoclonus in CLN2 disease. CLN2 disease is a neurodegenerative lysosomal storage disorder. It is caused by pathogenic mutations in *TPP1* gene, which encode the enzyme tripeptidyl peptidase 1 (TPP1), therefore resulting in deficient activities of this enzyme [1].

The seizure disorders of CLN2 were characterized by multiple types of seizures at the disease onset, with myoclonus predominating overtime. The current AED treatment for CLN2 generally follows accepted principles for epilepsy. A polytherapy of AEDs for myoclonus, including valproate, levetiracetam, benzodiazepines (clobazam, clonazepam), lamotrigine, phenobarbital, zonisamide, is usually suggested [3]. However, the myoclonus in CLN2 is often difficult and resistant to these therapies. Our patient had tried the above medications with optimal doses; however, the myoclonus still persisted and became nearly continuous. Therefore, perampanel was administered and showed efficacy in reducing >50% myoclonus, as observed by both care giver and physician. However, the follow-up EEG and her general neurological condition remained stationary.

Perampanel is a selective, noncompetitive antagonist of a-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA)-type glutamate receptors. It was licensed as adjunctive therapy for the treatment of primary GTCs and focal onset seizures [4,5]. Although the underlying mechanism is unclear, there were case reports in the literature showing the efficacy in treating seizures in PME, including Unverricht-Lundborg disease, sialidosis and Lafora disease, etc [6–9]. Some even showed improved neurological condition in addition to seizure reduction [8,9]. Our case had nearly continuous myoclonus, which was resistant under multiple AEDs. Although there was no neurological improvement after the use of perampanel, our case demonstrated that perampanel is also effective in controlling epileptic and non-epileptic myoclonus in CLN2. However, the underlying mechanism of the efficacy of perampanel in controlling myoclonus in PME is unclear. In CLN2, as in our case, it might be possible that the seizure might be controlled through the blocking of the AMPA receptors by perampanel, thus balancing the of excitatory and inhibitory neurotransmitters in the cerebral cortex.

4. Conclusion

In conclusion, perampanel adjuvant therapy may be considered in treating myoclonus of CLN2 like other patients with PME. Although present case showed significant improvement in myoclonus control, further clinical or animal studies are warranted as this is only based on a single clinical case observation.

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