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Case Report

# Seizure remission and improvement of neurological function in sialidosis with perampanel therapy

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ABSTRACT

A 15-year-old boy experienced myoclonic seizures for 3 years. He initially had occasional myoclonus, gradually progressive ataxia, tremors, and psychomotor and speech regression developed. Eventually, he exhibited nearly continuous myoclonus. He received treatment of sodium valproate, levetiracetam, clobazam, and phenobarbital, without efficacy. A ketogenic diet also proved ineffective. Adjunctive therapy with 4 mg/day of perampanel was started and was gradually titrated to 10 mg/day. The remission of myoclonic seizures was achieved within one month. The patient's neurological and cognitive functions improved to a certain degree during the following 20 months. Sialidosis was confirmed by the mutations of *NEU1* gene.



## 1. Introduction

Progressive myoclonic epilepsies (PMEs) constitute a group of rare disorders characterized by the development of relentlessly progressive myoclonus, tonic–clonic seizures, and neurological deterioration. Sialidosis, a rare cause of PMEs, is an autosomal recessive disorder resulting from the alpha-*N*-acetyl neuraminidase deficiency caused by a mutation in the neuraminidase 1 gene located on 6p21.33. Clinically, sialidosis is of two types. Sialidosis type I is a relatively mild form of the disease, which usually occurs in the second decade of life; it is also known as the cherry-red spot myoclonus syndrome. Depending on the age of onset, sialidosis type II can be classified into infantile and juvenile forms. In addition to cherry-red spots and myoclonus, patients with sialidosis type II exhibit somatic involvement including coarse face, corneal clouding, and dysostosis multiplex. Until now, no specific treatment has been established for sialidosis. Treatment for sialidosis is limited to symptom relief and supportive care. Myoclonic seizures are often resistant to antiseizure medication [1].

## 2. Case report

We report the case of a 15-year-old boy who experienced frequent myoclonic seizures and ataxia for 3 years. He had normal neuropsychiatric development before the initial onset of seizures at the age of 12 years. He presented with generalized and focal myoclonic seizures. Progressive ataxia and psychomotor and speech regression developed 6 months later. The myoclonic seizures were refractory to multiple antiepileptic drugs (AEDs) including clobazam, sodium valproate, levetiracetam, and phenobarbital in full dosage. Furthermore, he had dysarthria and poor feeding, which necessitated nasogastric tube feeding. He was completely bedridden for several months. When he was admitted to our hospital at the age of 15 years and 9 months, he had nearly continuous focal facial myoclonus, which subsequently spread to the extremities. The facial myoclonus lasted for 15–20 s and occurred more than 100 times per day. His electroencephalogram (EEG) (Fig. 1) revealed focal spikes arising from bilateral centrotemporal regions, followed by ictal myoclonic seizures with generalized muscle contraction activities lasting 15–20 s observed on the EEG. Because progressive myoclonic epilepsy was suspected, extensive workups were performed. The plasma amino acid test, tandem mass spectrometry, and muscle biopsy revealed nonspecific changes. Magnetic resonance images (Fig. 2) of the patient's brain showed mild brain atrophy. Apocrine skin biopsy did not show the presence of Lafora bodies. Genetic testing for EPM2A, EPM2B, and CSTB revealed negative results. However, abnormal somatosensory-evoked potentials with giant cortical waves were found. Cherry-red spots on bilateral maculae on the eye grounds were observed. Therefore, we performed genetic testing under the suspicion of sialidosis. Direct sequence analysis of PCR-amplified DNA of this patient had identified the presence of compound heterozygous mutations in *NEU1*. One of the mutations was a common missense mutation

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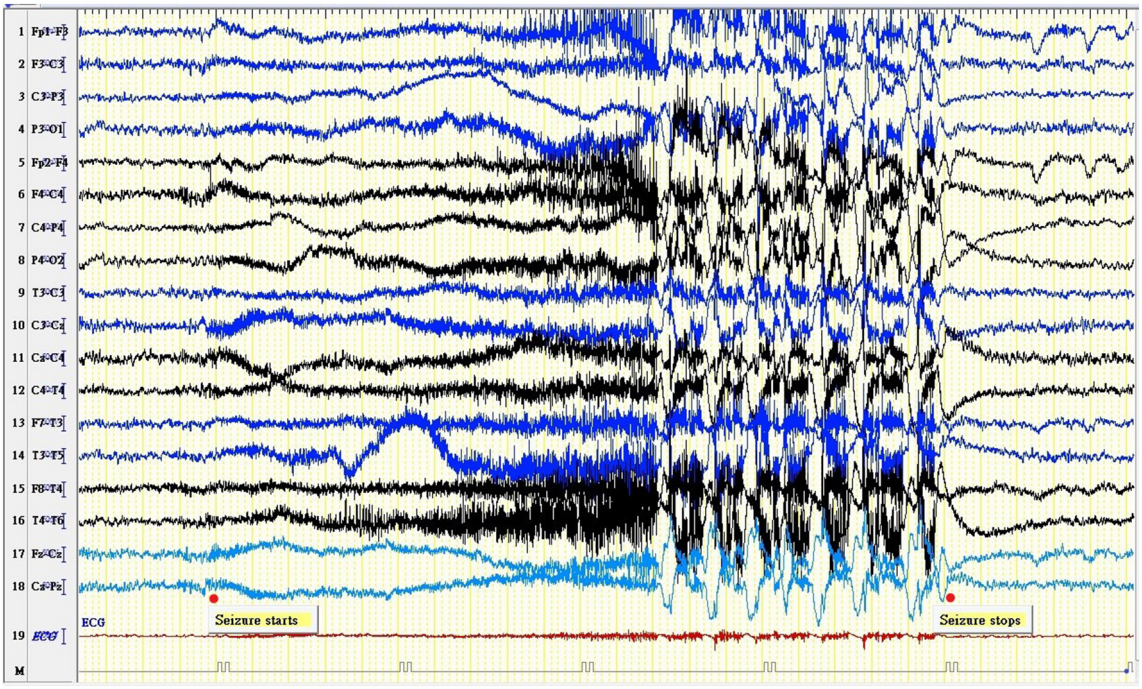


**Fig. 1.** Initial electroencephalogram with focal spikes arising from bilateral centrotemporal regions and associated ictal myoclonic seizures with generalized muscle contraction activities lasting for 20 s.

c.544A>G, causing the amino acid substitution Ser182Gly. The other one was a nonsense mutation c.619C>T, which yielded a termination codon, thus producing a truncated protein (Fig. 3). The diagnosis of PMEs with sialidosis type I was thus made.

After admission, the patient had a partial myoclonic status, which was resistant to many antiseizure medications and also did not respond to a ketogenic diet. The patient's condition was complicated by aspiration pneumonia and generalized tonic–clonic (GTC) seizures. Eventually, he was started on perampanel therapy at 4 mg/day, with rapid titration to 8 mg/day. He showed a positive response. The number of seizure episodes significantly reduced after 3 days' of treatment with 8 mg/day of perampanel. Complete remission of the myoclonus and GTCs was achieved after titration to 10 mg/day for 3 days. The patient's clinical condition also improved. He could speak a few sentences, and feed himself with assistance. After 2 months, he could walk several steps with device. During 20-month follow-up, complete remissions of the myoclonic seizures and GTCs sustained under combination therapy with topiramate, sodium valproate, levetiracetam, clobazam, and perampanel, with total weaning of phenobarbital. He is currently receiving a perampanel dose of 10 mg/day. His neurological and cognitive functions remained stable. He has returned to school and moves with a wheelchair. His recent intelligence quotient (IQ) was 52. No previous IQ data were available for this patient before the disease onset.

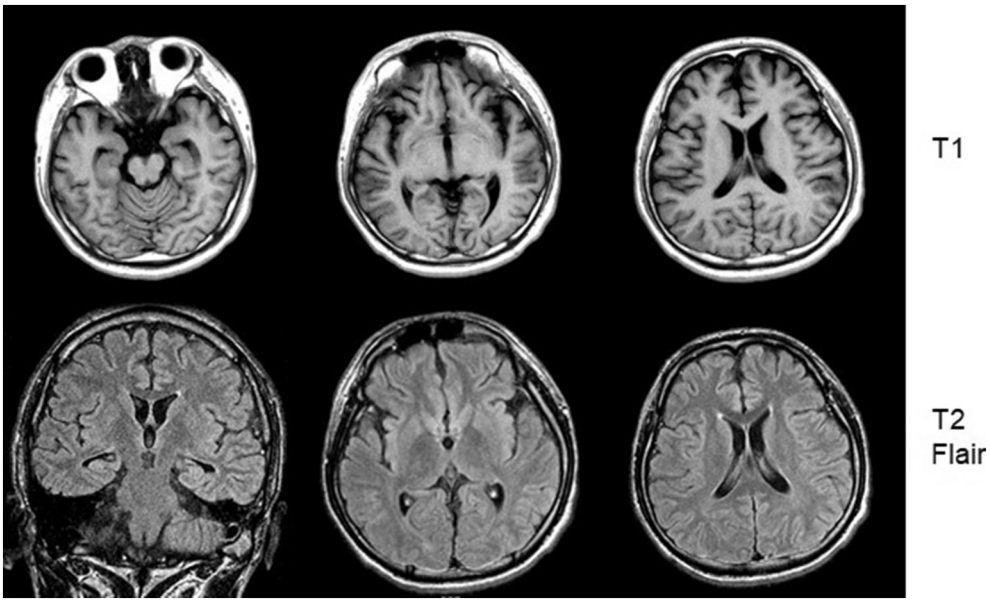


**Fig. 2.** Magnetic resonance image of the patient's brain showing mild brain atrophy.

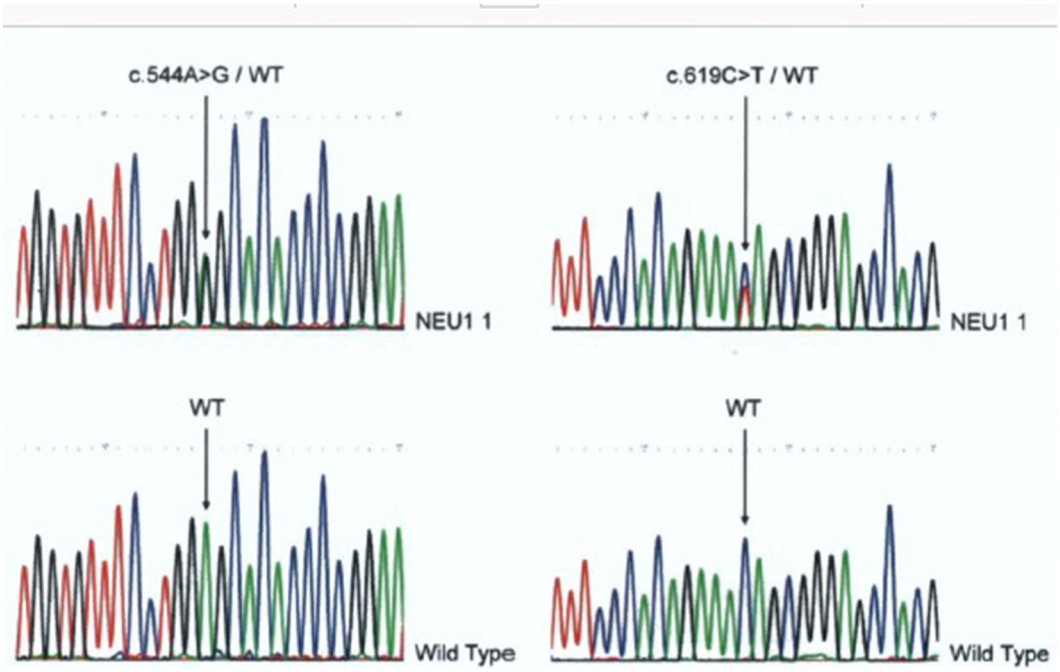


**Fig. 3.** Compound heterozygous mutations of c.544A>G and c.619C>T in *NEU1* gene.

## 3. Discussion

This is the first report describing the efficacy of perampanel as adjunctive therapy for sialidosis, to our knowledge. PMEs constitute a group of disorders characterized by myoclonic seizure, tonic–clonic seizure, and progressive neurological deterioration, which typically occur with cerebellar signs and dementia. A correct diagnosis always helps patients and their families to understand and accept the disease, even if it is incurable [2]. In our patient, evaluations were performed to identify the etiology of PMEs. A survey for aminoacidopathy and mitochondrial disease, as well as a biopsy of the axillary skin yielded negative results. The results of genetic studies for identifying mutations in genes associated with PMEs, such as those in EPM2A, EPM2B, and CSTB, were also negative. The diagnosis of sialidosis type 1 was made based on the clinical pictures and positive *NEU1* expression. A longitudinal study of Taiwanese patients with sialidosis type 1 also showed the presence of the c.544A>G mutation in *NEU1* in all 17 patients [3]. One patient exhibited a heterozygous mutation resulting in a stop codon [3].

The treatment of myoclonus and seizures in PMEs is difficult because both tend to be refractory and resistant to commonly used AEDs [4]. For the management of myoclonus, combinations of valproic acid, benzodiazepines, phenobarbital, piracetam, zonisamide, and levetiracetam may be used; however, they are not always effective. Our patient had been treated using most of the anticonvulsants that could be used for treating PMEs; however, the efficacy was unsatisfactory. Finally, the administration of perampanel resulted in the remission of the seizures, inhibition of neurological deterioration, and improvement of quality of life.

Perampanel has been shown to be effective for seizure control in PMEs such as Lafora disease [5–7], Unverricht-Lundborg disease [8], and dentatorubral-pallidoluysian atrophy [9]. Furthermore, a report indicated the efficacy of perampanel therapy for a chronic type of posthypoxic myoclonus and Lance–Adams syndrome [10]. Our case demonstrated that perampanel therapy is also effective for sialidosis. However, the mechanism underlying the antimyoclonic effect of perampanel remains unclear. Perampanel is a noncompetitive, selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist. AMPA receptors may play a pivotal role in the pathophysiology of epilepsy. The receptors may be involved not only in the occurrence of seizures but also in the progression of epilepsy. Thus, perampanel is prescribed as adjunctive therapy for primary GTCs and partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy and myoclonus [11,12]. The mechanism underlying the efficacy of perampanel in sialidosis might involve blocking of the AMPA receptors to normalize the balance of inhibitory and excitatory neurotransmitters in the cortex and cerebellum.

In conclusion, our experience suggests that perampanel is a candidate of choice for treating PMEs such as sialidosis, and we hypothesize that more satisfactory outcomes may be achieved if perampanel is prescribed at the early stage of the disease rather than at a later stage. Additional confirmatory reports may suggest specific drug efficacy of perampanel in the management of PME including sialidosis.

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