Case Report

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Improvement of Seizure in a Case of Zellweger Syndrome with Perampanel Therapy

Yukari Otsuka, Rieko Sakamoto*, Sasa Kurosawa, Jun Kido, Kenichi Tanaka, Tetsuo Naramura, Hiroshi Mitsubuchi, Shirou Matsumoto and Kimitoshi Nakamura

Department of Pediatrics, Kumamoto University Hospital, Kumamoto, Japan

***Corresponding author**: Rieko Sakamoto, Department of Pediatrics, Kumamoto University Hospital, Kumamoto, Japan, Tel: +81-96-373-5191; E-mail: hrieko48@kuh.kumamoto-u.ac.jp

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Abstract

Context: Zellweger spectrum disorders represent the major subgroup within the peroxisomal biogenesis disorders caused by defects in PEX gene. Zellweger syndrome is the most severe form of Zellweger spectrum disorders, causing death within the first year of life. Patients with Zellweger syndrome in the neonatal period often present typical dysmorphic features, severe neurological dysfunction with hypotonia andoccasionallyseizures, failure to thrive, liver dysfunction and skeletal defects. In addition, epileptic seizures are usually present and sometimes uncontrollable.

Case report: Our case was a female neonate, who was born at 38 weeks of gestational with 2582 gms of body weight. She presented hypotonia, poor feeding and epilepsy with episode of apnea. We diagnosed Zellweger syndrome by the examination of genetic analysis. She received treatment of levetiracetam, clobazam, and phenobarbital, however these were all without efficacy. Adjunctive therapy with 4 mg/day of perampanel was started, gradually up to 10 mg/day. That treatment ameliorated the symptoms of apnea and seizures. And home palliative care could be started.

Discussion: This is the first case of Zellweger syndrome treated with perampanel successfully. Perampanel may be useful and safety not only for Zellweger syndrome but also for other lysosomal disorders.

Keywords: Zellweger syndrome; Perampanel; Seizure; Palliative care

Introduction

Peroxisomes play an important role in numerous essential metabolic pathways, including the biosynthesis of phospholipids and bile acids, the α-oxidation and β-oxidation of fatty acids, the detoxification of glyoxylate and the metabolism of reactive oxygen species such as hydrogen peroxide and superoxide. Peroxisomal biogenesis disorders (PBDs), entail a total absence of peroxisomal functions due to mutation in any of the peroxisome assembly (PEX) genes [1].

The Zellweger syndrome spectrum (ZSS), which is caused by defect in the PEX genes, clinically described as the Zellweger syndrome (ZS), neonatal adrenoleukodystrophy, Infantile Refsum syndrome and Heimler syndrome. Zellweger syndrome, the most severe form of ZSS, causes death within the first year of life. Patients with ZS in the neonatal period often present typical dysmorphic features, severe neurological dysfunction with hypotonia andoccasionalseizures, liver dysfunction, and skeletal defects, and may fail to thrive [1]. Glutamate alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors mediate most of the excitatory neurotransmission in the mammalian central nervous system and also participate in forms of synaptic plasticity thought to underlie memory and learning, and the formation of neural networks during development. Recently, AMPA receptor inhibitor performed successfully treatment for lysosome diseases such as ceroid lipofuscinoses type 2 diseases, sialidosis and Niemann Pic C [2-4].

Case Report

The patient was a female neonate, and the fourth child. Birth was at 38 weeks *via* cesarean section, and birth weight was 2582 gms. She presented hypotonia, poor feeding, seizures, and distinctive facial features. Her skeletal radiograph showed punctate calcification of the joint, and prenatal ultrasonography indicated dilatation of ventricles in the brain. She presented abnormal respiratory conditions, seizures, renal tubular acidosis, and calcification of her knee (**Figure 1**). With approval of Ethical committee and informed consent taken from her parents, we diagnosed ZS by the examination of genetic analysis. The result was compound heterogenous mutation of PEX1 genes:c. 2T>G p. 1Met>Arg(ex1)/c. 2614Cdel(ex16). The clinical course is displayed in **Figure 2**. As her parents wanted to give her palliative care at home, we tried to start home medical care when she was 2 months old. However, she returned to our hospital because of her frequent seizures and apnea attacks. The patient's condition was complicated by apnea, aspiration pneumonia and generalized tonic–clonic seizures (GTCS). Apnea

was concomitant with GCTS. Eventually, she was started on perampanel therapy at 4 mg/day at the age of 3 month. She showed a positive response. The number of seizure episodes significantly reduced after 3 days of treatment with 6 mg/day of perampanel. Furthermore the GTCS and apnea became less severe after titration to 10 mg/day. Aspiration pneumonia improved and clinical condition was going well. Home palliative care could be started again.

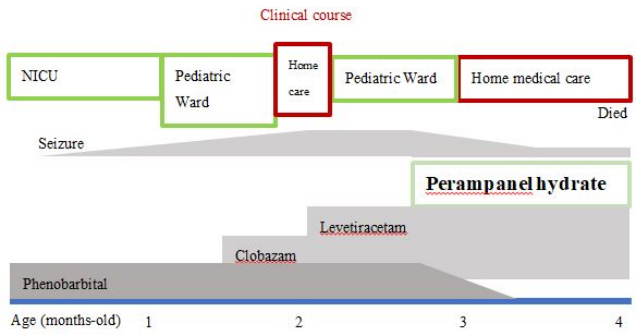

Figure 1: Clinical course of the case.

During 2-month follow-up, partial remissions of GTCS sustained under combination therapy with levetiracetam, clobazam and perampanel with total weaning of phenobarbital. Finally, she died at the age of 4 months because of respiratory dysfunction. Even if ZWS is extremely severe and life limited disorder, her family was pleased with the steps of being in home with her after taking with perampanel.

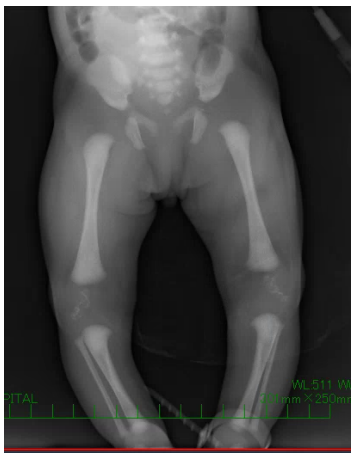

Figure 2: Abnormal calcification were detected by X-ray.

Discussion

This is the first case report describing the efficacy of perampanel as the adjunctive therapy for seizure in Zellweger syndrome. Perampanel is a noncompetitive, selective AMPA glutamate receptor antagonist. It is indicated that AMPA receptors may play a pivotal role in the pathophysiology of epilepsy in clinical cases.

Recent studies reported that perampanel improved myoclonic seizure in lysosomal disorders.

Hu et al. reported that adjunctive therapy with perampanel improved seizure and neurological functions in sialidosis [2]. In this case, 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. Another case is reported by Wong et al., that perampanel attenuated myoclonus in neuronal ceroid lipofuscinoses type 2 diseases [3]. *In vitro* study, D'Arcangelo et al. reported that notable differences in calcium influx during kainite (KA) and AMPA bath application in hippocampal culture of mouse model as Niemann-Pick C disease (NPC) [4]. The hyperexcitability in NPC, which is at the basis of the insurgence of seizures, is indicated to be due to the enhanced glutamatergic neurotransmission caused by an altered KA and AMPA receptor functioning. The depolarization of AMPA receptors is responsible for generating fast excitatory neurotransmission. The density of the post-synaptic AMPA receptor is regulated in a highly dynamic manner by endocytosis. Therefore, the endocytic process is positioned to have a critical influence on synaptic plasticity. Some lysosomal disorders cause dysfunction of autophagy in neurocytes. Peroxisomes are degraded by autophagy known as pexophagy. Pex3, known as peroxisomal membrane protein, is important for peroxisome degradation [5]. In Zellweger syndrome, which caused by defect in the PEX genes including PEX3, may lost normal function of pexophagy. The dysfunction of autophagy may have influenced the function of crathrin-mediated endocytosis of AMPA receptors [6,7]. Increased expression of AMPA receptors may cause highly susceptibility to seizures [8,9]. It is indicated that administration of Perampanel for seizures caused from lysosomal disorders including peroxisomal disorder is reasonable treatment.

Conclusion

In conclusion, perampanel attenuated seizure safety in the condition of liver dysfunction with Zellweger syndrome. Perampanel may be useful and safety not only for Zellweger syndrome but also for other lysosomal disorders.

Conflict of Interest

The authors declare no competing interests.

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