A rare case of hypomyelinating leukodystrophy-14 benefiting from ketogenic diet therapy

Aycan Ünalp1, Melis Köse2, Pakize Karaoğlu3, Yiğithan Güzin3, Ünsal Yılmaz4

1Department of Pediatrics, Division of Pediatric Neurology, University of Health Sciences Turkey, İzmir Faculty of Medicine, İzmir; 2Department of Pediatrics, Division of Inborn Errors of Metabolism, Katip Çelebi University Medical Faculty, İzmir; 3Department of Pediatrics, Division of Pediatric Neurology, University of Health Sciences, Dr. Behçet Uz Childrens Education and Research Hospital, İzmir, Turkey.

ABSTRACT

Background. Hypomyelinating leukodystrophy-14 (HLD14) is a rarely seen neurodevelopmental disease caused by homozygous pathogenic ubiquitin-fold modifier 1 gene variants. The disease has an autosomal recessive inheritance. All patients with this condition reported to date have drug-resistant epilepsy. The post-translational modification of proteins with ubiquitin fold modifier 1 is defective in these patients and is thought to be responsible for severe neurodevelopmental problems. There is no previous report on the effectiveness of the ketogenic diet in the treatment of drug-resistant epileptic seizures in this disease. Therefore, we present a pediatric case diagnosed with HLD14 and whose drug-resistant epileptic seizures were controlled by ketogenic diet therapy.

Case. The patient was a three-year-old male with drug-resistant epilepsy and developmental delay. His brain magnetic resonance imaging revealed cerebellar atrophy, periventricular white matter hypomyelination, and ventricular enlargement. Whole-exome sequencing analysis identified a homozygous pathogenic variant in the ubiquitin-fold modifier 1 gene on chromosome 13q13. Ketogenic diet therapy was initiated for his drug-resistant seizures and subsequently reduced seizure frequency by more than 75%. The patient is still on ketogenic diet therapy.

Conclusions. Ketogenic diet therapy may be beneficial for seizure control in HLD14 patients with drug-resistant seizures.

Key words: drug-resistant epilepsy, hypomyelinating leukodystrophy-14, ketogenic diet therapy, children.

Hypomyelinating leukodystrophy-14 (HLD14, OMIM:610553) is a rare neurodevelopmental disorder that occurs due to homozygous pathogenic UFM1 gene variants on chromosome 13q13. The disease starts in early infancy and is characterized by microcephaly, hypotonia, and cognitive and motor delay. In addition, most patients have spasticity, extrapyramidal movements, drug-resistant seizures, hearing loss, and vision loss. Patients often require gastric tube feeding and ventilator support, and most die within the first year of life. Brain imaging shows hypomyelination with cerebral and cerebellar atrophy.¹

Protein modification enables the regulation and expansion of genetic information. Ubiquitination is a protein modification system in which single or multiple ubiquitin molecules are attached to a protein and act as a signal transmitter that controls various cellular functions.² The ubiquitin-like modifier (UFM-1) has structural similarities to ubiquitin. UFM-1 can be linked to substrate proteins as a monomer or a lysine-linked polymer. UFMylation is a specialized ribosomal modification to facilitate metazoan-specific protein biogenesis in the endoplasmic...
The reticulum and is essential for nervous system development and function. The post-translational modification of proteins on lysine residues has an essential role in several cellular processes. Defective UFMylation is thought to be responsible for severe neurodevelopmental problems in HLD14. Ketogenic diet therapy (KDT), which is frequently used for drug-resistant epilepsy, may also be beneficial for myelination disorders.

Here we report a pediatric patient with a rare leukodystrophy, HLD14, who had drug-resistant seizures and benefited from KDT.

Case Report

The patient, a three-year-old boy, was delivered by cesarean section in the 38th week of gestation. This was the mother’s third pregnancy. He was born to consanguineous parents, after an uneventful pregnancy. He had two healthy older siblings. He had a history of admission for 16 days in the neonatal period due to respiratory distress. A tracheostomy and mechanical ventilation were required at the age of six months, after which feedings were initiated with a nasogastric tube. The patient was using phenobarbital, levetiracetam, vigabatrin, and vitamin B6 for his seizures. On physical examination, the patient weighed 28 kg (+3 SDS), had dysmorphic facial features including sloping forehead, micrognathia, low ears and plump cheeks, microcephaly, high palate, simian line, fusiform fingers, axial hypotonia with increased muscle tone on extremities, and dystonia. Edematous appearance in the limbs was noted. Deep tendon reflexes were normoactive with no pathological reflexes and limited dorsiflexion of the feet. He could not hold his head up and had no eye-tracking. He had bilateral sensorineural hearing loss. Complete blood count, serum biochemistry, thyroid functions tests, vitamin B12 level and creatine kinase level were within normal limits. Electroneuromyography was normal. Echocardiography revealed a patent foramen ovale. Electroencephalogram (EEG) showed generalized spikes and polyspike and slow waves creating burst activities with suppression periods and was interpreted as modified hypsarrhythmia (Fig. 1a). He had frequent seizures as spasms which did not respond to multiple antiepileptic drugs. Brain magnetic resonance imaging (MRI) showed cerebellar atrophy, hypoplastic corpus callosum, and periventricular white matter hypomyelination (Fig. 2a-b). Magnetic resonance spectroscopy did not reveal any specific metabolite concentration. Metabolic tests (serum ammonia, lactate, pyruvate, biotinidase activity, tandem mass spectrometry with carnitine and acylcarnitine profile, urine organic acids, plasma and urine amino acids, levels of lysosomal enzymes) were unremarkable. He was admitted to the inpatient ward due to having seizures while on multiple

Fig. 1a. Electroencephalogram before ketogenic diet therapy showed generalized spikes and polyspike and slow waves creating bursts with suppression periods and was interpreted as modified hypsarrhythmia.

Fig. 1b. Electroencephalogram after ketogenic diet therapy demonstrated mild epileptiform activity in the parietooccipital and temporooccipital regions of the right hemisphere.
antiepileptic drugs. The patient’s seizures were in the form of apnea, focal spasms, and generalized tonic seizures. A classic KDT with a 3.5:1 ratio (ratio of grams of fat to grams of carbohydrate plus protein) was introduced with -one meal per day when the patient was two years old. This was gradually increased, and multivitamins were added.

Using the hydrolyzed milk formulae (Pepti-Junior®), and a 4:1 ketogenic ratio formula (KetoCal®), meals of 50 kcal/day were prepared for the patient via a nasogastric tube. The patient’s beta-hydroxybutyrate levels in the blood were measured and ketone levels were monitored. Values between 4-6 mmol/L were accepted as normal, but the patient was considered to have hyperketonemia because his values were above 6 mmol/L. On the 10th day of KDT, the ratio was decreased to 2.5:1 due to this state of hyperketonemia.

The patient’s seizure frequency was reduced by more than 75% with KD. Before KDT, the patient had an average of two seizures per day with a duration of 3-5 minutes. After the third month of KDT, his seizures decreased to two times per week with a duration of 2-3 minutes. Figure 1b shows improved epileptic discharges on EEG after KDT. The patient’s seizures decreased and vigabatrin treatment was tapered and discontinued in the follow-up. Whole-exome sequencing analysis revealed a single homozygous deletion in the promoter region of UFM1, which is c.-273-271 delTCA. The variant is classified as “pathogenic” based on American College of Medical Genetics and Genomics (ACMG) recommendations. Via segregation analysis, both the patient’s parents and his healthy siblings were found to be heterozygous carriers. The patient was diagnosed with HLD14.

No significant side effects of KD developed during follow-up. The patient’s quality of life and that of his family increased with the control of his seizures. It was observed that the patient started to smile, make sounds, and had increased movements in his head, arms, and legs. The family stated that the care of the patient improved as his spasticity and dystonia decreased on KD.

A written consent form was obtained from the parents for publication purposes.
Discussion

HLD14 is a severe neurodevelopmental disorder with autosomal recessive inheritance in which most patients develop drug-resistant epilepsy. Impairment of post-translational protein UFMylation is thought to be responsible for severe neurodevelopmental problems.\(^1\)

Hamilton et al.\(^1\) identified 16 pediatric patients with brain MRI findings suggesting hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) who have a severe clinical phenotype with epileptic encephalopathy and developmental delay. Similar to our patient, they found homozygous pathogenic variants of the *UFM1* gene in these patients. All of their patients had severe clinical phenotype consisting of epileptic encephalopathy with early death.\(^1\)

Nahorski et al.\(^3\) reported four children with a homozygous missense mutation in the *UFM1* gene from two related families with HLD14. Three of the patients died before the age of two. The patients presented with hyper or hypotonia, malnutrition, and severe global developmental delay in infancy. They developed resistant seizures in the first weeks or months of life, and EEG showed hypsarrhythmia in two siblings. The patients had poor overall growth with secondary progressive microcephaly and peripheral edema. Similarly, our patient had cerebellar atrophy, hypoplastic corpus callosum, and extensive periventricular white matter hypomyelination on brain imaging.

A new post-translational protein modification known as ubiquitination is a modification system in which single or multiple ubiquitin molecules are attached to a protein, acting as a signal transmitter that controls various cellular functions.\(^7\) The ubiquitin-like modifier (*UFM1*) is a ubiquitin-like protein regulator and is required for embryonic development. Ubiquitin and UBL pathways play a role in controlling multiple functions, including signal transduction, transcriptional regulation, and stress response.\(^2\) Various studies show that there is a relationship between both neurodevelopment and neurodegeneration via *UFM1*.\(^8\) Most evidence points to the role of *UFM1* in endoplasmic reticulum homeostasis and protection against apoptosis.\(^8\)

Muona et al.\(^10\) found that reducing the gene expression of *UFM1* in the mouse brain resulted in death on the first day of life. Postmortem examination revealed microcephaly and increased neuronal apoptosis markers in specific brain regions. They suggested that infiltration could be spatially regulated and cell type-specific; only selective neural cell lines are vulnerable to promoter mutation.\(^10\) Available data show that the *UFM1* system is vital for neuronal development and function.\(^2,11\)

Epilepsy is characterized by recurrent unprovoked seizures and is associated with the involvement of neurons in the gray matter. Early or resistant seizures can occur but are an unusual feature of disorders mainly affecting brain white matter.\(^12\) While the focal onset and bilateral tonic-clonic seizures are more common in some cohorts, generalized tonic-clonic, infantile spasm, and myoclonic seizures have also been reported.\(^13-15\)

In a study conducted on patients with leukodystrophy, the incidence of epilepsy was reported to be 49%. The incidence of epilepsy varies among different types of leukodystrophies and was found to occur more frequently in leukodystrophies classified as astrocytopathy, compared to myelin diseases. This finding is likely due to the role that astrocytes play in the pathogenesis of epilepsy. When astrocyte dysfunction occurs, it impairs its extracellular glutamic acid and K\(^+\) elimination ability leading to extracellular accumulation of glutamic acid and K\(^+\), thereby increasing the excitability of neurons and inducing seizures.\(^16\) Zang et al.\(^17\) also found leukodystrophies with early subcortical involvement of white matter were more prone to epilepsy than other types of leukodystrophy. This may suggest subcortical white matter involvement is likely to affect neighboring neurons in the cerebral cortex and can lead to epilepsy.
Since our patient had epileptic encephalopathy and his seizures could not be controlled despite the use of three antiepileptic drugs, he was considered to have drug-resistant epilepsy. Thus, the decision was made to pursue KDT with a ketogenic formula. The patient and his family were extremely compliant with the diet. As the patient had swallowing dysfunction due to generalized muscle weakness, he was fed with a nasogastric tube. Gastrostomy was not found to be appropriate due to his high weight. Since it was stated that subcutaneous adipose tissue increased due to obesity and percutaneous endoscopic gastrostomy could not be done, his calorie intake was reduced to 40 kcal/day in the follow-up.

Lipids have an essential role in the normal functioning of neurons and the structural development of the brain. Neurodegenerative diseases involve dysregulated lipid metabolism. In the central nervous system (CNS), most of the myelin’s lipids are synthesized by oligodendrocytes. Pelizaeus-Merzbacher disease (PMD) is a fatal, untreatable, hypomyelinating leukodystrophy. In PMD, brain lipid metabolism is often disrupted as a result of the X-linked myelin gene PLP1 (proteolipid protein 1) duplication. Overexpression in the PLP gene induces endoplasmic reticulum stress, damaging the oligodendroglial trophic support on axons. Chronic injury leads to demyelination. Unmyelinated axons need more energy to deliver the transmission, causing cells to increase mitochondrial activity to produce this required energy. Demyelination stimulates the inflammatory response, leading to increased reactive oxygen and nitrogen production. It has been shown in vitro and in vivo that lipid supplementation increases myelination in hypomyelinating pathologies and thus supports repair.

Consumption of a high-fat / low-carbohydrate KD causes the liver to form ketone bodies. In the brain, ketone bodies such as beta-hydroxybutyrate facilitate sterol synthesis, which is essential for myelin membrane growth. Therefore, it has been questioned whether a KD that supports CNS lipid metabolism may be useful in hypomyelinating disease. Unlike glucose, ketone bodies are directly metabolized by the mitochondria, entering the tricarboxylic acid and oxidative phosphorylation pathways. It was thought that feeding using the KD would provide direct support for demyelinating axons by providing mitochondrial integrity. Bypassing the need for oligodendroglial support can correct axonal mitochondrial functions (and morphology) and correct energy deficits in the axons. It may even contribute to improved survival of mutant oligodendrocytes and improvement of PMD pathology. The KD may be considered a future treatment for myelin diseases. Its two critical therapeutic goals are to provide cholesterol for support of remyelinating oligodendrocytes and to provide ketone bodies for metabolic support of axons, and future clinical trials will reveal its feasibility.

Since our patient also had leukodystrophy, our decision to use classic KD could have been more appropriate because this option creates more ketosis than the medium-chain triglyceride (MCT) KD, which is important for both seizure control and mitochondrial integrity in myelin diseases. As mentioned above, the effect of KDT in hypomyelinating diseases is not directly caused by an increase in lipids, but indirectly by an increase in ketosis and an improvement in mitochondrial functions.

In conclusion, we emphasize that KDT should be considered as a treatment option in this rare leukodystrophy for drug resistant seizures.

**Ethical approval**

A written consent form was obtained from the parents for publication purposes.

**Author contribution**

The authors confirm contribution to the paper as follows: study conception and design: AÜ,
PK, YG; data collection: AÜ, MK, ÜY; analysis and interpretation of results: AÜ, YG, PK; draft manuscript preparation: AÜ, YG. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare that there is no conflict of interest.

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