pISSN: 2234-8646 eISSN: 2234-8840
https://doi.org/10.5223/pghn.2017.20.4.259
Pediatr Gastroenterol Hepatol Nutr 2017 December 20(4):259-262

Case Report

PGHN

Alpers-Huttenlocher Syndrome First Presented with Hepatic Failure: Can Liver Transplantation Be Considered as Treatment Option?

Sowon Park, Hoon-Chul Kang*, Jin-Sung Lee†, Young Nyun Park‡, Seung Kim, and Hong Koh

*Division of Gastroenterology, Hepatology and Nutrition, *Division of Neurology, and †Division of Clinical Genetics, Department of Pediatrics, Severance Children's Hospital, ‡Department of Pathology, Yonsei University College of Medicine, Seoul, Korea*

Mitochondria play essential role in eukaryotic cells including in the oxidative phosphorylation and generation of adenosine triphosphate via the electron-transport chain. Therefore, defects in mitochondrial DNA (mtDNA) can result in mitochondrial dysfunction which leads to various mitochondrial disorders that may present with various neurologic and non-neurologic manifestations. Mutations in the nuclear gene polymerase gamma (*POLG*) are associated with mtDNA depletions, and Alpers-Huttenlocher syndrome is one of the most severe manifestations of *POLG* mutation characterized by the clinical triad of intractable seizures, psychomotor regression, and liver failure. The hepatic manifestation usually occurs late in the disease's course, but in some references, hepatitis was reportedly the first manifestation. Liver transplantation was considered contraindicated in Alpers-Huttenlocher syndrome due to its poor prognosis. We acknowledged a patient with the first manifestation of the disease being hepatic failure who eventually underwent liver transplantation, and whose neurological outcome improved after cocktail therapy.

Key Words: Alpers-Huttenlocher syndrome, Liver failure

INTRODUCTION

Alpers-Huttenlocher syndrome (AHS), which first received attention from Alpers in 1931 [1] and was further described with its hepatic manifestation by Huttenlocher et al. [2] and Harding [3], is a rare mitochondrial disease characterized by its classic triad of refractory seizures, psychomotor regression, and hepatopathy [3]. In 1999, Naviaux et al. [4] established the biochemical and enzymatic relevance of polymerase gamma (*POLG*) in AHS with their description of mitochondrial DNA depletion and reduced *POLG* activity. In most cases, the first manifestation of AHS is a neurodevelopmental delay or in-

Received : May 3, 2017, Revised : May 18, 2017, Accepted : May 26, 2017

Corresponding author: Hong Koh, Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea. Tel: +82-2-2228-2050, Fax: +82-2-393-9118, E-mail: khong@yuhs.ac

tractable seizures, but it has been reported that in some rare cases its first manifestation is hepatic [5]. Hepatic failure is most commonly presented in the preterminal stage regardless of valproate exposure, and many patients die due to either hepatic failure or neurological deterioration [5,6].

Our team investigated a 10-month-old patient with AHS whose first manifestation was hepatic failure he received liver transplantation and later developed epilepsy and psychomotor regression. His prognosis was sufficiently good to be discharged from hospital with neurodevelopmental improvement.

CASE REPORT

A 10-month-old male patient was admitted for persistent hepatitis and jaundice. He did not have any perinatal, familial, or past history except that he had received treatment for bronchitis in another hospital two weeks prior to admission. His aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated upon his admission for bronchitis, and reactive hepatitis was suspected because of his intact liver function and clinical history. However, he eventually developed impending hepatic failure, and was referred to the hepatology department. The initial laboratory finding suggested acute liver failure with AST and ALT levels of 194 IU/L and 69 IU/L, total and direct bilirubin of 7.4 mg/dL and 6.3 mg/dL, ammonia of 57 μg/dL, and gamma-glutamyl transpeptidase of 101 IU/L, respectively. His initial blood gas analysis test, with normal pH of 7.40 and bicarbonate of 25.8 mmol/L, was not suggestive of definite metabolic acidosis, although the lacate level was slightly elevated to 2.4 mmol/L. Numerous evaluations such as viral, autoimmune, endocrinologic, and genetic studies for ATP7B and ABCB11 were performed that all turned out normal, and there were no remarkable findings in his imaging study. The lactate-to-pyruvate ratio was 82.5, and plasma amino acid assay suggested the possibility of lactic acidosis. Therefore, the whole exome sequencing (WES) anal-

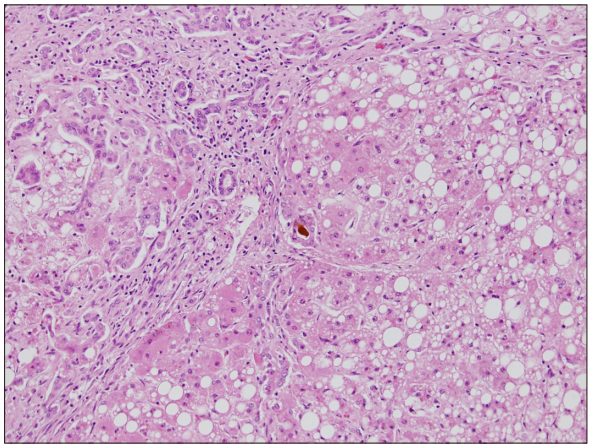

Fig. 1. Liver histopathology (H&E, ×100). The histopathology confirmed marked fatty change, cholestasis, ballooning degeneration and marked ductular proliferation, favoring metabolic disease.

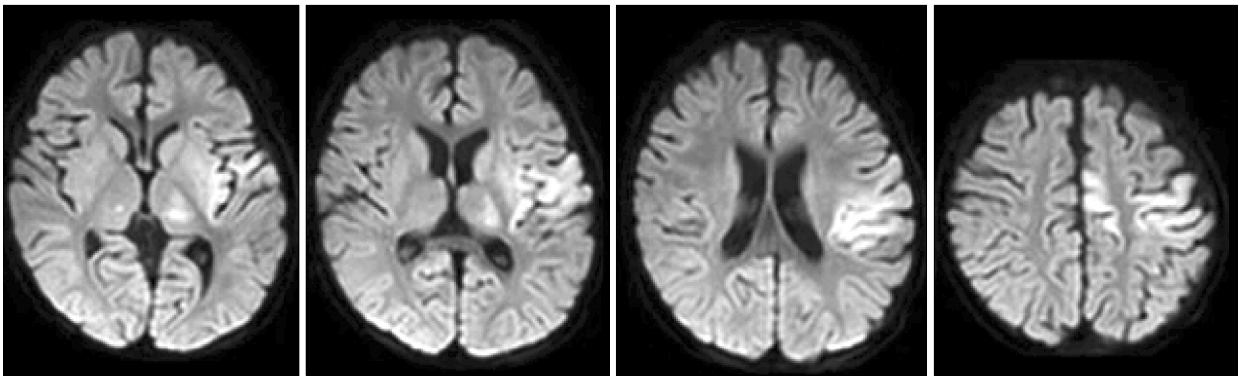

Fig. 2. Brain magnetic resonance imaging (MRI). MRI showed multifocal diffusion restriction area in left insula, deep gray matter and bilateral peri-rolandic area.

Table 1. Heterozygous Mutation of Polymerase Gamma (*POLG*) Gene

Gene	HGVS	Patient	Parent A	Parent B
POLG	NP_002684.1:p.Arg807His	O, hetero	X	O, hetero
POLG	NP_002684.1:p.Arg627Trp	O, hetero	O, hetero	X

Compound heterozygous mutation of *POLG* gene (p.Arg807His and p.Arg627Trp) was found.

ysis was sent out for further evaluation. Meanwhile, his mental status became drowsy with hyperammonemia, and he received a living donor liver transplantation at admission day 24. The pathologist confirmed cirrhosis with marked fatty change, cholestasis, ballooning degeneration and marked ductular proliferation, favoring metabolic disease (Fig. 1). The liver transplantation was successful, and he was discharged home with normal neurological function. One month later, he was readmitted to the neurology department for eye blinking and myoclonus on the right side of his face. Electroencephalogram (EEG) was performed, which determined left periodic lateralized epileptiform discharges, and brain magnetic resonance imaging (MRI) showed multifocal diffusion restriction areas in the left insula, deep gray matter and bilateral perirolandic area, suggesting metabolic disorder (Fig. 2). A combination therapy of six antiepileptic drugs did not improve his continuous myoclonic seizures, and other symptoms such as psychomotor regression, nystagmus, swallowing difficulty and frequent central apnea subsequently occurred. WES revealed the known compound heterozygous mutation of the *POLG* gene (p.Arg807His and p.Arg627Trp), confirming AHS (Table 1). The EEG pattern evolved to a generalized slow spike and waves with generalized paroxysmal fast activities in the left hemisphere, and follow-up MRI showed diffuse cerebral atrophy, especially on the left posterior quadrant. Valproate was discontinued immediately, and a mitochondrial cocktail therapy comprised of thiamine, coenzyme Q10 (CoQ10), and L-carnitine was started. After four months of this cocktail therapy, the number of apnea events had reduced and nystagmus and motor function had slightly improved. The feeding problem was resolved after the gastrostomy, and he could tolerate enteral feeding without reflux. Recently, he was able to intake some feeding per oral. He was discharged home after one year of hospitalization.

DISCUSSION

AHS is a mitochondrial disease caused by autosomal recessive *POLG* mutation [5]. *POLG* is the DNA polymerase in mitochondria that is responsible for mitochondrial DNA replication and repair in the mitochondria of eukaryotic cells [7]. Ultimately, a significant amount of mitochondrial DNA depletion is noted when mutation occurs in *POLG* which leads to dysfunction in multiple organs such as the brain and liver [7]. The first manifestation usually starts with seizures or psychomotor regression. Liver involvement was rarely reported as the first manifestation, and it is mostly associated with preterminal disease stage [5]. There is no available treatment with which the clinical course of the disease can be modified, and patients with this disease die within four years of the onset of features [5]. Therefore, liver transplantation is said to be contraindicated in the disease due to the poor prognosis even after the successful transplantation [5,6]. The treatment of this disease is focused on symptomatic treatment for the control of seizures, ventilation disorders, or nutritional issues [5]. Valproate is usually contraindicated in AHS since it can accelerate the dysfunction of mitochondria, leading to liver failure [6]. In our case, although the patient had already undergone liver transplantation, we decided to discontinue valproate since it did not seem to be essential for controlling his seizures. Cocktail therapy including vitamins and CoQ10 can be considered as a treatment option in mitochondrial disease by enhancing the mitochondrial function [8].

In the literature review, this was the first report of AHS presenting its first manifestation as liver failure [5]. The patient's neurological function was normal even after liver transplantation, and he was discharged to home and began to develop *epilepsia partialis continua* one month after liver transplantation. A cocktail therapy for mitochondrial disease was started after the diagnosis of *POLG* mutation, and it seemed to stabilize our patient's organ function even though we could not stop his partial seizures. We could presume that his organic dysfunction and clinical symptoms became more severe than the degree of his DNA depletion, which resulted in the positive prognosis of his clinical symptoms with CoQ10 and vitamin support.

AHS is one of the most severe phenotypes of *POLG* mutation and is a fatal disease for which there is no available treatment that modifies its clinical course. However, we want to make the point that liver transplantation can be considered as a treatment option if the disease's course is stable, especially when presenting at a late age. Moreover, in a patient with liver failure of unknown etiology, investigation including genetic study should always be considered when there are signs of metabolic disorders.

REFERENCES

1. Alpers BJ. Diffuse progressive degeneration of the gray matter of the cerebrum. Arch Neur Psych 1931;25: 469-505.
2. Huttenlocher PR, Solitare GB, Adams G. Infantile diffuse cerebral degeneration with hepatic cirrhosis. Arch Neurol 1976;33:186-92.
3. Harding BN. Progressive neuronal degeneration of childhood with liver disease (Alpers-Huttenlocher syndrome): a personal review. J Child Neurol 1990;5: 273-87.
4. Naviaux RK, Nyhan WL, Barshop BA, Poulton J, Markusic D, Karpinski NC, et al. Mitochondrial DNA polymerase gamma deficiency and mtDNA depletion in a child with Alpers' syndrome. Ann Neurol 1999; 45:54-8.
5. Saneto RP, Cohen BH, Copeland WC, Naviaux RK. Alpers-Huttenlocher syndrome. Pediatr Neurol 2013;48:167-78.
6. Hynynen J, Komulainen T, Tukiainen E, Nordin A, Arola J, Kälviäinen R, et al. Acute liver failure after valproate exposure in patients with POLG1 mutations and the prognosis after liver transplantation. Liver Transpl 2014;20:1402-12.
7. Cohen BH, Naviaux RK. The clinical diagnosis of POLG disease and other mitochondrial DNA depletion disorders. Methods 2010;51:364-73.
8. Avula S, Parikh S, Demarest S, Kurz J, Gropman A. Treatment of mitochondrial disorders. Curr Treat Options Neurol 2014;16:292.