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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

The first living newborn case with 7706G>A missense mutation: Alpers-Huttenlocher syndrome

7706G>A missense mutasyonuna sahip ilk yaşayan yenidoğan olgusu: Alpers-Huttenlocher sendromu

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To the Editor

Alpers-Huttenlocher syndrome (AHS, OMIM 203700) is an uncommon, lethal hepatocerebral degenerative mitochondrial (mtDNA) depletion syndrome with heterogeneous genetic inheritance. Bernard Alpers first defined in 1931 as "diffuse progressive degeneration of the gray matter of the cerebrum" with recurrent generalized seizures and Huttenlocher et al. considered a new syndrome of progressive neurodegeneration and hepatic dysfunction by in 1976[1,2].

The estimated incidence is between 1/100 and 1/250 000 births. It commonly develops due to a recessive mutation in the polymerase-γ gene (POLG) (OMIM 174763) on chromosome 15q25[3]. Additionally, other rare mutations are reported in case reports, such as *7706G>A* missense mutation in the Cox II gene[4]. Three clinical forms; neonatal, infantile and juvenile forms, have been defined using age of onset. Both juvenile and neonatal forms are very rare. Persistent seizures, hypotonia, recurrent vomiting, and rarely cardiomyopathy result in death before the childhood in neonatal-onset AHS[5].

This report aimed to describe the newborn case of AHS due to the *7706G>A* missense mutation in the Cox II gene first diagnosed while alive in the literature.

A 20-day-old boy was hospitalized to our clinic due to seizures, hypotonia and suspected meningitis. The baby was born at term by vaginal delivery and healthy until he was twenty days old. Her parents are first-degree cousins and aunts' children also had a similar history of seizures that resulted in death in infancy.

At 20 days of age, the baby admitted to another hospital due to decreased sucking, restlessness and seizure. A brain computed tomography (CT) scan showed no abnormality at the same time. High cerebrospinal fluid (CSF) protein levels were detected in lumbar puncture (140 mg/dL). First, ampicillin and cefotaxime and then vancomycin and meropenem were started due to suspection of menengitis. Three days after his hospitalization, sudden focal myoclonic jerks began, which resulted in generalized myoclonic status epilepticus. He was intubated and transported to our neonatal intensive care unit. He was hypotonic, deep tendon reflexes were increased and plantar reflexes were absent. Cerebral and cerebellar atrophy, bilateral hemispheric subcortical and periventricular signal increase, suspicious cystic cavitary area at supraventricular level (sequelae of infection? ischemia?) were detected in the first magnetic resonance imaging (MRI) (Figure 1). Acyclovir was added to his treatment because MRI spectroscopy was reported as suspected herpes infection. MRI venography was normal.

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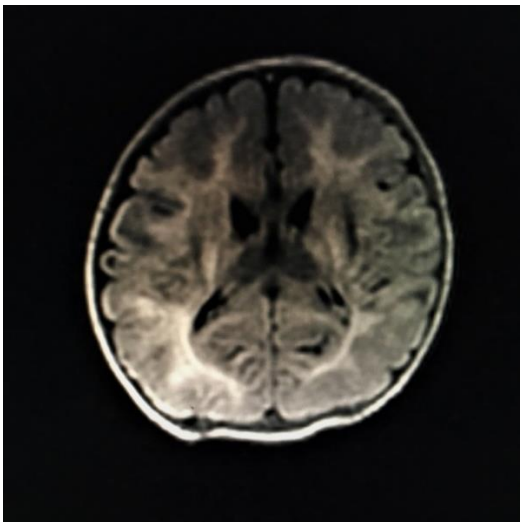

Figure 1. Cerebral and cerebellar atrophy, bilateral hemispheric subcortical and periventricular signal increase, suspicious cystic cavitary area at supraventricular level on the first MRI.

Arterial blood gas was normal except for lactate elevation (lactate: 5.1 mmol/L). His seizures were controlled with phenobarbital, levetiracetam, vigabatrin, L-carnitine, coenzyme Q and multivitamins. Tests including venous blood gases, ammonia, ceruloplasmin, phenylalanine, thyroid function tests, plasma amino acids and urine organic acids revealed no abnormalities. Serum lactate/pyruvate ratio: 85/3.3 (mg/dL) was found to be increased. Hepatic enzymes were mildly elevated with aspartate aminotransferase 61 U/L (normal 12-37), alanine aminotransferase 79 U/L (normal 20-65), gamma-glutamyl transferase 79 U/L (normal 6-26) and alkaline phosphatase 146 U/L (normal 100-450). Serum albumin and total bilirubin were normal. Virologic screening was negative. CSF analyze revealed normal lactate and pyruvate. Genetic examination of Menkes disease was normal. His electroencephalography showed an irregularity of rhythm. There was no evidence of any metabolic disease on eye examination. Echocardiography revealed small atrial septal defects and septal hypertrophy.

Repeated brain MRI, four weeks later, showed diffuse atrophy and cystic dilatations in both hemispheres and effusion in both subdural distances (Figure 2). The possibility of mitochondrial disease was entertained based on the clinical picture and positive family history of similar cases, and further molecular rapid gene analyze revealed the presence of a *7706G>A* missense mutation in the Cox II gene resulting in Alpers-Huttenlocher syndrome. Tracheostomy was performed due to prolonged intubation on the 81st day of hospitalization. On the 101st day, he died from hypoxemic respiratory failure. In the liver tests at this time, aspartate aminotransferase was high (317 U/L), while alanine aminotransferase was normal (15 U/L).

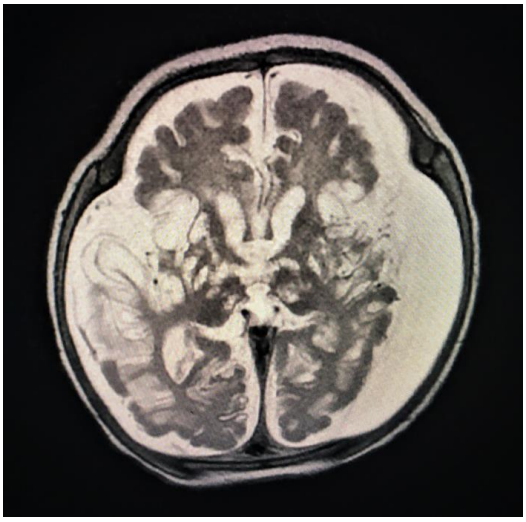

Figure 2. Diffuse atrophy and cystic dilatations in both hemispheres and effusion in both subdural distances on the second MRI

Alpers-Huttenlocher syndrome, also known as infantile diffuse cerebral degeneration with hepatic cirrhosis or progressive infantile poliodystrophy, was first diagnosed in a previously healthy 4-month-old child who presented with convulsions and cortical blindness[1]. After this description by Bernard Alpers and Alfons Maria Jakob in 1931, Huttenlocher reported histopathologic findings, liver dysfunction and increased cerebrospinal protein levels[6]. Psychomotor retardation, hepatic dysfunction and clinical symptoms of refractory seizures combined with at least two of the eleven diagnostic criteria for Alpers-Huttenlocher syndrome put the diagnosis[6]. In our case, protein elevation was detected in the cerebrospinal fluid when clinical signs began. This situation led to the initiation of antibiotics with a preliminary diagnosis of meningitis. In his further examinations, lactate levels were high in arterial blood gas and serum, which were also in the diagnostic criteria of Alpers-Huttenlocher syndrome.

Mitochondrial DNA depletion syndromes cause respiratory chain dysfunction with significant muscle, neurologic and liver involvement[7]. Developments in molecular genetics, such as Sanger sequencing techniques and next-generation sequencing, help to identify mutations in several genes involved in mtDNA depletion syndromes[8]. In our case, whole mitochondrial genome sequencing was performed with next-generation sequencing, and a *7706G>A* missense mutation was detected in the Cox II gene, different from the frequently detected genes. The *7706G>A* missense mutation resulted in convulsion, which is one of the clinical findings of AHS in the neonatal period (20 days). This may predict that the prognosis may be worse than other genetic mutations.

A case report by Uusimaa et al. was presented in 2002 in which the 7706G>A missense mutation in the Cox II gene causes AHS. The patient first applied when she was six months old with complaints of feeding problems and not gaining weight. She developed muscle weakness and exercise intolerance when she was six years old and died as a result of unexpected cardiac arrest. Postmortem autopsy revealed 7706G>A missense mutation as a result of genetics studied from liver tissue[4]. Compared to the published case report, our case was diagnosed much earlier. To our knowledge, our case is the first newborn AHS case in the literature due to the *7706G>A* missense mutation in the Cox II gene.

Proton MR spectroscopy can reveal an elevated lactate level and a reduced N-acetylaspartate/creatine (NAA/Cr) ratio on conventional MRI[9]. Consequently, MR spectroscopy has proven to be more sensitive regarding lactate detection than neurometabolic examination of the serum and CSF[10]. In our case, the first brain MRI revealed bilateral frontotemporoparietal, occipital subcortical and periventricular signal increases. In the control brain MRI one month later, a significant decrease in NAA peaks in the brain parenchyma, evident atrophy findings in the bilateral cerebral hemisphere, new cystic lesions developing in the brain parenchyma, and collections reaching a size of 15 mm in both subdural distances were detected.

In a study by Frydman M. et al., eight patients from two families were reported[5]. Four cases had convulsions in the first ten days, and one case died at fourteen days of age However, as reported, differential diagnoses were made with clinical and brain MRI/CT. In our case, there were both clinical and MRI findings. In contrast, *7706G>A* missense mutation was detected in the Cox II gene, which was previously associated with AHS, in mitochondrial genome sequencing.

Fatal liver failure, with characteristic histopathological changes such as fatty changes, liver fibrosis and abnormal bile duct structure, occurs at the end of disease progression or after administration of valproic acid[11]. Since our case was diagnosed in the neonatal period, there was a mild elevation of transaminases but no liver failure. In addition, we predicted drug-related liver failure of valproic acid, and the seizures of the case were treated with phenobarbital, levetiracetam and vigabatrin.

Alpers-Huttenlocher syndrome should be kept in mind in the differential diagnosis of patients with hypotonicity, seizures, and progressive neuroimaging findings in infancy, and mitochondrial genome sequencing analyze should be performed to detect rarer and perhaps more lethal mutations, such as the *7706G>A* missense mutation, which was detected in our case, as opposed to frequent mutations.

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