Case Report

Hypomyelination and Congenital Cataract: Three Siblings Presentation

Zeynep Selen Karalok, Esra Gurkasb[1], Kursad Aydinc[2], Serdar Ceylaner[3]

Department of Pediatric Neurology, Akdeniz University School of Medicine, Antalya, Turkey, [1]Department of Pediatric Neurology, Ankara Children's Hospital Hematology-Oncology Research and Training Hospital, Ankara, Turkey, [2]Department of Pediatric Neurology, Medipol University, İstanbul, Turkey, [3]Intergen Genetic Diagnostic Research Center, Ankara, Turkey

Abstract

Hypomyelination and congenital cataract (HCC) is a condition, which is caused by mutations in the *FAM126A* gene and is characterized by congenital cataract, progressive neurologic impairment, and myelin deficiency in both the central and peripheral nervous system. We present the findings of three siblings who applied to us with the same clinical features. These patients were referred to our clinic due to the presence of bilateral congenital cataract and progressive neurological impairment with peripheral neuropathy. Brain magnetic resonance imaging (MRI) showed diffuse hypomyelination, whereas neurophysiological studies showed sensorimotor peripheral polyneuropathy. Cases with hypomyelination in MRI represent the largest group of undiagnosed diseases among patients with leukoencephalopathies. To diagnose cases with peripheral neuropathy, their clinical and neuroradiological findings must be identified. These findings can guide clinicians to appropriate molecular investigations.

Keywords: *Cataract, FAM126A, MRI, myelination*

Introduction

Hypomyelination and congenital cataract (HCC, OMIM #610532) is a rare autosomal recessive disorder, which is characterized by congenital cataract, myelin deficiency in both the central and peripheral nervous system (PNS), progressive neurologic impairment, and mild-to-moderate cognitive defects. The neurological picture is characterized by pyramidal and cerebellar signs, and also muscle weakness and wasting of the lower limbs which indicate the involvement of the PNS. The presence of peripheral neuropathy was confirmed by neurophysiological and neuropathological studies.[1,2] This disorder is due to mutations in *FAM126A* that lead to the loss of the FAM126A/hyccin protein.[3]

Here, we describe the clinical and neuroradiological findings of three siblings who were diagnosed with HCC.

Patients and Methods

Our patients were siblings from Yemen whose parents were consanguineous. Patient #1 The first child of the family was a 9-year-old boy born by normal delivery at term after an uneventful pregnancy. Soon after the birth, bilateral congenital cataract was revealed and ocular surgery was performed at 6 months. Early developmental milestones were normal, but he was unable to walk or stand at 2 years. His speech was limited to a few words. He never suffered from seizures. In his last neurological examination, he was found to have mental retardation, nystagmus, truncal hypotonia with muscle weakness, spasticity and contractures in both the lower and upper limbs, bilateral Babinski sign, scoliosis, and swallowing difficulties. He was wheelchair-bound. Neurophysiological studies showed sensorimotor peripheral polyneuropathy. Magnetic resonance imaging (MRI) of the brain showed

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Address for correspondence: Dr. Zeynep Selen Karalok, Pınarbaşı Mah, Dumlupınar Bul. Akdeniz University Faculty of Medicine, Department of Pediatric Neurology, 07070, Konyaaltı, Antalya, Turkey.
E-mail: selen_z@yahoo.com

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diffuse supratentorial hypomyelination with areas of more pronounced T1-hypointensity and T2-hyperintensity, in the context of diffuse white matter volume loss with corresponding enlargement of the ventricular cavities and subarachnoid spaces [Figure 1].

The second child of the family was also born by normal delivery at term after an uneventful pregnancy. However, the child died after birth, etiology is unknown.

Patient #2 The third child of the family is a 5-year-old girl, who was born with bilateral congenital cataract and underwent ocular surgery at 6 months. She was able to sit without support at 1 year of age, and was able to walk with support at around 2 years. In her last neurological examination, she was found to have mild mental retardation, nystagmus, truncal hypotonia with muscle weakness, increased muscle tonus in the lower limbs, hyperreflexia in the lower limbs, normal tendon reflexes in upper limbs, and bilateral Babinski sign. It was also found that she could no longer walk, but could stand up. Her speech was limited to a few words and she could understand simple words. Motor nerve conduction velocity studies of the common peroneal nerves showed slowing of motor conduction. Brain MRI showed diffuse hypomyelination [Figure 2].

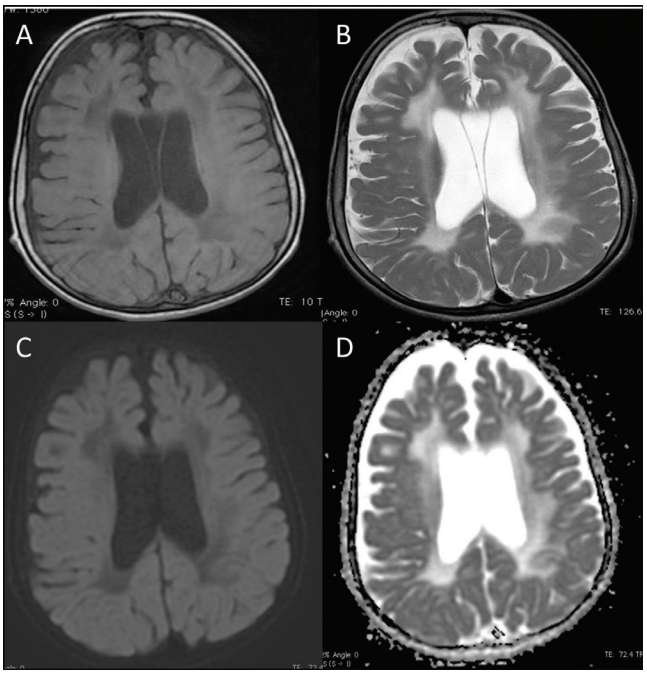

Figure 1: (A) Axial T1-weighted image showing diffuse hypointensity of the supratentorial white matter, resulting in blurred gray-white matter interface, consistent with hypomyelination. (B) Axial T2-weighted image showing diffuse white matter hyperintensity with hypomyelination and cortical cerebral atrophy. Due to cerebral atrophy seen ventricular enlargement. (C, D) Axial DWI and ADC showing shrunken white matter with markedly increased diffusivity

Patient #3 The last child of the family is a 4-year-old girl who was also born with bilateral congenital cataract and underwent ocular surgery at 6 months. She showed developmental delay in the first year of life; she was never able to walk even with support. She was able to sit without support by the age of 2. In her last neurological examination, she had mental retardation, nystagmus, truncal hypotonia, increased muscle tonus in both lower and upper limbs, and bilateral Babinski sign. Brain MRI showed diffuse supratentorial hypomyelination [Figure 3].

MR spectroscopy of patients could not be performed due to technical issues. TORCH infections were evaluated because all siblings had the same symptoms and family history of consanguinity, so primarily genetic tests performed.

Molecular Findings

Targeted sequence analysis of the *FAM126A* gene was planned by next-generation sequencing method, no amplification was detected after polymerase chain reaction (PCR) with in-house designed primers which had been previously optimized. We performed a deletion analysis with positive and negative controls; homozygote complete gene deletion was detected with PCR and gel electrophoresis. Due to the complete

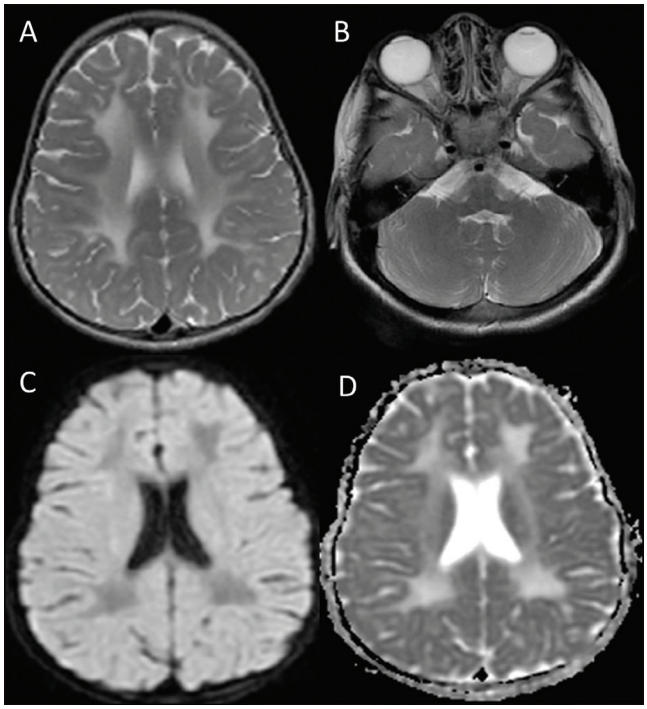

Figure 2: (A) Axial T2-weighted image showing diffuse white matter hyperintensity with hypomyelination. (B) Axial T2-weighted image showing that not seen lens at orbital area (sign for congenital cataract). (C, D) Axial DWI and ADC showing shrunken white matter with markedly increased diffusivity

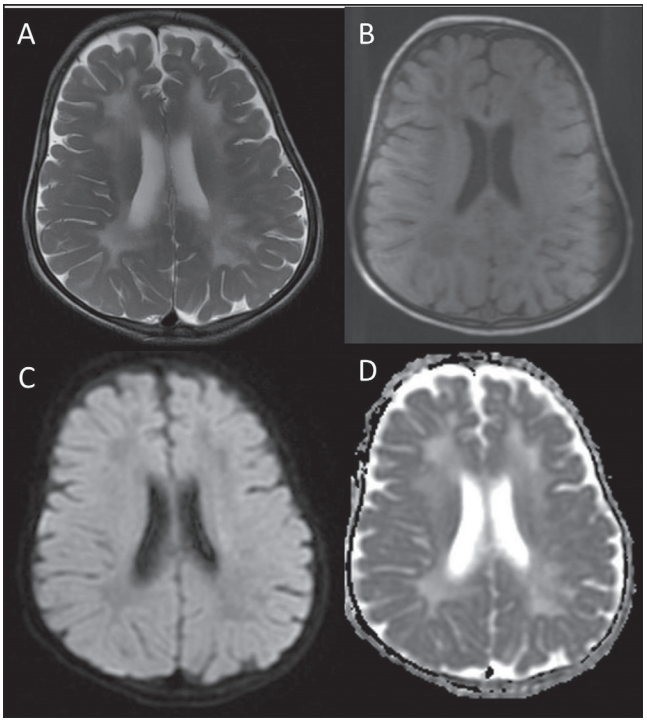

Figure 3: (A) Axial T2-weighted image showing diffuse white matter hyperintensity with hypomyelination and the signal intensity is lower than that of CSF. (B) Axial T1-weighted image showing diffuse hypointensity of the supratentorial white matter. (C, D) Axial DWI and ADC showing shrunken white matter with markedly increased diffusivity

loss of gene function, we evaluated this variant because it was a "pathogenic" variant. As there was no commercial MLPA product for this gene, family screening for heterozygotes could not be performed. Further molecular tests were planned, but contact with the family was lost.

Discussion

Genetic defects in the formation and maintenance of myelin result in leukodystrophies, a group of white matter diseases whose underlying mechanisms are poorly understood. Cases with hypomyelination represent the largest group of undiagnosed leukodystrophy cases, due to the uniform and nonspecific characteristics of MRI.[4,5] One of these disorders is the condition named HCC, which is caused by mutations in *FAM126A*, a gene that encodes a 521aa protein, named Hyccin. Hyccin gene activity has been observed in the central nervous system (CNS) and olfactory nuclei.[3] Phosphoinositides (PIPs) are phospholipids that play critical roles in many physiological processes in addition to their roles in the regulation, biosynthesis, and maintenance of myelin in oligodendrocytes and Schwann cells. The leukodystrophy protein, *FAM126A*/Hyccin, regulates PI4P synthesis at the plasma membrane.[6,7] Different degrees of reduction in myelinated fiber density, and presence of axons surrounded by a thin myelin sheath or devoid of myelin were observed in sural nerve biopsies of patients with HCC.[1]

Generally, the typical triad of HCC (progressive neurological impairment with peripheral neuropathy, bilateral congenital cataract, and hypomyelination pattern on brain MRI) is present in patients. Developmental delay becomes apparent around the end of the first year of life. The MRI criteria for the diagnosis of hypomyelination are as follows: presence of high signal intensity on T2-weighted images and a low, intermediate or high signal intensity on T1-weighted images of the white matter.[8,9] HCC is relatively common in and around the Mediterranean area. Most cases in the literature have been reported from Southern Italy, Morocco, Turkey, and Israel.[10,11]

Although the evaluation of our patients shows high similarities regarding neurological findings, Patient 2 was found to be mildly different, with relatively better neurological signs than her two siblings. Regarding MRI findings, the older sibling was found to have greater ventricular enlargement, probably due to advanced cerebral atrophy.

A study by Ugur and Tolun[12] reported that congenital cataract was not essential to the diagnosis of HCC and that it could be seen later in life. Similarly, Biancheri *et al*.[10] showed that one of their patients had mild lens opacity which was diagnosed by the third year of life. Furthermore, the age at which neurologic impairment presented was shown to vary among patients. When evaluated together, it can be said that patients with HCC may show clinical variability regarding the age of cataract onset and the progression of neurological symptoms and their severity.

Our study reports findings of three patients with HCC who presented with congenital cataract and neuroradiological features of hypomyelinating leukodystrophy, which suggested the diagnosis of HCC. The analysis of *FAM126A* mutations should be the first diagnostic step in patients who are strongly suspected to have HCC. It is also crucial to provide appropriate genetic counseling to families.

Ethical policy and institutional review board statement

Informed consent was obtained from parents of the patients for publication of the case report.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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