The First Case of 4H Syndrome with Type 1 Diabetes Mellitus

Running Head: 4H Syndrome with Type 1 Diabetes Mellitus

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INTRODUCTION

Leukodystrophies constitute a heterogeneous, rare inherited group of diseases that mainly affect the white matter of the central nervous system (1). The clinical signs of the disease are generally nonspecific and may occur at different ages, from the neonatal period to late adulthood (2). Patients may present with non-neurological findings as well as the neurological findings. Non-neurological symptoms can be used to categorize leukodystrophies more accurately (3). Ophthalmological, dental, musculoskeletal, gastrointestinal, and skin problems have also been reported in addition to the endocrine problems, such as adrenal insufficiency, hypogonadism, hypothroidism, growth hormone (GH) deficiency, and ovulation insufficiency (2). 4H syndrome inherited in an autosomal recessive manner is a rare progressive hypomyelinating leukodystrophy. It was first described in 2006 by Timmons et al. and is characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism (4). Its clinical course is highly variable. In addition to cases with severe neurological signs, some cases presented only with idiopathic hypogonadotropic hypogonadism in late adolescence have also been reported (5, 6). While the most common endocrine abnormalities associated with this disorder have been reported to date, a case accompanied by type 1 DM has not been seen in the literature. We do not know exactly whether this is coincidental or the expansion of the phenotype. So that reporting such cases helps to determine the appropriate genotype–phenotype correlation in patients.

What this study adds?

We report two siblings with bi-allelic pathogenic variants of the POLR3A gene. This is the first case of 4H syndrome accompanied by type 1 DM in the literature. It is not exactly known whether this is coincidental or the expansion of the phenotype. 4H syndrome may present with neurological and non-neurological findings in addition to classic features of 4H syndrome. Progressive neurological deterioration may occur, and endocrine dysfunction may be progressive. Although multiple endocrine abnormalities associated with this disorder have been reported to date, a case accompanied by type 1 DM has not been seen in the literature. We do not know exactly whether this is coincidental or the expansion of the phenotype. So that reporting such cases helps to determine the appropriate genotype–phenotype correlation in patients.

KEYWORDS: 4H leukodystrophy; POLR3A, hypogonadotrophic hypogonadism, type 1 diabetes mellitus.

Case presentation

Case 1

A 16-year-old Turkish female (II-1) was referred to our hospital with the complaint of secondary amenorrhea. After menstrual bleeding twice at an interval of 1 month at the age of 13.5 years, she didn’t have menstrual bleeding again. Patient was born as a term baby, with a birth weight of 4750 g, from a first-degree consanguineous marriage. Her neuromotor development was consistent with her peers. She started to walk at the age of 10 months, walked without support by 12 months of age, started speaking single meaningful words by 12 months of age and spoke in short sentences by 2 years of age. After the age of 12, she could not continue school due to the gradual decrease in her academic success and the increase in forgetfulness. When she applied to endocrinology department, her body weight was measured as 50.7 kg (-0.88 standard deviation score (SDS)), height was 161.1 cm (-0.22 SDS), and body mass index was 19.5 kg/m² (-0.8 SDS). Other systemic and detailed neurological examinations of the patient with Tanner stage 5 were normal. The laboratory examination results were found to be compatible with impaired fasting glucose, impaired glucose tolerance, euthyroid Hashimoto’s thyroiditis, and hypogonadotropic hypogonadism (Table 1).

Case 2

A 13.5-year-old Turkish male (II-2) was referred to our hospital with the complaint of secondary amenorrhea. After menstrual bleeding twice at an interval of 1 month at the age of 10 months, he didn’t have menstrual bleeding again. He was born a term baby, with a birth weight of 4750 g from a first-degree consanguineous marriage. His neuromotor development was consistent with his peers. He started to walk at the age of 6 months and 6 years, his epilepsy medication was discontinued at the age of 6, and he did not have seizure again. T2-weighted magnetic resonance images showed increased signal intensity secondary to hypomyelination at patients. They were subsequently found to have homozygous mutation in the POLR3A gene. 4H syndrome may present with neurological and non-neurological findings in addition to classic features of 4H syndrome. Progressive neurological deterioration may occur, and endocrine dysfunction may be progressive. Although multiple endocrine abnormalities associated with this disorder have been reported to date, a case accompanied by type 1 DM has not been seen in the literature. We do not know exactly whether this is coincidental or the expansion of the phenotype. So that reporting such cases helps to determine the appropriate genotype–phenotype correlation in patients.
The patient, whose antibody levels for type 1 DM were found to be positive, was initially planned to be followed-up without insulin by adjusting her diet. On brain magnetic resonance imaging (MRI); pathological hyperintensity on T2-weighted images secondary to hypomyelination was seen in periventricular white matter and centrum semiovale (Figure 1). Mild atrophy of the cerebrum, cerebellum, and corpus callosum was also detected. Metabolic investigations involving very-long-chain fatty acids, free carnitine, urinary organic acids, urinary and plasma amino acids, lactic and pyruvic acids, arylsulfatase A, b-galactocerebroside and total hexosaminidase were normal. Since our patient did not have findings such as fatty and oily stools, diarrhea, gas, bloating, abdominal pain, unexplained weight loss, no evaluation was made in terms of pancreatic exocrine functions. Her psychometric evaluation with the Wechsler Intelligence Scale showed that her IQ score was 70-79. There were no signs of hypo-glyco-globulidaemia, or any other dental anomaly. Ophthalmic examination showed no abnormality. It was considered to possibly be 4H syndrome due to the presence of hypogonadotropic hypogonadism and hypomyelination.

In genetic analyses, genomic DNA was extracted from the patient's peripheral blood lymphocytes (QIAGEN Inc., Hilden, Germany) by obtaining an informed consent form from the patient's parents. All 31 exons and exon-intron boundaries of the POLR3A (NM_007055.4) gene were analyzed with the Next Generation Sequencing (NGS) system according to manufacturers' instructions (Myseq, Illumina Inc., San Diego, CA, USA). The homozygous c.2005C>G (p.R669G) (p.Arg669Gly) missense variant on exon 15 of the POLR3A gene was detected and evaluated as likely pathogenic according to the guidelines. The variant was not found in any healthy population (GnomAD) and in-silico analyzing tools have pathogenic predictions about it. The variant was reported previously and registered as a disease-causing variant in the Human Genome Variation Database (CM1411442). Segregation analyses of the variant were performed with QIAseq® FX DNA Library Kit (Qiagen, Hilden, Germany) in all of the family members and the results were visualized in Figure 2. In the follow-up after 3 months, her fasting plasma glucose level measured 400 mg/dL, while her insulin was 3 mU/L, c peptide was 0.3 µU/mL, and HbA1c was 10%; therefore, intensive insulin therapy was started.

Case 2

The younger brother of the proband was evaluated at age 13.5 years (II-3). Body weight was measured as 57.4 kg (4.6 SDS); height was measured 167 cm (0.65 SDS). Between the ages of 6 months and 6 years, he was followed with the diagnosis of epilepsy in another hospital. MRI and electroencephalography (EEG) findings of that period could not be reached. Epilepsy treatment was initiated at the age of 6 years and he did not have epileptic seizures afterward. We were able to reach the MRI findings of 7 years old, as the oldest plate. Increased signal intensity was also detected in the MRI at that time. However, since the diagnosis was unknown, further investigation was recommended in terms of metabolic disease or hypogonadotropic hypopituitarism. It was learned that his school success was poor and he had a problem of forgetting. IQ score was found 68 by Wechsler Intelligence Scale. He was in Tanner stage 3-4. The patient's neurological and hormonal examinations were evaluated as normal and were shown in Table 1. EEG monitoring was normal. T2-weighted images showed increased signal intensity secondary to hypomyelination in bilateral periventricular white matter (Figure 1). The same homozygous missense variant as in his sister was confirmed with genetic testing. Consanguineous parents of siblings were also found as heterozygous carriers.

DISCUSSION

RNA polymerase III (POLR3) related leukodystrophy, also known as 4H leukodystrophy, are the 2 fusion genes that were named for overlapping clinical phenotypes described previously, which comprise 1) hypomyelination, hypogonadotropic hypogonadism (4H syndrome); 2) ataxia, delayed dentition, and hypomyelination; 3) tremor-ataxia with central hypomyelination; 4) leukodystrophy with oligodendria; and 5) hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (15, 16). It is found that biallelic pathogenic variants in POLR3A, POLR3B, POLR1C, and POLR3K gene cause 4H leukodystrophy (7). Mutations in these genes either disturb the proper assembly of the RNA polymerase III enzyme or impair its ability to bind to DNA (12, 13). Disruption of this function is very important for the maintenance and development of myelin, which can affect the development and function of many parts of the body (13). However, the precise role of the pathophysiology of the disease is not fully understood. It remains a mystery how mutations in POLR3 lead to disorders with clinical features largely restricted to the central nervous system and a few other tissues, all of which originate from neural crest cells (14). The mutations are spread throughout the genome and there is no obvious genotype-phenotype correlation.

Classical clinical findings with typical brain MRI features are helpful in addressing the diagnosis of 4H leukodystrophy. While hypomyelination, hypodontia, and hypogonadotropic hypogonadism are the 3 classic features of 4H leukodystrophy, patients may also present with neurological findings, such as ataxia, dysarthria, dysmetria, tremor, eye movement abnormalities and non-neurological features include cataract, progressive myopia, dental abnormalities, endocrine abnormalities (6, 11, 15, 16). Diagnostic MRI findings include cerebellar atrophy, progressive thinning of the corpus callosum, and high-intensity areas in the white matter on the T2-weighted images (17, 18). The disease progresses insidiously and may result in death. In a study examining the endocrine abnormalities of 150 patients with 4H leukodystrophy, delayed puberty and short stature were found to be the most common endocrine problems. Most of the patients who underwent Luteinizing hormone releasing hormone (LHRH) stimulation test had abnormally low levels of LH and FSH. Also, immunohistochemical analysis of the anterior pituitary gland in the same study revealed that there was no immunostaining of anterior gut and anti-LH antibodies. All of them emphasized that the hypogonadism was hypogonadalgia. A delay in puberty may be one of the earliest signs of the disease. In patients with POLR3A gene mutation, which was stated to be followed by POLR3B. Patients with 4H leukodystrophy had short stature as compared to the general population. So that growth and height should be evaluated at least once a year. In 41% of patients, pubertal levels were found to be abnormal (elevated (18%) or deficient (23%) levels). Hypothyroidism was reported in 4% of patients. No goiter was detected in the cortisol axis (11).

In the cases (17) and (18), they have mild neurological manifestations. Patients are able to walk independently. They have no cerebellar, pyramidal or extrapyramidal signs. Cognition began to deteriorate slowly after 12 years old, but language comprehension and nonverbal communication were preserved until now. As we know, POLR3A mutations tend to a more severe disease course compared to POLR3B mutations but the disease starts slightly later in POLR3A-mutated patients in contrast to POLR3B-mutated patients (6). From our country, a 3-year-old Turkish male patient with POLR3A gene was reported. His first neurological complaints started at the age of 25. Signs of cognitive dysfunction and dental anomaly was not detected (19). Our patients with POLR3A mutation has an exceptionally mild clinical course. Dental abnormalities aren’t present in our patients. In addition to hypogonadotropic hypogonadism; hypoprolactinemia, type 1 DM and antibodies Hashimoto's thyroiditis were detected in the sister. Other anterior pituitary hormones were found to be normal. It was found that there was no one with type 1 DM in the patient’s family, and the autoimmune thyroid antibodies of the parents were negative. To date, more than 100 patients have been reported to have POLR3A, POLR3B mutations in the literature. As far as could be seen, this is the first case of the syndrome accompanied by type 1 DM in the literature. It is not exactly known whether this is coincidental. In the literature, no relation is found between the POLR3A gene and pancreas.

In conclusion, we are still far from understanding the pathogenesis of 4H leukodystrophy. It is great importance for radiologists, endocrinologists and neurologists to recognize the clinical and imaging characteristics of this disorder. The present patient showed not only hypogonadotropic hypogonadism but also some of other endocrine disorders. Reporting such cases will contribute to the genotype-phenotype relationship of the disease.

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Compliance with Ethical Statements

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Author Contribution
• Gonul Buyukyilmaz, Keziban Toskoy Adiguzel, Mehmet Adiguzel, Busra Erozan Cavdarli were responsible for data collection and drafted the initial manuscript, substantial contributions to the conception and design of the work.
• Gonul Buyukyilmaz, Fatih Gurbuz, Busra Erozan Cavdarli, Cigdem Seher Kasapkarla, Esra Gurka were responsible for drafting the work or revising it critically for important intellectual content.
• Gonul Buyukyilmaz, Keziban Toskoy Adiguzel, Mehmet Boyraz, Cigdem Seher Kasapkarla, Esra Gurka were responsible for final approval of the version to be published.

References
Table 1: The laboratory findings of siblings

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<thead>
<tr>
<th>Test</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Reference ranges</th>
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<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>104</td>
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<td>Fasting insulin (mU/L)</td>
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<td>5.4</td>
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<tr>
<td>Prolactin (µg/L)</td>
<td>2.3</td>
<td>4.8</td>
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OGTT: Oral glucose tolerance test; Anti-GAD: Glutamic acid decarboxylase antibody; ICA: Islet cell antibody; TSH: Thyroid stimulating hormone; HbA1c: Hemoglobin A1c; Anti TG: Anti thyroglobulin; Anti TPO: Anti-thyroid peroxidase, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, LHRH: Luteinizing-hormone releasing hormone; ACTH: Adrenocorticotropic hormone; NA: Not available

Figure 1. On axial T2-weighted MRI images, hyperintense areas (black arrows) secondary to hypomyelination are seen in bilateral centrum semiovale (a) and periventricular white matter (b).
Figure 2. Schematic presentation of the genomic locus of the POLR3A gene on chromosome 10, and the results of segregation analysis of POLR3A gene c.2005C>G variant on the pedigree of the family.

Figure 3. Axial T2-weighted MR image shows (white arrows) increased signal intensity secondary to hypomyelination in bilateral periventricular white matter.