CASE REPORT

DOI: 10.4274/jcrpe.galenos.2023.2023-1-15

J Clin Res Pediatr Endocrinol 2025;17(1):103-108

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

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What is already known on this topic?

4H syndrome is a rare, autosomal recessive disorder characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism. Biallelic pathogenic variants in *POLR3A, POLR3B, POLR1C*, and *POLR3K* gene cause 4H syndrome. There is no obvious genotype/phenotype correlation. In addition to the three classic features, patients may present with other system involvements.

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 diabetes mellitus, but in only one of the siblings, in the literature. It is not exactly known whether this is coincidental or an expansion of the phenotype.

Abstract

4H syndrome is a rare, progressive, hypomyelinating leukodystrophy. Hypomyelination, hypodontia, and hypogonadotropic hypogonadism are the three classic features of 4H syndrome. Biallelic pathogenic variants in *POLR3A*, *POLR3B*, *POLR1C*, and *POLR3K* gene cause 4H leukodystrophy. Herein, we present clinical features in two siblings with 4H syndrome. The first patient (16 years) presented with hypogonadotropic hypogonadism, euthyroid Hashimoto's thyroiditis and type 1 diabetes mellitus (DM). The second patient (13.5 years) showed normal physical, biochemical and hormonal examination at presentation. The second patient was followed up for epilepsy between the ages of 6 months and 6 years, when his epilepsy medication was discontinued, and he did not have seizure again. T2-weighted magnetic resonance images showed increased signal intensity secondary to hypomyelination in both. They were subsequently found to have a homozygous variant 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 previously been published. We do not know if this was a coincidence or an expansion of the phenotype. However, reporting such cases helps to determine the appropriate genotype-phenotype correlation in patients.

Keywords: 4H leukodystrophy, *POLR3A*, hypogonadotropic hypogonadism, type 1 diabetes mellitus

Cite this article as: Büyükyılmaz G, Erozan Çavdarlı B, Toksoy Adıgüzel K, Adıgüzel M, Kasapkara ÇS, Gürbüz F, Boyraz M, Gürkaş E. The first case of 4H syndrome with type 1 diabetes mellitus. J Clin Res Pediatr Endocrinol. 2025;17(1):103-108

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Conflict of interest: None declared
Received: 26.01.2023
Accepted: 28.02.2023
Epub: 27.03.2023
Publication date: 19.03.2025

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 condition 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 neurological findings. Non-neurological symptoms have been used to categorize leukodystrophies more accurately (3). Ophthalmological, dental, musculoskeletal, gastrointestinal, and skin problems have also been reported, in addition to endocrine problems, such as adrenal insufficiency, hypogonadism, hypothyroidism, growth hormone deficiency, and ovarian 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. (4) and is characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism. Its clinical course is highly variable. In addition to cases with severe neurological signs, some cases presenting with only idiopathic hypogonadotropic hypogonadism in late adolescence have been reported (5,6). While the most common endocrine abnormalities in 4H syndrome have been reported as hypogonadotropic hypogonadism, we present two siblings, both of whom had 4H syndrome and one of whom had diabetes mellitus (DM).

Case Reports

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 with an interval of 1 month at the age of 13.5 years, there had been no subsequent menstrual bleeding. She was born at term, with a birth weight of 4,750 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 attended endocrinology, her body weight was 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 hypogonodism (Table 1).

Table 1. The laboratory findings of siblings on admission

	Case 1	Case 2	Reference ranges
Fasting plasma glucose (mg/dL)	104	73	< 100
2. hour glucose during an OGTT (mg/dL)	142	NA	< 140
Fasting insulin (mU/L)	14.4	6.7	3-25
2. hour insulin (mU/L)	36.6	NA	22-79
C peptide (µg/L)	1.1	1.1	0.8-3.8
HbA1c (%)	5.6	5.4	< 5.7
Anti-GAD (IU/mL)	61.2	5.7	< 17
ICA (U/mL)	54.9	3.8	< 28
FSH (U/L)	4.6	6.1	
LH (U/L)	0.5	2.8	
Estradiol (ng/L)	< 11.8		11.8-36.6
Testosterone (ug/L)		1.51	0.23-7.42
LHRH peak LH (U/L)	3.6	NA	
TSH (mU/L)	1.6	3.3	0.5-4.9
fT4 (ng/dL)	1.09	1.01	0.83-1.43
Anti-TG (IU/mL)	31.1	< 1.3	< 4.5
Anti-TPO (U/mL)	32	< 28	< 60
ACTH (pg/mL)	14	16	< 46
Cortisol (µg/dL)	10	11	5.2-22
Prolactin (µg/L)	2.3	4.8	4.3-23 (female) 3.2-13.5 (male)

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

The patient, whose antibody levels (Table 1) 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, or 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-oligodontia, or any other dental anomaly. Ophthalmic examination showed no abnormality. The possible diagnosis of 4H syndrome was considered 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 a Next Generation Sequencing 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 (7). The variant was not found in any healthy population (GnomAD) and *in silico* analyzing tools predicted pathogenicity (7). The variant was reported previously and registered as a disease-causing variant in the Human Genome Variation Database (CM141442). 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 are shown 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 0.53 µg/L, 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 (0.38 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 from that period could not be re-evaluated. Epilepsy treatment was completed at the age of 6 years and he did not have epileptic seizures afterward. We were able to obtain the MRI findings when he was 7 years old, as the oldest date. 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 hypoxic ischemic encephalopathy. It was learned that his school success was bad and he had a problem of forgetfulness. IQ score was 68 by Wechsler Intelligence Scale. He was at Tanner stage 3-4 in terms of puberty progression.

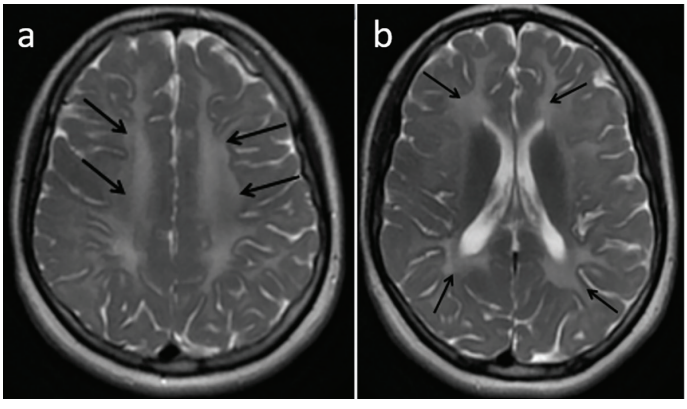

Figure 1. On axial T2-weighted MRI images, hyperintense areas (black arrows) secondary to hypomyelination are seen in bilateral centrum semiovale (a) and periventricular white matter (b)

MRI: magnetic resonance imaging

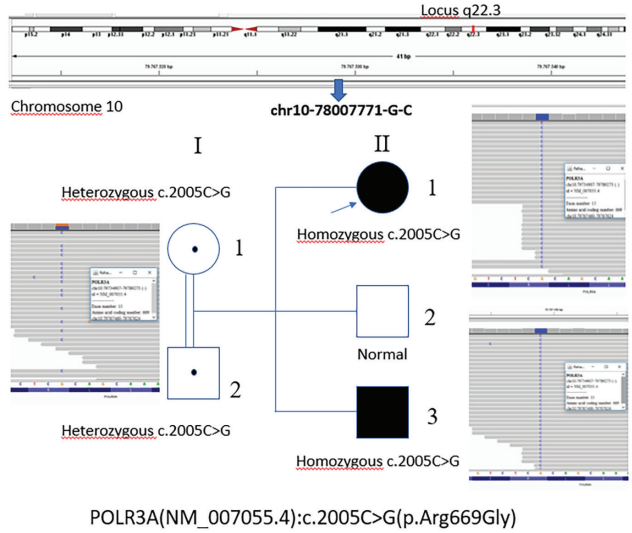

Figure 2. Schematic presentation of the genomic locus of the *POLR3A* gene on chromosome 10, and the results of segregation analysis of *POLR3A* gene c.2005C > G variant on the pedigree of the family

The patient's biochemical and hormonal examinations were evaluated as normal and are shown in Table 1. EEG monitoring was normal. T2-weighted images showed increased signal intensity secondary to hypomyelination in bilateral periventricular white matter (Figure 3). The same homozygous missense variant as in his sister was confirmed with genetic testing. The consanguineous parents of these siblings were found to be heterozygous carriers.

Discussion

RNA polymerase III (POLR3) related leukodystrophy, also known as 4H leukodystrophy, are both terms accepted for five overlapping clinical phenotypes described previously, which comprise 1) hypomyelination, hypodontia, hypogonadotropic hypogonadism (4H syndrome); 2) ataxia, delayed dentition, and hypomyelination; 3) tremor-ataxia with central hypomyelination; 4) leukodystrophy with oligodontia; and 5) hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (8). Biallelic pathogenic variants in *POLR3A, POLR3B, POLR1C*, and *POLR3K* gene cause 4H leukodystrophy (9,10,11,12). Variants in these genes either disturb the proper assembly of the RNA POLR3 enzyme or impair its ability to bind to DNA (13,14). 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 (14). However, the molecular basis of the pathophysiology of the disease is not fully understood. It remains a mystery how variants 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 (15). The variants are spread throughout the gene and there is no obvious genotype/phenotype correlation.

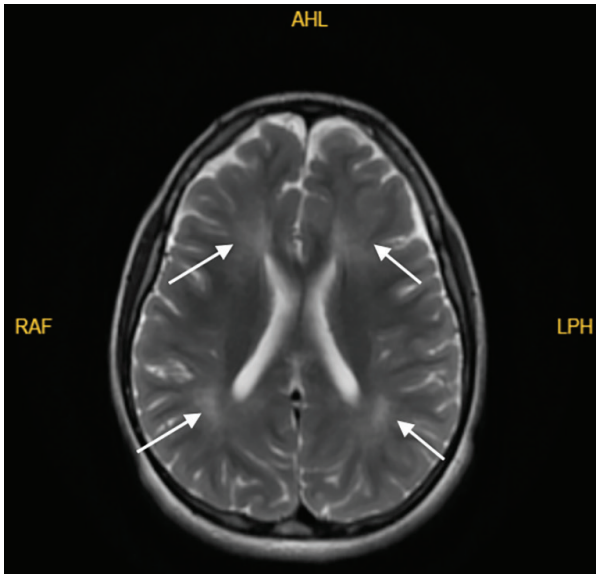

Figure 3. Axial T2-weighted MRI shows (white arrows) increased signal intensity secondary to hypomyelination in bilateral periventricular white matter

MRI: magnetic resonance imaging

Classical clinical findings with typical brain MRI features are helpful in making the diagnosis of 4H leukodystrophy. While hypomyelination, hypodontia, and hypogonadotropic hypogonadism are the three classic features, patients may also present with neurological findings, such as ataxia, dysarthria, dysmetria, tremor, and eye movement abnormalities, while non-neurological features include cataract, progressive myopia, dental abnormalities, and various endocrine abnormalities (6,12,16,17). 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 (18,19). The disease progresses insidiously and may result in early death.

In a study examining the endocrine problems of 150 patients with 4H leukodystrophy, delayed puberty and short stature were the most common endocrine problems. Most of the patients who underwent luteinizing hormone (LH) releasing hormone stimulation test had abnormally low levels of LH and follicle stimulating hormone (FSH). Moreover, immunohistochemical analysis of the anterior pituitary gland in the same study revealed that there was no immunostaining for anti-FSH and anti-LH antibodies. All of these findings implied that the hypogonodism was hypophyseal. A delay in puberty was detected more frequently in patients with *POLR3A* gene variant, which was followed by patients with *POLR3B* variants. Patients with 4H leukodystrophy have short stature compared to the general population. So that growth and height should be evaluated at least once a year. In 41% of patients, prolactin levels were found to be abnormal, either elevated (18%) or deficient (23%). Hypothyroidism was reported in only 4% of patients. No problems were detected in the cortisol axis (12).

The cases (II-1) and (II-3) have mild neurological manifestations. Patients are able to walk independently. They have no cerebellar, pyramidal and extrapyramidal signs. Cognition began to deteriorate slowly after 12 years old, but language comprehension and nonverbal communication are present at the time of writing. *POLR3A* variants tend towards a more severe disease course compared to *POLR3B* variant but the disease starts slightly later in patients harboring *POLR3A* variants in contrast to *POLR3B*-harboring patients (6). A 38-year-old Turkish male patient with *POLR3A* associated leukodystrophy was previously reported. His first neurological complaints started at the age of 25 years. Signs of endocrine dysfunction and dental

anomaly was not detected (20). The patients in the current report with *POLR3A* variant have exceptionally mild clinical courses. Dental abnormalities are not present. In addition to hypogonadotropic hypogonadism, hypoprolactinemia, type 1 DM and euthyroid Hashimoto's thyroiditis were detected in the sister. Other anterior pituitary hormones were normal. On questioning, no other family member suffered from type 1 DM and the autoimmune thyroid antibodies of the parents were negative. To date, more than 100 patients have been reported to have POLR3A or POLR3B variants in the literature. To the best of our knowledge, this is the first case of 4H syndrome due to *POLR3A* variant accompanied by type 1 DM in the literature. However, given the younger brother has exactly the same homozygous variant and has no sign of type 1 DM (yet), it is unclear if this was coincidental. In the literature, no relation was found between the *POLR3A* gene and pancreatic abnormalities.

Conclusion

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

Ethics

Informed Consent: Informed consent form was obtained from the patient's parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Gönül Büyükyılmaz, Büşra Erozan Çavdarlı, Keziban Toksoy Adıgüzel, Fatih Gürbüz, Concept: Gönül Büyükyılmaz, Büşra Erozan Çavdarlı, Mehmet Adıgüzel, Fatih Gürbüz, Esra Gürkaş, Design: Gönül Büyükyılmaz, Büşra Erozan Çavdarlı, Mehmet Adıgüzel, Fatih Gürbüz, Esra Gürkaş, Data Collection or Processing: Gönül Büyükyılmaz, Büşra Erozan Çavdarlı, Keziban Toksoy Adıgüzel, Mehmet Adıgüzel, Çiğdem Seher Kasapkara, Fatih Gürbüz, Analysis or Interpretation: Gönül Büyükyılmaz, Büşra Erozan Çavdarlı, Literature Search: Gönül Büyükyılmaz, Çiğdem Seher Kasapkara, Fatih Gürbüz, Writing: Gönül Büyükyılmaz, Büşra Erozan Çavdarlı, Keziban Toksoy Adıgüzel, Çiğdem Seher Kasapkara, Fatih Gürbüz, Esra Gürkaş.

Financial Disclosure: The authors declared that this study received no financial support.

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