Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Uncertain significance mutation in the POLR3B gene in a Syrian boy with leukodystrophy: a case report

Zulfiqar Hamdan[a,*], Diana Alasmar[b]

Introduction: 4H leukodystrophy, one of the POLR3-related leukodystrophy, is a rare hereditary brain white matter disease with characteristic clinical presentation and imaging findings. Hypomyelination, hypodontia, and hypogonadotropic hypogonadism is mainly presented in patients with 4H leukodystrophy.

Case presentation: A 4-year-old boy presented in the neurologic clinic with delayed psychomotor development and progressive neurologic symptoms that started from the age of 20 months. Physical examination revealed ataxic features and a global development delay. The MRI was significant for hypomyelination. The most common causes of leukodystrophy were rolled out. He was referred to an inherited metabolic disease specialist under suspect of inborn metabolic errors because of laboratory analysis, which showed elevated levels of lactic acid, pyruvate, 4-Hydroxy-Phenylactic acid, 3-Hydroxy propionic acid, and decreased levels of PCO2, HCO3, total CO2, 25-Hydroxyvitamin D. These results were unspecific and mitochondrial disease was highly suspected. However, the genetic study was requested to get a defined diagnosis and treatment; the whole exon sequencing result showed a homozygous variant of uncertain significance mutation; related to an amino acid change from Ile to Thr at position 1002 in the POLR3B gene, which helped us to reveal the final diagnosis, and the genetic counseling were recommended for the next pregnancies.

Conclusion: POLR3-related Leukodystrophy is a very rare disease. The early diagnosis should be raised depending on clinical history and MRI findings after other conditions were rolled out, and the confirmed diagnosis depends on the genetic study.

Keywords: 4H leukodystrophy, hypomyelination, POLR3B, POLR3-related leukodystrophy

Introduction

The 4H leukodystrophy, an autosomal recessive disorder with specific features on brain MRI, is typically characterized by the triad of hypomyelination, hypodontia, and hypogonadotropic hypogonadism in an onset time ranging from the neonatal period to late childhood[1–3]. It was first described by Timmons *et al.*[4] in four adult patients. Additional signs such as severe myopia and small stature emerged, but patient numbers were too small to confirm that they are typical of 4H[1,5]. The primary clinical features include cerebellar symptoms (i.e. spasticity, ataxia, tremor, and cognitive regression); dental abnormalities (i.e. tooth delay, tooth agenesis, fewer teeth, and abnormal tooth form and arrangement), short stature, dysphagia, hypogonadotropic hypogonadism, and progressive eye abnormalities (e.g. myopia and optic atrophy)[3]. Some rare features have also been reported in other studies (Table 1)[1,3,6–8].

In 2011 Bernard *et al.*[9] reported that 4H leukodystrophy was caused by POLR3A nucleotide variation. Daoud *et al.*[10] found that nucleotide variation in POLR3A OR POLR3B could cause 4H leukodystrophy, and proposed that POLR3A nucleotide mutations are more common and frequent in 2013. An international cross-sectional study was performed on 150 patients with 4H leukodystrophy between 2015 and 2016 demonstrated that 56 (37.3%) patients carried the mutations in POLR3A, 81 (54%) in POLR3B,

HIGHLIGHTS

- Leukodystrophies are a class of rare inherited central nervous system disorders that affect the white matter of the brain.
- POLR3-Related Leukodystrophy is one of the most common types of Leukodystrophy for which no curative treatment or disease modifiying therapy is available till this date.
- Suspicious of POLR3-Related Leukodystrophy should be raised when classic clinical features and typical brain MRI findings are presented.
- The treatment is supportive including individualized care by a multidisciplinary team to improve the quality of life.

[a]Faculty of Medicine and [b]Pediatric Department, Damascus University Damascus, Syria

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Faculty of medicine, Damascus university, G748 +VRH, Damascus, Syria. Tel.: +963 954 760 941 E-mail: zulficarhamdan@gmail.com (Z. Hamdan).

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Annals of Medicine & Surgery (2023) 85:4126–4130

Received 16 May 2023; Accepted 20 June 2023

Published online 28 June 2023

http://dx.doi.org/10.1097/MS9.0000000000001033

Table 1

Clinical manifestations of POLR3-related leukodystrophy patients.

	Classical manifestation	Rare manifestation
Neurology	Cerebellar features: gait ataxia, dysarthria, dysmetria, tremor, nystagmus, swallowing deterioration; cognitive degression; pyramidal signs.	Microcephaly; seizures; extrapyramidal signs; dystonia.
Dental	Natal teeth, delayed dentition, abnormal order of teeth eruption, hypodontia.	—
Endocine	Hypogonadotropic hypogonadism with delayed, arrested or absent puberty; short stature.	late-onset GH deficiency
Ocular	Myopia	Cataract; optic atrophy
Bone	Short status	Osteosclerosis; hyperostosis frontalis; thick frontal bones; Vertebral Anomalies.
Bladder	—	Chronic bladder dysfunction
Brain MRI imaging		
Hypomyelination	ventrolateral thalamus, optic radiation, globus pallidus, pyramidal tracts within the posterior limb of the internal capsule and dentate nucleus.	Selective hypomyelination of the corticospinal tracts; cerebellar atrophy with or without focal hypomyelination; Involvement of the striata and red nuclei; supratentorial and infratentorial; peripheral hypomyelination.
Atrophy	Cerebellar; thinning of the corpus callosum.	Cortical.
MR spectroscopic abnormality	—	Decrease of choline-containing compounds; increased myoinositol.

and 13(8.7%) in POLR1C[11]. Hence, since 4H leukodystrophy, one of POLR3-related leukodystrophy, is a rare hereditary brain white matter disease; we present the first diagnosed 4H leukodystrophy caused by mutation in POLR3B gene in Syria.

Case presentation

Clinical history and investigations

A 4-year-old boy presented to the clinic with the main complaint of psychomotor delay and shivering started at the age of 20 months. The perinatal history showed that his delivery was cesarean with a birth weight of 2.9 kg; because abnormal labor and coiling of the cord. A review of early milestones reveals that the sittings was achieved normally but there were a delayed in walking when the patient's mother noticed the abnormal symptoms. The physical examination showed delayed speech and language development, delayed dentition, difficulty running, gait imbalance, dysarthria, a short attention span, and medial strabismus in his left eye. Over time gait disturbances and cerebellar signs became more pronounced. The patient has an 11-year-old brother clinically diagnosed with Noonan syndrome, and a sister died at the age of 4-days because of a pulmonary infection (Fig. 1).

The MRI without contrast showed T2 bilateral hyperintense areas symmetrically in the periventricular white matter, centrum semiovale, and cerebellum white matter (Fig. 2).

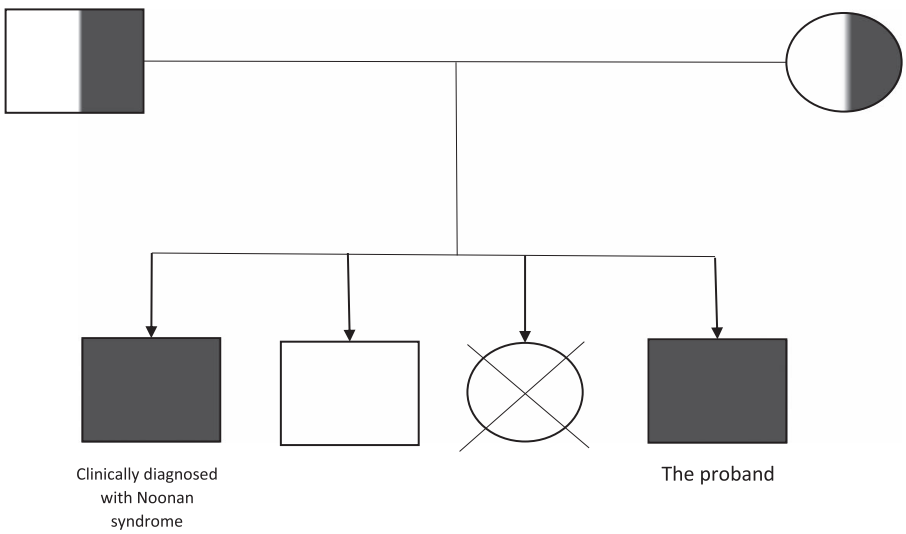

Figure 1. Pedigree of the investigated proband patient.

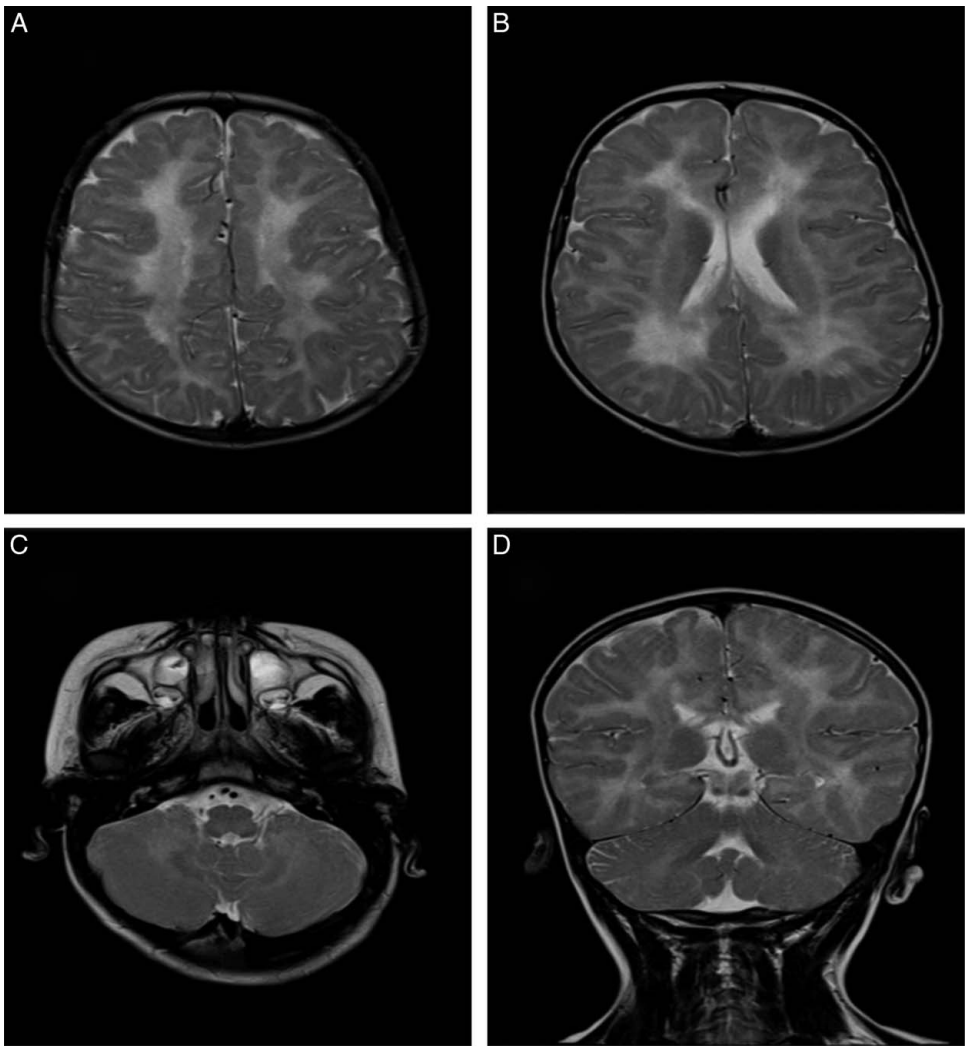

Figure 2. MRI without contrast of the brain with T2 bilateral hyperintense areas symmetrically in the centrum semiovale (A), periventricular white matter (B), cerebellum white matter (C). Figure 2-D. Coronal slice shows the affected areas in the white matter.

Biochemistry and blood tests were as follows:

The patient's cortisol and ACTH were within the normal range. Urine organic acids by gas chromatography showed slightly elevated levels of 4-Hydroxy-Phenylactic acid and 3-Hydroxy propionic acid. Tandem mass spectrometry showed unremarkable results. TSH, Calcium, and the rest of the biochemistry and blood tests were within the normal range. Amino acids electrophaphoresis showed that the amino acids were within the normal range. Next generation sequencing, whole exon sequencing at CENTOGENE GmbH in Germany, for a peripheral blood sample were performed for the patient; the test identified a missense homozygous variant of uncertain significance mutation in the POLR3B gene, NM_018082.5:c.3005T > C; the variant causes an amino acid change from Ile to Thr at position 1002. Pathogenic variants in this gene are associated with autosomal recessive Hypomyelinating leukodystrophy-8.

Diagnostic strategy

The newborn hypoxia due to the coiling of the cord was the first differential diagnosis of the psychomotor development delay, but the child parents went to a neurologist after they noticed the abnormal shivering, the clinical examination showed that there might be an injury in the central nervous system. The computerized tomography imaging of the brain showed a morbidity in the white matter; so he requested a MRI without contrast to study the tissues and identify the affected areas accurately. The MRI report overbalanced that the pathological existence in the image goes with the pelizaeus-merzbacher disease more than the MLD, but the laboratory analysis was not guided to pelizaeus-merzbacher disease or metachromatic leukodystrophy. However, the fetal

Table 2

Abnormal findings in laboratory analysis.

Lactic acid	28.7 mg/dl	Normal range: 5.4–20.7 mg/dl
Pyruvate	1.12 mg/dl	Normal range: 0.2–0.9 mg/dl
PCO2	31.5 mmHg	Normal range: 35–45 mmHg
HCO3	20.3 mmol/l	Normal range: 22–26 mmol/l
O2SAT	100%	Normal range: 54–99%
Total CO2	21.3 mmol/l	Normal range: 22–29 mmol/l
25-Hydroxyvitamin D	20.45 ng/ml	Normal range: 32–150 ng/ml

asphyxia, normal apgar score, no delayed in birth screaming, and the abnormal findings in (Table 2); overbalanced a metabolic disease caused the white matter morbidity. The amino acids electrophaphoresis result was normal, and the urine test showed slightly elevated level of 4-Hydroxy-Phenylactic acid, 3-Hydroxy propionic acid, and lactic acid; these results are not specific and the source of them is Krebs cycle and mitochondrial diseases. Even though the parent announce a slight improvement after a cocktail of vitamins (B1, B2, CoQ10, and carnitine) get started, but the clinical examination still the same. We decided to do the genetic study to confirm our diagnosis, that genetic study can help to identify the etiology, any possibility of treatment and decide whether the genetic counseling in the next pregnancies is recommended or not. The whole exon sequencing result revealed and helped us to make our final diagnosis; also we recommended the genetic counseling to the parents for the next pregnancy.

Treatment and follow-up

The vitamin cocktail has been stopped after the genetic result that there are no benefit of this kind of treatment; the steam cell therapy will be a future treatment for this patient.

Discussion

In this report, we present a diagnosed 4H leukodystrophy caused by a homozygous variant of uncertain significance in the POLR3B gene (class3). 4H leukodystrophy, one of the POLR3-related leukodystrophy, is a rare autosomal recessive disease characterized by hypomyelination, hypodontia, hypogonadotropic hypogonadism, and ocular abnormalities[3,12]. The typical brain MRI findings are characterized by diffuse cerebral hypomyelination manifesting as diffuse hyperintense T2 and FLAIR white matter signal abnormality[12]. However, it should be noted that diffuse hypomyelination is not a mandatory diagnostic imaging feature[2]. The pituitary gonad axis will be studied later around the puberty age; because of the probability of developing hypogonadotropic hypogonadism[3]. The mutations in POLR3A and POLR3B are the most frequently reported etiology for 4H leukodystrophy. In addition, Gauquelin *et al.*[13] reported 23 patients with biallelic POLR1C variants causes a POLR3-related leukodystrophy in a cross-sectional observational study involving 25 centers worldwide. The study reported that about half of the patients (52%), development was delayed; this was usually noted between the age of 1 and 2 years. Nineteen children (17%) were never able to walk independently (4 with POLR3A, 15 with POLR3B mutations), and only one patient, a 21-year-old woman diagnosed at age 16 years when she developed optic neuritis, had no cerebellar signs. Wolf *et al.*[1] revealed that patients with POLR3A mutations are more severely affected than patients with POLR3B mutations with faster regression and shorter life expectancy. Perrier *et al.*[14] in a review published in 2021 explored potential therapeutic approaches, which included cell therapy, gene therapy, and gene editing techniques and all presented exciting results in recent years. However, the expert consensus for treatment is still undocumented, and the available treatment is supportive treatment including individualized care by a multidisciplinary team including a pediatric neurologist, physiotherapist, speech and language pathologist, and primary care physician[3]. In view of this, genetic counseling is recommended for this patient if he have a request for fertility.

Conclusion

POLR3-related leukodystrophy is a very rare disease. The diagnosis depends on the genetic study and the combination of classic clinical findings, and typical brain MRI features. The suspicion for this rare disease should be raised when classic clinical features and typical brain MRI findings are present. Confirmation is made by molecular genetic testing.

Ethical approval

No ethical approval was needed.

Consent

Written informed consent was obtained from the patient's parents for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

Sources of funding

There was no source of funding for this study.

Author contribution

Z.H.: reviewed the literature, wrote and revised the manuscript, and made grammar and spelling language editing; D.A.: provided medical treatment, supervise the scientific and academic aspects of the manuscript, and revised it.

Conflicts of interest disclosure

There were no conflicts of interest.

Research registration unique identifying number (UIN)

No registration was needed, because it is a case report not clinical trial.

Guarantor

Zulfiqar Hamdan.

Data availability statement

All data are available.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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