

CASE REPORT

A rare case of SRD5A3-CDG in a patient with ataxia and telangiectasia: A case report

Sayyed Hesamedin Nabavizadeh¹  | Rafat Noeiaghdam¹  | Leila Johari¹  |
Seyed Ali Hosseini²  | Hossein Esmailzadeh¹  | Soheila Sadat Alyasin¹ 

¹Allergy Research Center, Department of Pediatrics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

²School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence

Rafat Noeiaghdam, Allergy Research Center, Department of Pediatrics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
Email: noi.rafat@yahoo.com

Abstract

Steroid 5 α -reductase type 3 congenital disorder of glycosylation (SRD5A3-CDG) is an extremely rare congenital disease. Common manifestations are developmental delay, intellectual disability, ophthalmological abnormalities, cerebellar abnormalities, ataxia, and hypotonia. Here, we discuss a seven-year-old boy with SRD5A3-CDG (homozygous variant c.57G>A [p.Trp19Ter]), featuring the unprecedented finding of telangiectasia.

KEYWORDS

Allergy and immunology, Genetics, Pediatrics, SRD5A3-CDG

1 | INTRODUCTION

Steroid 5 α -reductase type 3 congenital disorder of glycosylation (SRD5A3-CDG) is an extremely rare congenital disease, common manifestations of which are global development delay, intellectual disability, ophthalmological abnormalities (retinitis pigmentosa/retinal dystrophy, optic nerve hypoplasia), cerebellar abnormalities, and hypotonia.¹ At least 54 cases of this disease have been reported worldwide, presenting with a highly variable phenotype; while ataxia is mentioned in around half of these cases, telangiectasia is yet to be reported.²⁻¹⁰

Ataxia and telangiectasia are clinical signs that characterize a neurodegenerative disorder known as ataxia-telangiectasia, but can also be seen in other genetic disorders like congenital disorders of glycosylation (CDG).¹¹ Classically, ataxia-telangiectasia involves multiple organ systems, particularly the nervous and immune

systems. From early childhood, those who inherit this autosomal recessive disease develop ataxia: a disability in movement coordination.¹² This manifests as problems with walking, balance, and hand coordination, as well as chorea, myoclonus, and neuropathy; a wheelchair is usually needed by adolescence. Patients also suffer from oculomotor apraxia, a condition where looking from one side to the other is difficult. Slurred speech is also prominent. Telangiectasia is one of the two major components of this condition, where enlarged blood vessels are seen in the eyes and skin.

An important note for physicians is that alternative genetic disorders must not be overlooked when a child presents with ataxia and telangiectasia. In this case report, we discuss a seven-year-old boy with a delayed diagnosis of SRD5A3-CDG (MIM 612379; homozygous variant c.57G>A [p.Trp19Ter]), where a diagnosis of ataxia-telangiectasia had been presumed.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

2 | CASE PRESENTATION

A seven-year-old boy, presumed case of ataxia-telangiectasia, was referred to our pediatric immunology clinic by a pediatric neurologist for further workup due to ocular involvement. He was born from non-consanguineous parents, gravid four, with a history of developmental delay in the previous child but no history of abortion or death. The proband weighed 3.5 kg at birth (full-term), at which time asphyxia did not occur. At the age of 8 months, the parents became concerned about a delay in sitting and standing, but neuroimaging was normal without any evidence of cerebellar or vermian hypoplasia or other anomalies. He developed telangiectasia in the eyes at 15 months of age, at which time vision problems also manifested. He had a delay in global development and speaking; by 4 years, he could only correctly say one or two words. The convulsion history was negative. Due to his attention disorder, methylphenidate and risperidone were prescribed for him at the age of five.

At 7 years of age, he had a weight of 29 kg (+2 standard deviations [SD]), a height of 120 cm (−1 to 0 SD), with a head circumference of 52 cm (−1 SD). Our physical examination revealed slight facial coarseness, mildly deep-set eyes, round nasal tip, full cheeks and thick lips (Figure 1), central hypotonia, and ataxia. Deafness, ichthyosis, and hand stereotypes were not noted.

Our ophthalmologic consultant reported pigmentary retinopathy with optic disc paleness on examination of the fundus. Telangiectasia and nystagmus were also reported, though ocular coloboma was not seen. The visual-evoked potential demonstrated an extinguished response.



FIGURE 1 Slight facial coarseness, mildly deep-set eyes, round nasal tip, full cheeks, and thick lips.

On laboratory workup, routine hematology and biochemical tests (renal/hepatic function) were normal, as were the essential metabolic screening, arterial lactate, and blood ammonia. Interestingly, the insulin-like growth factor (IGF)-1 level was normal. Other normal tests included an electroencephalogram, brainstem-evoked potential, karyotype study, and chromosomal microarray.

Considering the patient's clinical manifestations (pigmentary retinopathy, hypotonia, ataxia, and telangiectasia), we suspected congenital disorders of glycosylation (CDG) and requested serum isoelectric focusing and whole-exome sequencing. Exome sequencing identified the presence of homozygous pathogenic variant c.57G>A (p.Trp19Ter) in the *SRD5A3* gene. The mutation was confirmed by Sanger sequencing, and the diagnosis of *SRD5A3*-CDG was established.

3 | DISCUSSION

The *SRD5A3* gene, at its 4q12 locus, encodes a protein that plays a role in testosterone production. This protein is a member of the polyprenol reductase subfamily within the steroid 5- α reductase family. To achieve N-linked glycosylation of proteins, androgen 5- α dihydrotestosterone (DHT) must convert polyprenol to dolichol, with this process being hindered in the *SRD5A3*-CDG disease.¹³ Congenital defects in type Iq glycosylation are linked with mutations in the *SRD5A3* gene; products of this gene expressed in the hippocampus and cerebellum are essential for brain development.⁶

SRD5A3-CDG (MIM 612379) is an extremely rare congenital, multisystem disease that manifests with a highly variable phenotype.¹⁴ The main disease characteristics include ocular abnormalities (optic nerve hypoplasia/atrophy, iris and optic nerve coloboma, congenital cataract, or glaucoma), intellectual disability, nystagmus, hypotonia, ataxia, and/or ichthyosiform skin lesions.¹⁵ Cerebellar or vermian hypoplasia is seen in roughly fifty percent of cases; liver enzyme and coagulation abnormalities, and microcytic anemia, kyphosis, congenital heart defects, hypertrichosis, and retinitis pigmentosa have also been reported.^{1,3} Recent years have witnessed a rise in the number of detected cases considering the emergence of next-generation sequencing.² In the literature, although a systematic review is yet to be published, at least 54 cases of *SRD5A3*-CDG have been described.^{2–10} Our patient is the first confirmed case of *SRD5A3*-CDG to be reported from Iran, though some familial cases have been described in nearby countries like Turkey and Pakistan.²

Although the phenotype of SRD5A3-CDG is highly variable,¹⁵ our case fits in with the literature in terms of features such as developmental delay, hypotonia, ataxia, pigmentary retinopathy, and nystagmus. However, an unprecedented finding is telangiectasia, which is yet to be reported in cases of SRD5A3-CDG. In fact, this clinical manifestation moved our colleagues toward presuming a diagnosis of ataxia-telangiectasia. This, coupled with the gradual emergence of the manifestations and the lack of prior access to whole-exome sequencing, led to a seven-year delay in arriving at the final diagnosis. When the patient was referred to us, we suspected a congenital disorder of glycosylation (CDG) due to manifestations such as pigmentary retinopathy, hypotonia, ataxia, and telangiectasia, and requested the related diagnostic tests. A diagnostic challenge was that the insulin-like growth factor (IGF)-1 level was normal, which is unexpected in CDG. The final diagnosis of SRD5A3-CDG was achieved quite late, stressing the importance of increased understanding of this disorder.

Our report highlights the significance of carefully evaluating children who present with developmental delay alongside manifestations such as ataxia and telangiectasia. Further reports are needed to improve our understanding of SRD5A3-CDG, with the hope of achieving better management strategies and patient outcomes.

AUTHOR CONTRIBUTIONS

SHH was involved in study concept, study design, and article revising. RN was involved in study design, data collection, and article writing. LJ, SAH, HE, and SA were involved in data collection, article writing, and revising. All authors read and approved the final article and accept accountability for this work.

ACKNOWLEDGMENTS

None.

FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The guidelines of the Declaration of Helsinki were followed in completing this study.

CONSENT

Written informed consent was obtained from the guardians of the patient for publication of this case report.

ORCID

Sayed Hesamedin Nabavizadeh  <https://orcid.org/0000-0001-8181-0539>

Rafat Noeiaghdam  <https://orcid.org/0000-0003-0797-6439>

Leila Johari orcid.org/0000-0001-6785-1588

Seyed Ali Hosseini  <https://orcid.org/0000-0003-4397-1539>

Hossein Esmaeilzadeh  <https://orcid.org/0000-0003-0288-8181>

Soheila Sadat Alyasin  <https://orcid.org/0000-0001-7183-545X>

REFERENCES

1. Kousal B, Honzik T, Hansikova H, et al. Review of SRD5A3 disease-causing sequence variants and ocular findings in steroid 5 α -reductase type 3 congenital disorder of glycosylation, and a detailed new case. *Folia Biol.* 2019;65:134-141.
2. Gupta N, Verma G, Kabra M, Bijarnia-Mahay S, Ganapathy A. Identification of a case of SRD5A3-congenital disorder of glycosylation (CDG1Q) by exome sequencing. *Indian J Med Res.* 2018;147(4):422-426.
3. Jaeken J, Lefeber DJ, Matthijs G. SRD5A3 defective congenital disorder of glycosylation: clinical utility gene card. *Eur J Hum Genet.* 2020;28(9):1297-1300.
4. Tachibana N, Hosono K, Nomura S, et al. Maternal uniparental isodisomy of chromosome 4 and 8 in patients with retinal dystrophy: SRD5A3-congenital disorders of glycosylation and RP1-related retinitis pigmentosa. *Genes.* 2022;13(2):359.
5. Lipiński P, Cielecka-Kuszyk J, Czarnowska E, Bogdańska A, Socha P, Tylki-Szymańska A. Congenital disorders of glycosylation in children – Histopathological and ultrastructural changes in the liver. *Pediatr Neonatol.* 2021;62(3):278-283.
6. Kamarus Jaman N, Rehse P, Henderson RH, Löbel U, Mankad K, Grunewald S. SRD5A3-CDG: emerging phenotypic features of an ultrarare CDG subtype. *Front Genet.* 2021;12:737094.
7. Rieger M, Türk M, Kraus C, et al. SRD5A3-CDG: twins with an intragenic tandem duplication. *Eur J Med Genet.* 2022;65(5):104492.
8. Ben Ayed I, Ouarda W, Frikha F, et al. SRD5A3-CDG: 3D structure modeling, clinical spectrum, and computer-based dysmorphic facial recognition. *Am J Med Genet A.* 2021;185(4):1081-1090.
9. Bogdańska A, Lipiński P, Szymańska-Rożek P, et al. Clinical, biochemical and molecular phenotype of congenital disorders of glycosylation: long-term follow-up. *Orphanet J Rare Dis.* 2021;16(1):17.
10. Khan AO. Phenotype-guided genetic testing of pediatric inherited retinal disease in the United Arab Emirates. *Retina.* 2020;40(9):1829-1837.

11. Moeini Shad T, Yazdani R, Amirifar P, et al. Atypical ataxia presentation in variant ataxia telangiectasia: Iranian case-series and review of the literature. *Front Immunol.* 2022;12:779502
12. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: a review. *Orphanet J Rare Dis.* 2016;11(1):159.
13. Cantagrel V, Lefeber DJ, Ng BG, et al. SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder. *Cell.* 2010;142(2):203-217.
14. Kara B, Ayhan Ö, Gökçay G, Başboğaoğlu N, Tolun A. Adult phenotype and further phenotypic variability in SRD5A3-CDG. *BMC Med Genet.* 2014;15(1):10.
15. Genetic and Rare Diseases Information Center. SRD5A3-CDG (CDG-Iq) - About the Disease 2022. Accessed 25 June

2022. <https://rarediseases.info.nih.gov/diseases/12397/srd5a3-cdg-cdg-iq>

How to cite this article: Nabavizadeh SH, Noeiaghdam R, Johari L, Hosseini SA, Esmailzadeh H, Alyasin SS. A rare case of SRD5A3-CDG in a patient with ataxia and telangiectasia: A case report. *Clin Case Rep.* 2022;10:e06564. doi: [10.1002/ccr3.6564](https://doi.org/10.1002/ccr3.6564)