AACE Clinical Case Rep. 10 (2024) 229–231

Clinical Case Reports™
www.aaceclinicalcasereports.com

Case Report

Endocrine Care of a 19-year-old Woman With Isolated Hypogonadotropic Hypogonadism due to 4H Syndrome

Bright Nwatamole, MBBS [1], Sumana Kundu, MBBS [2], God-dowell O. Odukudu, MD [3,*], Prava Basnet, MBBS [4], Lubna Mirza, MD, FACE [5]

[1] *IM Trainee United Kingdom, St. James University Hospital, United Kingdom*
[2] *Department of Internal Medicine, R. G. Kar Medical College, Kolkata, India*
[3] *Department of Internal Medicine, Morehouse School of Medicine, Atlanta, Georgia*
[4] *Department of Internal Medicine, Hebei Medical University, Shijiazhuang, China*
[5] *Department of Endocrinology, Endocrine ParaThyroid Center, Norman, Oklahoma*

ARTICLE INFO

Article history:
Received 30 September 2023
Received in revised form
31 July 2024
Accepted 7 August 2024
Available online 10 August 2024

Key words:
POLR3B gene mutation
4H Leukodystrophy
POLR3-Related Leukodystrophy

ABSTRACT

Background/Objective: 4H syndrome is a rare form of leukodystrophy characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism. In 95% of cases, hypomyelination is present, but other clinical features, such as hypodontia and hypogonadotropic hypogonadism, are not always present and may not be necessary for diagnosis. Hypogonadotropic hypogonadism is the most common endocrine complication that can occur in 4H syndrome. Other endocrine abnormalities are short stature and growth hormone deficiency.

Case Report: We present a 19-year-old female with 4H syndrome due to POLR3B gene mutations who presented with primary amenorrhea. She was referred to our endocrinology clinic by her primary care physician. She was diagnosed with 4H syndrome at age 15 by her pediatrician when she initially presented with primary amenorrhea, ataxia, and tremors and underwent karyotyping and confirmatory genetic tests. However, she received no endocrine care before coming to our clinic at 19. Neurologic exam revealed slight tremors in outstretched hands. A brain MRI study revealed no intracranial abnormalities. We subsequently placed her on Loestrin birth control, an estrogen/progestin combination contraceptive, and she begun having her menstrual periods.

Discussion: The prevalence of POLR3-related leukodystrophy is currently unknown. It can appear during childhood or later in life. Early onset increases the risk of mortality in young adulthood. Endocrine care entails hormone replacement therapy and monitoring for dysfunction over time.

Conclusion: Early diagnosis of hypogonadotropic hypogonadism in women, with or without other hormonal deficiencies caused by 4H syndrome, is crucial for effective treatment. Treatment should be multidisciplinary and aimed mainly at correcting low estrogen levels.

Introduction

We present a rare case of 4H syndrome in a 19-year-old female with biallelic POLR3B gene mutations who presented with primary amenorrhea. 4H syndrome is a rare disorder of progressive hypomyelination leukodystrophy characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism.[1] Mutations in the POLR3A and POLR3B genes are responsible for causing the 4H syndrome. Each of these genes codes for a different subunit of RNA polymerase III. POLR3A gene mutations are associated with more severe disease in patients than POLR3B gene mutations.[2] In 95% of

Abbreviations: ACTH, adrenocorticotropic hormone; ADDH, ataxia, delayed dentition, and hypomyelination; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin hormone-releasing hormone; HCAHC, hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum; LH, luteinizing hormone; LO, leukodystrophy with oligodontia; MRI, magnetic resonance imaging; OCP, oral contraceptive pill; RNA, ribonucleic acid; TACH, tremor-ataxia with central hypomyelination; TSH, thyroid-stimulating hormone.

* Address correspondence to Dr God-dowell O. Odukudu, Resident Physician, Department of Internal Medicine, Morehouse School of Medicine, 720 Westview Dr SW, Atlanta, GA 30310.
E-mail address: goddowell4@gmail.com (G.-d.O. Odukudu).

https://doi.org/10.1016/j.aace.2024.08.001

cases, hypomyelination is present, but other clinical features, such as hypodontia and hypogonadotropic hypogonadism, are not always present and may not be necessary for diagnosis. Hypogonadotropic hypogonadism is the most common endocrine complication that can occur in 4H syndrome. When present, it often manifests as the absence of early changes during puberty or the delay or arrest of puberty.

Some individuals with 4H may also experience other endocrine abnormalities, such as short stature (reported in 50% of cases), growth hormone deficiency, and abnormal thyroid function.[2-4] Abnormal prolactin levels and disturbances in the hypothalamic-pituitary-adrenal axis, although not common, have also been reported.[4]

Our case sheds more light on the variability of clinical features associated with 4H syndrome. This understanding is crucial for effectively managing the disease in affected patients. Additionally, it has provided further insights into the hormonal management of patients with hypogonadotropic hypogonadism secondary to 4H syndrome.

Highlights

- Hypogonadotropic hypogonadism from 4H syndrome requires hormone replacement therapy.
- These patients, with/without hormonal deficits require prompt interdisciplinary care.
- 4H syndrome diagnosis entails clinical findings, brain MRI, and genetic tests.
- Patients should get genetic counseling given its autosomal recessive inheritance.
- It is important to screen for signs of ACTH, GH, and TSH deficiency every few years.

Clinical Relevance

Patients with 4H syndrome can have endocrine problems such as hypogonadotropic hypogonadism and growth hormone deficiency. Early diagnosis is crucial, especially when neurologic symptoms are not severe. This case improves our knowledge and understanding of the clinical features and management of 4H syndrome.

Case Report

A 19-year-old female was referred to our Endocrinology clinic by her primary care physician for further evaluation and treatment of primary amenorrhea and hypogonadotropic hypogonadism secondary to congenital leukodystrophy (4H syndrome). At age 15, she was diagnosed by her pediatrician with 4H syndrome following presentation with primary amenorrhea, ataxia, and tremors, and after she underwent karyotyping and confirmatory genetic tests that revealed a positive biallelic mutation of the POLR3B gene. She was subsequently lost to follow-up and only started seeing a primary care physician when she turned 18. At 19, she was concerned about her ability to have children, and her primary care physician then referred her to us. She had not received any treatment for hypogonadism before her presentation at our clinic. Her medical history was significant for poor vision from severe myopia for which she has been using corrective lenses since the age of 4, hereditary ataxia, sphingolipidoses, depression treated with escitalopram 10 mg once daily, and anxiety. She also had tremors and balance problems with a history of falls without fractures. She was born at term with normal birth weight, received all required vaccinations, and had no history of past surgeries or hospitalizations. She had a reasonably functional status, living independently as a college student. She did not smoke or drink alcohol and had no history of recreational drug use. She didn't have poor dentition. Her family history is significant for Type 4 leukodystrophy, hypothyroidism, and diabetes mellitus type 2 in her sister. Her mother also has hypothyroidism. A review of the systems revealed bilateral tinnitus, snoring, excessive sweating, and thirst, sleeping with multiple pillows, anxiety, and low mood.

On examination, her blood pressure was 126/74mmHg, her heart rate was 84 b/m, and her respiratory rate was 12 c/m. She was 157.5 cm tall and weighed 88.5 kg, with a body mass index of 35.7 kg/m2. She had Tanner stage 2 pubic hair and breast development. Her head was normocephalic, and her neck was supple without thyromegaly or lymphadenopathy. Cardiovascular, respiratory, and abdominal exams were normal. Neurologic exam showed a slight tremor in outstretched hands but fair balance. Her deep tendon reflexes were 2+ symmetrically.

A comprehensive hormonal panel and MRI imaging of the brain were requested on her initial visit. MRI study showed no abnormalities in the pituitary or any other part of the brain. The comprehensive metabolic panel showed normal electrolytes, liver, and renal functions. Her karyotype is 46, XX, and her estradiol level was <15 pg/mL with a follicle-stimulating hormone level of 1.3 mIU/mL, luteinizing hormone level of 1.8 mIU/mL and serum prolactin of 3.98 ng/mL. A leuprolide stimulation test was not done. Her thyroid stimulating hormone was 4.75 μU/mL (0.4-5.0) with a free thyroxine level of 0.8 ng/dL (0.6-2.00). Her insulin-like growth factor-1 was 168 ng/mL (83-377). Dehydroepiandrosterone sulfate was 95 μg/dL. Her 8 AM morning cortisol was normal at 16.4 μg/dL with an adrenocorticotrophic hormone level of 29 pg/mL.

Based on these results, our patient was diagnosed with isolated hypogonadotropic hypogonadism and treated with oral contraceptive therapy. We commenced her on Loestrin 1/20 birth control, an estrogen/progestin combination oral contraceptive. She began to have periods right after starting the OCP. The periods were regular. She has been on the same dose of Loestrin ever since. She has not reported any side effects, and following the treatment, she has now reached Tanner stage 3 for pubic hair and breast development.

Discussion

We present a case of a 19-year-old woman with primary amenorrhea and hypogonadotropic hypogonadism secondary to 4H syndrome. The 4H syndrome is a rare progressive hypomyelination leukodystrophy characterized by hypodontia, hypomyelination, and hypogonadotropic hypogonadism.[5] The term 4H syndrome was first used in 2006 [(6)]. The prevalence of 4H syndrome is not known.[5] The age of onset typically occurs in early childhood, although late-onset cases have also been reported. Earlier onset has been linked to a higher mortality risk in young adulthood.[6] However, lifespan depends on supportive measures to prevent secondary complications.[6] This autosomal recessive disorder is caused by mutations affecting the POLR3A, POLR3B, and POLR1C genes.[7] Such mutations are proposed to alter the levels of the small RNAs necessary for the normal development of white matter, resulting in hypomyelination.[8] POLR3A gene mutations lead to more severe manifestations than POLR3B gene mutations.[2] Our patient's genetic testing confirmed a biallelic mutation in the POLR3B gene.

Aside from the 4H syndrome, POLR3-related leukodystrophies can have 4 other overlapping clinical phenotypes, including 1. Hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCAHC); 2. Leukodystrophy with oligodontia

(LO); 3. Tremor-ataxia with central hypomyelination (TACH); 4. Ataxia, delayed dentition, and hypomyelination (ADDH).[1,2] There are 4 major clinical characteristics. These are 1. Neurologic dysfunction, predominantly including motor dysfunction (ie, cerebellar, pyramidal, and extrapyramidal) and cognitive dysfunction; 2. Abnormal dentition (hypodontia, oligodontia, delayed dentition, and abnormally shaped or placed teeth); 3. Endocrine abnormalities such as hypogonadotropic hypogonadism presenting as delayed, arrested, or absent puberty with low baseline LH and FSH levels, no response to pituitary stimulation with GnRH, and less commonly short stature (in ~50% of individuals) with or without growth hormone deficiency; 4. Ocular abnormality, for example, progressive myopia, as in our case.[8]

POLR3-related leukodystrophy is diagnosed by combining characteristic clinical findings, typical brain MRI presentation, and molecular genetic testing.[6] These clinical findings strongly indicate the diagnosis; however, some of these features may be absent in some individuals with POLR3-related leukodystrophy.[6] Our patient exhibited hypogonadotropic hypogonadism, myopia, tremor, and balance issues but had normal dentition. Brain MRI can demonstrate a hypomyelination leukodystrophy pattern characterized by T2 mild hyperintensity and T1 hyperintensity, isointensity, or mild hypointensity of the white matter when compared with gray matter structures.[9] Different types of molecular testing exist, including single-gene, multigene, and genomic testing (exome and genome sequencing).

Due to the multisystem involvement, most patients with 4H leukodystrophy require multidisciplinary care from several subspecialists, including an endocrinologist, neurologist, dentist, and clinical geneticist.[10] The endocrine management of this disorder involves 3 main components: continuously monitoring for the development of endocrine dysfunction over time, considering and starting hormone replacement therapy, and inducing ovulation or spermatogenesis if the patient desires fertility, although there is limited guidance available [(10)]. At present, there exist no established protocols for the institution of hormone replacement therapy with sex steroids in patients with 4H leukodystrophy.[4] It has been suggested that the same principles of hormone replacement therapy used in patients with other forms of hypogonadotropic hypogonadism can be applied to patients with 4H leukodystrophy.[10] After a review of available literature for the management of hypogonadal adult women, we commenced our patient on combined hormone replacement therapy.[4,11] She began having her periods after starting hormonal therapy and has now reached Tanner stage 3 of breast and pubic hair development. The American College of Obstetricians and Gynecologists recommends systemic hormone treatment in patients with primary ovarian insufficiency who also have low estrogen levels like our patient.[11] This treatment reduces long-term health risks such as osteoporosis and cardiovascular disease.[11] Estrogen is essential for bone growth and remodeling, and its deficiency results in increased bone resorption and, during menopause, loss of cortical and cancellous bone.[12] Even though we did not do a bone density study for this patient, we recommend that patients presenting as adults or late teens with hypogonadotropic hypogonadism have bone density studies as part of their workup to determine its impact on bone mineralization. Treating hypogonadotropic hypogonadism would allow the development of secondary sexual characteristics and induce a growth spurt, and this could also be beneficial, particularly in younger patients who are concerned about their physical appearance and would want to compare themselves to their peers experiencing pubertal changes.[4] Overall, initiation of sex steroid treatment should be considered on an individual basis, taking into account the benefits, such as improved health and possible drawbacks like rapid growth with retrogression, and should only be made after abnormal sex hormone levels have been confirmed through testing.[4]

Regular screening for the clinical manifestations of growth hormone, thyroid-stimulating hormone, and adrenocorticotropic hormone deficiency is recommended every couple of years.[10] However, the most effective method for monitoring endocrine function is not clearly defined, so managing physicians should maintain a high index of suspicion to correctly identify signs or clinical symptoms when they appear. A biochemical evaluation of pituitary hormones can be conducted as indicated.[10] Considering the risk of neurologic deterioration and the autosomal recessive inheritance pattern, patients with 4H syndrome should be offered genetic counseling. As the condition is extremely uncommon, there is currently no established protocol for routine carrier testing.[10]

Conclusion

Women with hypogonadotropic hypogonadism due to the rare 4H syndrome need to be treated to correct low estrogen levels to minimize long-term complications, including cardiovascular disease and osteoporosis.

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgment

We obtained informed consent from the patient in this case report. We are grateful to the patient for graciously giving consent for this case to be published.

References

1. Wang C, Wang S, Xie H, Yang S. Clinical and imaging characteristics of 4H syndrome: a case report. *CNS Neurosci Ther*. 2022;28:458–460. https://doi.org/10.1111/cns.13790
2. Wolf NI, Vanderver A, van Spaendonk RML, et al. Clinical spectrum of 4H leukodystrophy caused by POLR3A and POLR3B mutations. *Neurology*. 2014;83:1898–1905. https://doi.org/10.1212/WNL.0000000000001002
3. Potic A, Brais B, Choquet K, Schiffmann R, Bernard G. 4H syndrome with late-onset growth hormone deficiency caused by POLR3A mutations. *Arch Neurol*. 2012;69:920–923. https://doi.org/10.1001/archneurol.2011.1963
4. Pelletier F, Perrier S, Cayami FK, et al. Endocrine and growth abnormalities in 4H leukodystrophy caused by variants in POLR3A, POLR3B, and POLR1C. *J Clin Endocrinol Metab*. 2021;106(2):e660–e674. https://doi.org/10.1210/clinem/dgaa700
5. Timmons M, Tsokos M, Asab MA, et al. Peripheral and central hypomyelination with hypogonadotropic hypogonadism and hypodontia. *Neurology*. 2006;67:2066–2069. https://doi.org/10.1212/01.wnl.0000247666.28904.35
6. Bernard G, Vanderver A. POLR3-Related leukodystrophy. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, Gripp KW, Amemiya A, eds. *GeneReviews®*. University of Washington, Seattle; 1993.
7. Thiffault I, Wolf NI, Forget D, et al. Recessive mutations in POLR1C cause a leukodystrophy by impairing biogenesis of RNA polymerase III. *Nat Commun*. 2015;6:7623. https://doi.org/10.1038/ncomms8623
8. Tétreault M, Choquet K, Orcesi S, et al. Recessive mutations in POLR3B, encoding the second largest subunit of Pol III, cause a rare hypomyelinating leukodystrophy. *Am J Hum Genet*. 2011;89:652–655. https://doi.org/10.1016/j.ajhg.2011.10.006
9. Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. *Neurology*. 2009;72:750–759. https://doi.org/10.1212/01.wnl.0000343049.00540.c8
10. Billington E, Bernard G, Gibson W, Corenblum B. Endocrine aspects of 4H leukodystrophy: a case report and review of the literature. *Case Rep. Endocrinol*. 2015;2015:314594. https://doi.org/10.1155/2015/314594
11. Hormone therapy in primary ovarian insufficiency. Committee opinion No. 698. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2017;129:e134–e141.
12. Väänänen HK, Härkönen PL. Estrogen and bone metabolism. *Maturitas*. 1996;23(Suppl):S65–S69. https://doi.org/10.1016/0378-5122(96)01015-8