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Case Report

Normal intellectual ability and hyperprolactinemia as unique clinical manifestations of congenital hypothyroidism: A case report and review of hypotheses

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Abstract

Congenital hypothyroidism is the deficiency of thyroid hormone in infants and hyperprolactinemia is frequently observed. Previously reported cases typically involve intellectual disability, highlighting this particular unique case report to the first reported patient demonstrating normal intellectual ability despite experiencing growth and gonad dysfunction. This study aims to present a case and review medical hypotheses related to the patient's condition. A 19-year-old female presented with a chief complaint of irregular menstruation for up to 40 days or not occurring at all. The patient experienced the first menstruation at the age of 16 years old. The patient's height was 133 cm, body weight 40 kg, and body mass index 22.61 kg/m^2; other family members were normal. Physical examination showed no abnormalities, and laboratory examination showed suppressed serum free T4 (FT4) level (6.41 pmol/L), elevated thyroid stimulating hormone (TSH) level (333.700 µIU/mL), and elevated prolactin hormone level (32.03 ng/mL). Ultrasound of the thyroid gland found hypoplasia of the left and right thyroid glands. The patient was a college student enrolled in a public national university and had never complained about academic performance throughout the patient's education. The patient was diagnosed with congenital hypothyroidism and hyperprolactinemia. The patient was administered up to 100 µg daily of oral levothyroxine, which improved the patient's menstrual cycles. The patient's delayed diagnosis may be attributed to central congenital hypothyroidism being underdiagnosed. We hypothesized that thyroid-releasing hormone receptor (*TRHR*) gene mutation might contribute to the underlying cause of hyperprolactinemia and normal intellectual ability of the patient. Further study on the significance of *TRHR* gene mutations in congenital hypothyroidism is required to improve diagnosis and treatment.

Keywords: Congenital hypothyroidism, hyperprolactinemia, intellectual ability, gene mutation, medical hypothesis

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Introduction

Congenital hypothyroidism is the deficiency of thyroid hormone in infants [1] and it occurs in approximately 0.025% to 0.05% of infants and oftentimes does not present with specific clinical

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manifestations [2,3]. Trans-placental passage of some maternal thyroid hormones is likely to cause the condition, while many infants produce some thyroid production of their own [2]. If congenital hypothyroidism is not diagnosed and treated correctly soon after birth, it can cause severe mental retardation and growth dysfunction, as well as developmental issues [4,5].

Hyperprolactinemia is frequently observed in individuals with congenital hypothyroidism, often leading to ovulatory failure. However, the exact mechanisms behind the development of hyperprolactinemia remain poorly understood and studies on the co-occurrence of hyperprolactinemia and congenital hypothyroidism are limited. Furthermore, previously reported cases typically involve intellectual disability, highlighting the uniqueness of congenital hypothyroidism with normal intellectual ability. The aim of this study was to present a case of congenital hypothyroidism with normal intellectual ability and hyperprolactinemia and to provide a brief review of medical hypotheses related to the patient's condition. Our case report was prepared following the CARE guidelines [6].

Case

A 19-year-old Acehnese female presented to the Endocrine Clinic at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, with a chief complaint of irregular menstruation. Irregular menstruation ranging from 30 to 40 days, and would occasionally up to 2–3 months without menstruation. The patient experienced the first menstruation at the age of 16 years old. The patient appeared to have short stature and was the only one in the family with this characteristic. At the time of the initial diagnosis, the patient was a college student enrolled in a national university in Indonesia. The patient had never complained about academic performance or grades throughout the patient's education.

Vital signs were unremarkable. Physical examination of head, neck, thyroid glands, lymph nodes, thorax, heart, abdomen, and extremities were within normal limits. The patient's height was 133 cm, body weight 40 kg, and body mass index (BMI) 22.61 kg/m^2. Secondary sexual characteristics examination showed normal growth of underarm hair, breast enlargement at Tanner stage 1, and pubic hair growth at Tanner stage 4.

Laboratory examination indicated suppressed free thyroxine level (FT4) 1.89 pmol/L (reference range 9–20 pmol/L), elevated thyroid-stimulating hormone level (TSH) 100.00 µIU/mL (reference range 0.25–5 µIU/mL), and elevated prolactin level 32.03 ng/mL (reference range 5.18–26.53 ng/mL). Thyroid grayscale ultrasound found size reduction, measuring 1.02x1.08 cm for the right lobe and 1.28x0.63 cm for the left lobe, and homogeneous echo intensity of the right and left thyroid lobes, without any solid or cystic masses or calcifications; hence categorized as hypoplasia of both the right and left thyroid glands. A contrast-enhanced computed tomography (CT) scan of the head was normal. The patient was diagnosed with congenital hypothyroidism and hyperprolactinemia.

Subsequently, the patient was prescribed oral levothyroxine therapy at a dose of 50 µg, and the dosage was increased gradually. Five months after the treatment, a follow-up laboratory examination showed FT4 6.41 pmol/L, TSH 333.700 µIU/mL, and anti-thyroid peroxidase (anti-TPO) 1.23 IU/mL (reference range <5.61 IU/mL). Three months after the last laboratory examination, a significant improvement was observed in the patient's condition, indicated by FT4 13.6 pmol/L. The patient exhibited good adherence to the prescribed medication regimen, ameliorating the menstrual cycle. Regular follow-up visits were scheduled to monitor the patient's progress, and no adverse events were reported. One year after being diagnosed, the patient's TSH level was 0.617 µIU/mL, indicating thyroid-stimulating hormone level remained within the normal range.

Discussion

Congenital hypothyroidism can have devastating neurodevelopmental consequences if not detected and treated immediately [2]. While the apparent incidence of congenital hypothyroidism has increased in recent decades, the underlying cause remains obscure in most cases [5]. In our case report, several notable aspects require further explanation, such as the delayed diagnosis

until 19 years of age, the presence of normal intellectual ability despite congenital hypothyroidism, and hyperprolactinemia.

Congenital hypothyroidism arises from thyroidal or central issues (primary and central congenital hypothyroidism). Primary congenital hypothyroidism results from thyroid gland development issues (thyroid dysgenesis) or hormone biosynthesis defects (dyshormonogenesis). Central congenital hypothyroidism is thyroid hormone (TH) deficiency at birth due to the pituitary's insufficient stimulation of the thyroid gland [6]. Central congenital hypothyroidism is rare, with early estimates of its incidence ranging from approximately 0.0009–0.0034% [7-9]. The patient's delayed diagnosis may be attributed to central congenital hypothyroidism being underdiagnosed, as it is often not detected by the TSH-based newborn screening programs for congenital hypothyroidism that are implemented in most countries [8]. However, the scarcity of identified clinical cases and the complexity of hypothalamic-pituitary regulation of the thyroid axis have left the molecular mechanisms underlying central congenital hypothyroidism largely unknown [10].

The thyroid hormone plays a vital role in optimal growth and neurological development, especially throughout childhood. Hypothyroidism during this period is a significant cause of preventable intellectual disability worldwide [5,11]. In this particular case, the patient did not exhibit intellectual disability typically associated with congenital hypothyroidism. Further investigation of this intriguing finding leads us to consider a genetic perspective. Recent advances in phenotypic descriptions of patients, high-throughput sequencing technologies, and the use of animal models have contributed to the discovery of new genes involved in thyroid gland development and function [11].

Five genes, attributing immunoglobulin superfamily member 1 (*IGSF1),* insulin receptor substrate 4 *(IRS4),* transducin beta like 1 X-linked *(TBL1X),* thyroid-releasing hormone receptor (*TRHR*), and thyroid stimulating hormone subunit beta (*TSHB*), responsible for central congenital hypothyroidism have been identified, but their relative frequencies and the phenotypes of hypothalamic/pituitary units are still unclear [7,12]. TRHR is a G-protein–coupled receptor located in pituitary thyrotropes and is activated by the hypothalamic thyroid-releasing hormone (TRH). *TRHR* defects are rare recessive disorders that are typically associated with incidentally identified central congenital hypothyroidism and short stature in childhood cases [13], as observed in the present case. We hypothesized that the *TRHR* might have a role in hyperprolactinemia in the present case since *TRHR* is expressed in both thyrotrophs and lactotrophs, which means that intravenous TRH typically triggers peaks in both TSH and prolactin levels [1]. In addition, while primary congenital hypothyroidism commonly results in thyroid dysgenesis, it has been observed that *TRHR* gene mutations could lead to thyroid hypoplasia, as documented in the present case [14].

Untreated thyroid issues can cause subfertility or infertility due to elevated prolactin, disrupted hormone levels, and anovulation [15]. Hypothyroidism boosts TRH secretion, affecting prolactin and TSH levels via pituitary stimulation [16]. Lower triiodothyronine hormone elevates prolactin synthesis and prolactin clearance [17,18]. A link between serum prolactin and TSH levels was observed in secondary amenorrhea, suggesting hyperprolactinemia and thyroid dysfunction contribute to amenorrhea-related infertility risk [19].

Regarding normal intellectual ability in the present case, two previous studies also reported central congenital hypothyroidism cases with normal intellectual ability and confirmed to have *TRHR* gene mutations [20,21]. Although accepting delayed treatment at the ages of 9 and 11 years old, no significant intellectual disabilities were documented, implying that adequate production of thyroid hormones during childhood may have prevented severe developmental delay [20,21]. Since the patient in our case was incidentally diagnosed with congenital hypothyroidism at the age of 19 years old, we did not have access to the patient's childhood thyroid hormone level to directly compare it with the previous case reports. Therefore, we were unable to provide definitive evidence regarding the relevance of the earlier case reports [20,21] to our patient's condition.

There were no abnormalities discovered in the patient's family history in our case. As described previously it was presumed that the *TRHR* mutation might be a homozygous gene mutation due to the presence of parental consanguinity, which would support an autosomal recessive mode of inheritance, with one of the parents being heterozygous [22].

Proteogenomic testing for the patient was not possible in this study due to financial and facility constraints. As a result, further examinations are required to identify whether the patient has a *TRHR* mutation. Nevertheless, the hypothesis proposed in this study aligns with the existing previous studies [20,21]. Based on the elaboration provided, *TRHR* mutation might explain the patient's condition, characterized by normal intellectual abilities and hyperprolactinemia. However, the pathogenesis and association between central congenital hypothyroidism and *TRHR* gene mutations remain unclear. Therefore, further research is necessary to enhance our understanding of the role of *TRHR* gene mutations in congenital hypothyroidism to improve the diagnosis and treatment of this disease.

Conclusion

TRHR gene mutation might contribute to the underlying cause of hyperprolactinemia with normal intellectual ability in the present case. Further study to determine the pathogenesis and association of *TRHR* in congenital hypothyroidism is needed to improve the diagnosis and treatment of this particular case.

Ethics approval

The patient provided written informed consent to be published as a case report.

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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References

1. Peters C, van Trotsenburg ASP, Schoenmakers N. Diagnosis of endocrine disease: Congenital hypothyroidism: update and perspectives. Eur J Endocrinol 2018;179(6):R297-317.
2. Rastogi M V, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis 2010;5(1):17.
3. Wassner AJ. Congenital hypothyroidism. Clin Perinatol 2018;45(1):1-18.
4. Cherella CE, Wassner AJ. Congenital hypothyroidism: Insights into pathogenesis and treatment. Int J Pediatr Endocrinol 2017;2(1):11.
5. Gagnier JJ, Kienle G, Altman DG, *et al*. The CARE guidelines: consensus-based clinical case reporting guideline development. Case Reports 2013;23(1):bcr2013201554-bcr2013201554.
6. Lauffer P, Zwaveling-Soonawala N, Naafs JC, *et al*. Diagnosis and management of central congenital hypothyroidism. Front Endocrinol 2021;9:12.
7. Sugisawa C, Takamizawa T, Abe K, *et al*. Genetics of congenital isolated TSH deficiency: mutation screening of the known causative genes and a literature review. J Clin Endocrinol Metab 2019;104(12):6229-6237.

8. Persani L. Central hypothyroidism: Pathogenic, diagnostic, and therapeutic challenges. J Clin Endocrinol Metab 2012;97(9):3068-3078.
9. Persani L, Brabant G, Dattani M, *et al*. 2018 European Thyroid Association (ETA) guidelines on the diagnosis and management of central hypothyroidism. Eur Thyroid J 2018;7(5):225-237.
10. García M, Fernández A, Moreno JC. Central hypothyroidism in children. Endocrine Development. Basel; 2014:79-107.
11. Stoupa A, Kariyawasam D, Polak M, *et al*. Genetics of congenital hypothyroidism: Modern concepts. Pediatr Investig 2022;6(2):123-134.
12. Heinen CA, Losekoot M, Sun Y, *et al*. Mutations in *TBL1X* are associated with central hypothyroidism. J Clin Endocrinol Metab 2016;101(12):4564-4573.
13. García M, González DBJ, Jiménez-Rosés M, *et al*. Central hypothyroidism due to a *TRHR* mutation causing impaired ligand affinity and transactivation of Gq. J Clin Endocrinol Metab 2017;102(7):2433-2442.
14. Biebermann H, Schöneberg T, Krude H, *et al*. Mutations of the human thyrotropin receptor gene causing thyroid hypoplasia and persistent congenital hypothyroidism. J Clin Endocrinol Metab 1997;82(10):3471-3480.
15. Koyyada A, Orsu P. Role of hypothyroidism and associated pathways in pregnancy and infertility: Clinical insights. Tzu Chi Med J 2020;32(4):312.
16. Surks MI, Ortiz E, Daniels GH, *et al*. Subclinical thyroid disease. JAMA 2004;291(2):228.
17. Ansari MS, Almalki MH. Primary hypothyroidism with markedly high prolactin. Front Endocrinol 2016;26;7.
18. Cave WT, Ann PM. Effects of altered thyroid function on plasma prolactin clearance. Endocrinology 1980;107(1):85-91.
19. Shrestha S, Neupane S, Gautam N, *et al*. Association of thyroid profile and prolactin level in patient with secondary amenorrhea. Malays J Med Sci 2016;23(5):51-56.
20. Collu R, Tang J, Castagné J, *et al*. A novel mechanism for isolated Central hypothyroidism: Inactivating mutations in the thyrotropin-releasing hormone receptor gene. J Clin Endocrinol Metab 1997;82(5):1561-1565.
21. Bonomi M, Busnelli M, Beck-Peccoz P, *et al*. A Family with complete resistance to thyrotropin-releasing hormone. N Engl J Med 2009;360(7):731-734.
22. Koulouri O, Nicholas AK, Schoenmakers E, *et al*. A novel thyrotropin-releasing hormone receptor missense mutation (*P81R*) in central congenital hypothyroidism. J Clin Endocrinol Metab 2016;101(3):847-851.