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Case Report
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A Case of Familial Abnormal Albumin Hyperthyroxinemia in a Child

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Abstract

A 4-year-old girl was admitted to the Department of Pediatrics of the Second Hospital of Hebei Medical University in July 2021 because of "elevated FT4 on physical examination." Repeated laboratory examinations and genetic testing identified the presence of a heterozygous mutation, c.725G>A (P.R218H), in exon 7 of the *Albumin* (*ALB*) gene, and the diagnosis of familial abnormal albumin hyperthyroxinemia was confirmed. The patient is currently in a good general condition and does not require pharmacologic intervention. Because cases of familial abnormal albumin hyperthyroxinemia are rarely reported in China, it is important to raise clinicians' awareness to increase the diagnosis of this disease.

Keywords: Familial abnormal albumin hyperthyroxinemia; *Albumin gene*; Thyroid binding protein

Introduction

The autosomal dominant condition Familial Dysalbuminemic Hyperthyroxinemia (FDH) is caused by mutations in the gene encoding the protein serum Albumin (ALB). The mutation results in an unusually high affinity between albumin and serum thyroxine (T4), which causes an increase in thyroxine levels and restores normal thyroid function [1].

First described by Henneman [2] and Lee [3] in 1979, globally reported cases of FDH have rapidly increased recently. However, as most cases are identified accidentally, the incidence remains unknown. There are few reports of FDH in China. In this paper, we describe a case of FDH in a child that was identified through genetic testing in the father and a previous patient.

Case Presentation

A 4-year-old child was admitted to our hospital's outpatient department owing to an increased FT4 (42.53 pmol/L; the usual reference range is 12.3 pmol/L-22.8 pmol/L). Since childhood, the child was thin; with typically no irritability, palpitations, fatigue, fear of heat, excessive sweating, appetite, body pain, tetany, polydipsia, polyuria, nausea, vomiting, dizziness, headache, mental state, sleep, or noticeable change in weight. The child was delivered at full-term, weighing 3,300 g, by cesarean section to her mother in Hebei Province, and there were no birth defects. Her cerebral development was typical, and her growth and development history matched that of typical youngsters of her age. She denied having any medical history of trauma, illnesses of the central nervous system, lung conditions, particular medication use, or dietary or pharmacological sensitivities. There had not previously been a thyroid illness diagnosis or examination in the family, and the parents were in good health. (A family tree diagram is shown in Figure 1; the precertified individual's mother and father underwent genetic testing) (Table 1).

Physical examination findings: Height: 99.2 cm; weight: 12.5 kg; BMI: 12.70 kg/m^2; normal development; good nutrition; clear mentation; cooperative examination; no moist, yellowish staining or rash on the skin or mucous membranes of the whole body; superficial lymph nodes were not big; no deformity of the head; no protrusion of eyeballs; no enlargement of the thyroid gland; no palpation; no vascular murmur was heard on neck auscultation, respiratory sounds of the lungs were clear; no rales were heard. Heart rate was 90 beats per minute, rhythmic, heart sounds were strong; no pathologic murmurs were detected in the valvular regions; abdomen was soft, no pressure pain; liver, spleen, and subcostal areas were not palpable; liver and kidney regions were not tender; no mobile murmurs were detected; both hands were negative for fine tremors; there was no swelling of the lower limbs; limb activity was normal; physiologic reflexes were present; and pathologic reflexes were not elicited.

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Table 1: Thyroid function of the patient and her father.

Patient and date	TSH	FT3	FT4	T3	T4
Patient (2021-07-19)	1.05 mIU/mL (0.70-5.97)	10.01 pmol/L (3.69-8.46)	42.53 pmol/L (12.3-22.8)		
Patient (2021-07-27)	1.97 μIU/mL (0.64-6.27)	9.80 pmol/L (3.50-6.50)	29.63 pmol/L (11.50-25.70)	3.09 nmol/L (1.09-2.60)	290.30 nmol/L (63.50-167.30)
Patient's father (2021-08-26)	0.515 mIU/mL (0.55-4.78)	8.54 pmol/L (3.5-6.5)	24.50 pmol/L (11.5-22.7)	2.31 nmol/L (0.92-2.79)	189.80 nmol/L (58.10-140.60)

Auxiliary examination: A chemiluminescence assay of serum thyroid function revealed: TSH 1.97 μIU/mL (0.64-6.27), FT3 9.80 pmol/L (3.50-6.50), FT4 29.63 pmol/L (11.50-25.70), TT3 3.09 nmol/L (1.09-2.60), TT4 290.30 nmol/L (63.50-2.60), TG 5.97 ng/mL (3.5-77.00), TGAb 11.34 IU/mL (0-115), TRAb 1.01 IU/L (0.00-1.75), TPOAb <28.00 U/mL (0-60), ALT 12.3 U/L (7-40), ALP 198.3 U/L (96-297), GGT 11 U/L (7-45), AST 30 U/L (13-35), TBIL 5.99 μmol/L (0-23), ALB 42.8 g/L (40-55), urea 4.08 mmol/L (2.9-8.2), Cr 26 μmol/L (18-53), UA 241 μmol/L (155-357), TC 3.61 mmol/L (3.11-5.20), TG 1.47 mmol/L (0.56-1.70), HDL-C 0.68 mmol/L (1.04-1.55), LDL-C 2.38 mmol/L (2.07-3.37), ApoA1 0.92 g/L (1.00-1.60), ApoB 0.85 g/L (0.55-1.30), Lp(a) 1.27 mg/dL (0.00-30.00), and 25OHD 29.44 ng/mL. Routine blood samples showed no abnormalities.

Ultrasound examination: revealed the normal size and morphology of the thyroid gland, with homogeneous internal echogenicity, no obvious abnormal echogenicity in the bilateral parathyroid region, and no signals of abnormal blood flow. Dual-energy X-ray bone densitometry (DXA) revealed normal bone density in the lumbar spine and both hip joints. MRI examination showed that the size, shape, and signal of the pituitary gland were not obviously abnormal, the upper edge was straight, the height was approximately 3.8 mm, the pituitary stalk was centered, the pterygoid saddle, the suprasellar pool and the third ventricle were not obviously enlarged and deformed, the morphology and structure of the optic intersection were not abnormal, and there were no signs of space occupancy.

The patient's peripheral blood was subjected to whole-exome sequencing at the Beijing Zhiyin Eastern Translational Medicine Research Center Ltd. The results revealed a heterozygous c.725G>A mutation in exon 7 of the *ALB* gene, resulting in the mutation of the arginine at position 218 to histidine. This alters the molecular conformation of serum Albumin and significantly increases its affinity for binding T4. Her father had an identical mutation. In the patient, no alterations were discovered in any additional genes linked to parathyroid adenomas.

Follow-up: Two years of follow-up have been performed, and the child is currently 6 years and 6 months old. Her height (118 cm) and weight (20 kg) are in the middle of the range for girls of her age. With regard to thyroid function of the girl and her father, no special measures have been taken. Overall, the girl is in good health, with no symptoms such as palpitations, exhaustion, hunger, and hyperphagia, and no weight loss.

Discussion

FDH is the most common genetic disorder that causes hyperthyroidism in healthy Caucasians, with a prevalence of approximately 1:10,000, although the prevalence varies in some groups, with the largest prevalence occurring in People of Portuguese Descent and Hispanic populations [4]. The prevalence of FDH was 0.17% in females and 0.16% in males, according to Arevalo et al. [5] study of 15,674 serum samples over the course of a year.

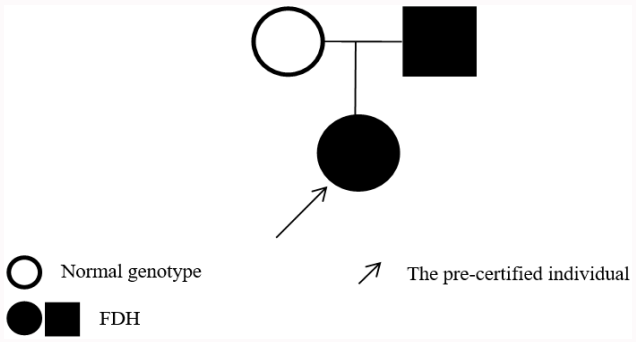

Figure 1: Family chart of the patient with FDH (the precertified individual and her father and mother, all genetically tested).
FDH: Familial Abnormal Albumin Hyperthyroxinemia

This finding is consistent with the familial transmission pattern of autosomal dominant inheritance. The study demonstrated that there are occasional cases of FDH; however, as there are few case reports on Chinese patients with FDH, endocrinologists in China are still not well-versed in the condition. Consequently, patients with FDH are frequently misdiagnosed with hyperthyroidism, leading to unnecessary medication or surgical procedures.

There are three primary serum thyroxine-binding proteins: Thyroxine-Binding Globulin (TBG), Thyroxine Transporter Protein (TTR), and Human Serum Albumin (*HSA*). Of these, 99.97% and 99.70% of extracellular T4 and T3, respectively, are protein-bound [6]. Individuals' serum thyroid hormone levels may change if mutations in the genes coding in these transport proteins occur, although patients with clinically normal thyroid function do not require treatment [7]. The most significant protein that binds thyroid hormone is TBG; it has the highest affinity for the hormone and binds approximately 75% of it in the bloodstream. Mutations in the relevant genes can alter TBG protein synthesis, secretion, and stability, resulting in defects in TBG protein synthesis and secretion. Changes in the affinity of TBG for thyroid hormones and/or the quantity of TBG bound to THs can cause irregularities in blood thyroid hormone levels. These deficiencies can be caused by mutations in the genes that affect TBG protein synthesis, secretion, and stability [8,9]. TTR, also known as Thyroxine-Binding Prealbumin (TBPA), binds approximately 20% of the Thyroid Hormone (TH) in the blood, and the TTR protein is the most important thyroid hormone-binding protein. Amyloidosis and non amyloidosis are the two primary variations in these illnesses; the former mostly causes familial amyloidosis-like polyneuropathy, whereas the latter can disrupt the ability of TTR to bind and transport TH [10,11]. *HSA* is the most abundant protein in serum, with the content 100 times higher than TTR and 2,000 times higher than TBG. *HSA* has the lowest affinity for TH and only binds about 5% of TH in the blood [6,12]. As TBPA binds to approximately 20% of the TH in the blood, the changes in *HSA* concentration and their correlation with TH may be related to the presence of TBPA. Consequently, only when the affinity of *HSA* for TH is markedly increased, leading

to raised serum TT3 and/or TT4 concentrations, do changes in the concentration of *HSA* and its decreased affinity for TH cause major aberrations in blood TH levels.

The first cases of FDH were reported in 1979 when Henneman et al. [2] discovered two patients with normal serum T3 and serum reverse T3 (rT3) levels but elevated serum T4 and FT4 levels. They then proposed that this "high total T4, normal T3 syndrome with normal thyroid function" was autosomally dominantly inherited, with normal serum FT4 levels found in the other affected family members. In the same year, Lee et al. [3] reported that a patient with comparable serum TH levels also had lower T4-Binding Globulin (TBG) levels and lower affinity for T4-binding serum albumin, concluding that this was an autosomal dominant pattern of inheritance by studying the serum of fraternal twins and her parents.

The TT4 abnormality was first linked to a modified *HSA* molecule [13] in early FDH studies based on electrophoretic, chemical, and immunological characterization. However, the precise defect was not identified until 1994 by Petersen et al. [14,15] who sequenced the entire coding region of the *albumin* gene in FDH subjects. In 1997, Wada et al. [16] reported the first case of FDH in Asia; Tang et al. [17] reported the first case of FDH in China; Tiu et al. [18] reported an FDH family line in Hong Kong, China, comprising seven patients over two generations with the R218H mutation; and Dai, Weixin et al. [19] reported the first case of an FDH family in mainland China, comprising four patients over three generations also with the R218H mutation. We diagnosed R218H mutation type in the patient's family line. Through analysis of prior research, it appears that R218H, a similar mutation type to that found in Caucasians, may be the most prevalent FDH mutation in the Chinese population.

FDH is classified as either FDH-T3 or FDH-T4 depending on whether the aberrant *HSA* attaches predominantly to T3 or T4. A point mutation in exon 7 of the *HSA* gene (*ALB*) is responsible for the pathophysiology of FDH-T4. This mutation causes other amino acids that have a lower molecular weight to replace arginine at positions 218 and 222 in the mature *HSA* molecule, reducing the spatial constraints on the binding site and forming a high-affinity binding site. Stronger ligand binding with higher affinity for T4 is the outcome of these modifications, as well as some accompanying minor conformational changes. The R218H mutation is most prevalent in FDH-T4, followed by the R218P mutation [20]. The Guanine (G) to Adenine (A) mutation in the second nucleotide of the Arg218 codon, which results in the change from CGC to CAC, is the molecular basis of the R218H type of albumin mutation. This mutation is usually linked to an *ALB* polymorphism at the SacI site. The most prevalent mutation causing this disease is R218H and it was the first FDH-T4 type-mutation to be reported. Typically, in clinical testing, homozygous T4 levels are approximately 2-fold the normal levels, whereas heterozygous T4 levels are 1.1-1.8-fold the normal level, T3 levels are 0.6-1.2-fold the normal level, and rT3 levels are 0.7-1.4-fold the normal levels [6]. Another missense mutation (G to C) in the same nucleotide results in a proline replacing the Arg218 in the R218P type of FDH-T4. This mutation type results in a significantly higher binding capacity of *HSA* molecules to THs than the R218H mutation. Clinically detected T4 levels in patients with this mutation type can reach 8-15-fold higher than the normal level, and FT4, T3, FT3, and rT3 are elevated to varying degrees. More patients with this mutation have been found in Japan than anywhere else in the world; however, because of their elevated serum T4 and T3 levels, they are more likely than other forms of FDH cases to be misdiagnosed as other conditions, such as TSH incorrect secretion syndrome [21,22].

The majority of patients with FDH are identified by chance when they attend a clinic for other reasons. The elevated levels of TT4 in the patients' serum are actually to compensate for the abnormal affinity of T4 for albumin, which FT4 in the serum to maintain a normal level. In fact, the thyroid gland of patients with FDH may have normal function, but the disease still needs to be distinguished from drugs or other diseases that cause elevated T4 levels [23].

Summary

The case described in this article was discovered by chance during a physical examination and was clearly confirmed by genetic testing. No specific treatment was initiated, and the child's follow-up process was smooth, with no special symptoms appearing. There are currently very few documented cases of FDH in China; however, because the patients do not exhibit any overt clinical signs, there may be more unreported cases that are yet to be identified. To prevent the administration of unnecessary medication, clinicians should consider FDH as a differential diagnosis when they encounter asymptomatic patients with unexplained high levels of T4 and normal levels of TSH.

Project

Hebei Province 2021 Medical Science Research Project Program (No. 20210165 Application of whole exome sequencing in the etiological diagnosis of children with difficult critical illnesses in Hebei Province).

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