Hyprolactinemia as a clue to diagnosis of mild central hypothyroidism due to IGSF1 deficiency

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Abstract
Loss-of-function mutations of IGSF1 are an X-linked cause of central hypothyroidism (CeH) and hyprolactinemia. A currently 15.2 year-old boy presented at the age of 7.69 years for evaluation of obesity. Previous thyroid function evaluation suggested CeH (FT4 0.6 ng/ml, TSH 2.2 mIU/L) but his physician took no action. At presentation he was clinically and biochemically euthyroid, prepubertal, obese; serum PRL was undetectable. Biochemistry was normal except for mild hypercholesterolemia, total cholesterol 198 mg/dl. Subsequently FT4 and TSH levels fluctuated between 0.72-0.95 ng/dl (normal 0.8-2.0) and 1.94-5.77 mIU/L (normal 0.3-5.0), respectively. Sequencing of IGSF1 gene revealed a novel genetic change c.3805C>T in exon 19 that resulted in substitution of aminoacid Arginine 1269 with a «stop» codon and the production of an altered protein product. The patient additionally presented delayed adrenarche, low height velocity that resolved spontaneously and normal pubertal onset associated with increased FSH levels. At 14 years-of-age, while the patient was at Tanner stage 4, PRL levels became detectable rising gradually to 2.3 ng/ml at last examination. Thyroxine replacement therapy resulted in decrease in total cholesterol 103 mg/dl. A high index of suspicion for the disorder is needed since several measurements of thyroid function may be required for central hypothyroidism to be disclosed. The patient’s normal FT4 levels and normal intelligence would have resulted in a missed diagnosis if he had not serum PRL levels measured. This case highlights the importance of determining PRL levels in a boy with low normal FT4 and normal TSH levels.

Keywords: Central hypothyroidism, hyprolactinemia, IGSF1

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Introduction
Loss-of-function mutations of the immunoglobulin superfamily, member 1 (IGSF1) gene have been recently described as an X-linked cause of congenital central hypothyroidism (1), with an estimated prevalence of 1/100000 (2). Central hypothyroidism (CeH) is the hallmark of the disorder, however, patients additionally may present with hyprolactinemia, transient partial Growth Hormone Deficiency (GHD), normal timing of testicular enlargement but delayed testosterone rise in puberty resulting in delayed adolescent growth spurt, and adult macroorchidism (3). IGSF1 gene resides on X-chromosome therefore its mutations affect mainly males, although female heterozygous carriers may present central hypothyroidism (3). The prevalence of low FT4 in female carriers is reported to be 18% (4). IGSF1 gene encodes an immunoglobulin superfamily glucoprotein of plasma membrane. IGSF1 protein was observed in somatotropes, thyrotropes, and lactotropes of anterior pituitary, whereas it was absent in gonadotropes or corticotropes. Moreover, IGSF1 protein is predominantly expressed in testis, muscle, heart and pancreas.

We present a boy with mild CeH due to a novel mutation of IGSF1 gene. Additionally, the patient presented undetectable PRL levels that was the clue to diagnosis.

CASE REPORT
A currently 15.2 year-old boy presented to our pediatric endocrinology clinic at the age of 7.69 years for obesity evaluation. He is the first child of unrelated parents, born after normal delivery with normal body weight and length. Developmental milestones were achieved at a normal age. During the preschool years he had normal height velocity but increase in body weight. Thyroid function tests (TFT) ordered by his pediatrician, at 3 and 4 years-of-age, were compatible with CeH (FT4 0.5 ng/ml, TSH 2.2 mIU/L) but his physician took no action. At presentation he was clinically and biochemically euthyroid, prepubertal, obese; serum PRL was undetectable. Biochemistry was normal except for mild hypercholesterolemia, total cholesterol 198 mg/dl. Subsequently FT4 and TSH levels fluctuated between 0.72-0.95 ng/dl (normal 0.8-2.0) and 0.65 ng/ml, TSH 2.2 mIU/L, respectively, however, no action was taken. His parents and siblings (a girl and twin boys currently 13 and 9.5 years old respectively) are healthy. Mother did not breast-feed any of her four children because of inadequate milk production.

At presentation, patient’s height was 122.5 cm (HSDS -0.55). The boy was prepubertal and euthyroid, (i.e. no fatigue, constipation, bradycardia etc.) weight was 35.1 kg (WSDS 1.67), BMI 23.4 kg/m2 (BMISDS 2.89). Thyroid gland was non-palpable. School performance was reported as very good. Target height (TH) SDS was +1.1. TFT showed FT4 1.0 ng/dl (0.8-2.0), TSH 1.98 mIU/L (0.3-5.0), PRL <0.7 ng/ml (3-18), IGF1 126 ng/ml (110-565), and bone age was 6.7 years. Biochemistry was normal except for mild increase in total cholesterol 198 mg/dl (<170), HDL-cholesterol 68 mg/dl (>40), LDL-cholesterol 123 mg/dl (<129) and triglycerides 36 mg/dl (<150). During the next 2 years there was fluctuation of FT4 levels between 0.72-0.95 ng/ml, of TSH levels between 1.94-5.77 mIU/L, whereas PRL was always undetectable. TRH test showed a normal TSH response, 0':3.44 mIU/L, 30':14.73 mIU/L, 60':11.71 mIU/L, and an abnormal PRL response 0':<0.4 ng/ml, 30':1.7 ng/ml, 60':0.9 ng/ml. Basal PRL levels became detectable 1.7 ng/ml at the age of 14 years, at Tanner stage 4, increasing slightly to 2

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Children with IGSF1 deficiency present disharmonious pubertal development, i.e. pubertal onset at a normal age but delayed alterations are related to IGSF1 deficiency. Testosterone increase occurring at an advanced TV. In adult life testosterone levels are usually low or low normal. Late adolescent classified as overweight and 21% as obese (4), being in accord with the phenotype of our patient. It is unclear how these metabolic abnormalities carry the same mutation as the proband, but no mutation was found in his sister. Molecular analysis Analysis of IGSF1 gene revealed a genetic change c.3805C>T in exon 19 (Figure 2), that resulted in substitution of aminoacid Arginine at position 1269 with a «stop» codon and the production of an altered protein product. This genetic change has not been reported previously in patients with CeH. We also performed analysis of the gene in the boy’s mother and sister. His mother was found to carry the same mutation as the proband, but no mutation was found in his sister. IGSF1 gene analysis was not performed in his brothers because of normal thyroid function in both of them. DISCUSSION We identified a novel IGSF1 nonsense mutation in a Greek patient with congenital central hypothyroidism. The molecular defect observed in our patient (p.Arg1269X) prematurely truncates the IGSF1 protein at the end of the 12th Ig loop in the extracellular portion of the C-terminal domain. The IGSF1 protein includes 12 Ig-like domains in two sets of 5 and 7 motifs separated by a linker region, followed by a transmembrane domain and a short cytoplasmic tail (3). The N-terminal part undergoes translational proteolysis while the C-terminal is expressed extracellularly at the plasma membrane. The precise molecular role of IGSF1 remains unclear. To date, more than 30 distinct mutations have been described including missense, nonsense, frameshift and whole gene deletions (6,7) that lead to loss of protein function. All but one reported mutations are located in the C-terminal domain of the protein and impairs IGSF1 trafficking from the endoplasmic reticulum to the plasma membrane. There is no clear genotype-phenotype correlation, while variation in the extent of hypothyroidism and other clinical features even within families has been reported (8,9). IGSF1 is expressed in thyrotrhop cells of anterior pituitary. Igsf1-deficient male mice have reduced serum TSH and decreased pituitary Thr mRNA levels (1), while others have shown that the principal impairment is attenuated TRH actions in pituitary thyrotrhopes (10). Garcia et al, in a patient with severe congenital CeH due to complete deletion of IGSF1 gene, described markedly decreased TSH bioactivity, poor response to TRH stimulation and decreased TRHR expression (11). Our patient showed a normal TSH response to TRH stimulation suggesting impaired endogenous TRH action. Moreover, he had a hypoplastic thyroid gland, a finding observed in 74% of IGSF1-deficient patients (4). IGSF1 protein is detected in pituitary lactotropes, however prolactin deficiency is present in about 67% of IGSF1-deficient patients (3). No explanation for the lack of PRL deficiency has been given. Our patient had undetectable serum PRL, and very poor PRL response to TRH stimulation suggesting pituitary dysfunction. However, Basal PRL levels became detectable at the age of 14 years showing a gradual increase. It remains to be seen whether PRL will normalize as the child grows older. Increased birth weight or length is observed in a substantial number of patients (12). 67% of IGSF1-deficient male children were classified as overweight and 21% as obese (4), being in accord with the phenotype of our patient. It is unclear how these metabolic alterations are related to IGSF1 deficiency. Children with IGSF1 deficiency present disharmonious pubertal development, i.e. pubertal onset at a normal age but delayed testosterone increase occurring at an advanced TV. In adult life testosterone levels are usually low or low normal. Late adolescent and adult patients commonly present macro-orchidism, however, TV may be normal (13) or increased from the prepubertal years. Our patient entered puberty at a normal age. At onset of puberty the patient’s basal FSH levels were increased, LH levels were normal for pubertal onset and showed a normal progression according to pubertal status, whereas testosterone levels at early puberty were low for TV but normalized as puberty progressed. What causes the disharmonious pubertal development is not clear. Patients with IGSF1 deficiency have been reported to present delayed adrenarche (14). Our patient presented the marker of biochemical adrenarche, i.e. serum DHEAS 40 μg/dl, after the age of 12 years, and pubarche at the age of 13 years [median age of pubic hair development for Greek boys is 11.2 years (15)]. Transient partial GH deficiency has been reported in a subset of patients with IGSF1 deficiency. It is not clear why our patient presented growth deceleration, although subnormal GH secretion, low normal IGF1 levels and the delayed bone age might suggest transient GH deficiency that resolved before adolescence. The period between 6 and 11 years of age in boys constitutes the juvenile phase of growth characterized by growth deceleration relative to the preceding childhood phase and by increase of adrenal androgens (adrenarche) (16). Based on the very low DHEAS levels of our patient during this period we can speculate that low adrenal
androgens may exaggerate the normal growth decelerating pattern of juvenility. Normalization of height velocity, which occurred prior to thyroid hormone substitution, might be attributed to the gradual increase of adrenal androgens. In conclusion, we present a male patient with central hypothyroidism and PRL deficiency due to a novel mutation of IGSF1 gene. Additionally, he presented obesity, disharmonious puberty, and delayed adrenarche, all features of the IG SF1 syndrome. The patient had mostly low normal FT4 levels, thus PRL deficiency was the clue to diagnosis. Most reported cases of CeH due to IG SF1 deficiency are symptomatic necessitating L-thyroxine treatment. We believe, however, that a significant number of patients are undetected because symptoms may be absent or subtle. Diagnosis is important for genetic consultation, since no clear genotype-phenotype correlation is observed even within the same family. Furthermore, in the TSH-based neonatal congenital hypothyroidism screening programs diagnosis will be delayed. Children of female carriers and female children of male patients should be screened in neonatal life for FT4 and TSH levels. This case highlights the importance of determining PRL levels in a boy with low normal FT4 and normal TSH levels.

References

Figure legends

Figure 1. Progression of height. Height velocity normalized spontaneously after the age of 10 years. Squares denote bone ages. Arrow depicts initiation of L-thyroxine treatment.

Figure 2. Sequencing of the IGSF1 gene showing the c.3805C>T (p.Arg1269Ter) genetic change in exon 19: (a) patient, (b) mother
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