

Two sisters with homozygous deletion mutation in the PROP-1 gene

PROP-1 geninde homozigot delesyon mutasyonuna sahip iki kız kardeş

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Abstract

Defects in the PROP-1 gene produce clinical findings by affecting somatotrophs, thyrotrophs, lactotrophs, gonadotrophs and corticotrophs. The first finding in cases with PROP-1 gene mutation is growth retardation associated with growth hormone (GH) deficiency and central hypothyroidism. Other hormone deficiencies are added over time. We describe two sisters with deletion mutation in the PROP-1 gene. The parents were first-degree cousins. The female patient identified as the index case was 4.6 and the other sister was 1.9 years old when they presented with failure to thrive and short stature. Central hypothyroidism and GH deficiency was determined in both sisters. Homozygous deletion mutation was determined in the PROP-1 gene at genetic analysis. PROP-1 mutation should be considered in patients presenting with combined GH deficiency and central hypothyroidism, and the diagnosis must be confirmed with genetic analysis.

Keywords: Growth hormone deficiency, PROP-1 gene mutation, short stature.

Öz

PROP-1 genindeki bozukluklar somatotrop, tirotrop, laktotrop, gonadotrop ve kortikotropoları etkileyerek klinik bulgulara yol açar. PROP-1 gen mutasyonu olan vakalarda ilk bulgu büyüme hormonu eksikliği ve santral hipotiroidi ile ilişkili büyüme geriliğidir. Diğer hormon eksiklikleri zamanla eklenir. Burada, PROP-1 geninde silme mutasyonu olan iki kız kardeşi bildirdik. Ebeveynler birinci derece kuzendi. Büyüme gelişme geriliği ve boy kısalığı yakınması ile başvuran olgulardan indeks kız hasta 4,6 yaşında, kız kardeşi ise 1,9 yaşındaydı. Her iki kız kardeşte de santral hipotiroidizm ve büyüme hormonu eksikliği (BH) belirlendi. Genetik analizde, PROP-1 geninde homozigot delesyon mutasyonu saptandı. Büyüme hormonu eksikliği ve santral hipotiroidi ile başvuran hastalarda PROP-1 mutasyonu düşünülmeli ve genetik analiz ile tanı doğrulanmalıdır.

Anahtar Sözcükler: Büyüme hormonu eksikliği, PROP-1 gen mutasyonu, kısa boy.

Introduction

Combined pituitary hormone deficiency (CPHD) is defined as concomitant deficiency of growth hormone (GH) and at least one other anterior pituitary hormone (1). Although genetic causes play a significant role, the etiology of CPHD has not yet been fully explained. Mutations in various

transcription factor genes, such as POU1F1, PROP-1, HESX1, LHX3 and LHX4, which play a role in pituitary morphogenesis, can lead to CPHD (2). PROP-1 and LHX3 mutations are autosomal recessive (AR), while HESX1, POU1F1 and LHX4 mutations are acquired both AR and autosomal dominant (AD) (3).

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Defects in the PROP-1 gene constitute the most prevalent genetic causes of CPHD (4). In humans, defects in PROP-1 cause deficiencies in thyroid-stimulating hormone (TSH), GH, follicle-stimulating hormone/luteinizing hormone, and prolactin (4). Adrenocorticotrophic hormone (ACTH) deficiency may develop in some patients (5). The severity and onset of hormone deficiencies in pediatric patients vary. Point mutations, small deletions and insertions in the PROP-1 gene have been reported (3). More rarely, complete homozygous deletions in PROP-1 gene have also been observed.

The purpose of this study is to report a case of two sisters with homozygous deletion mutation in the PROP-1 gene. Informed consent was received from the patients' father.

Case 1 (index patient)

A 4.6-year-old girl was referred to our pediatric endocrinology clinic due to failure to thrive and short stature. She was born at term weighing 3000 g, and her parents were first-degree cousins. The patient was 88 cm tall (SDS:-4.14) and weighed 11.1 kg (SDS:-3.34) (body mass index, BMI: 14.5, -0.70 SDS). The target height was 161 cm (SDS:-0.53), and bone age was consistent with 18 months. The patient's basal hormone levels are shown in (Table-1). Na-L thyroxin therapy was initiated because of central hypothyroidism. Pituitary magnetic resonance imaging was evaluated as normal.

While the patient was euthyroid, the GH stimulation test was applied with clonidine and L-dopa and the responses to peak serum GH were found to be 0.56 ng/ml and 0.33 ng/ml, respectively. Were determined. GH deficiency was diagnosed on the basis of these results, and treatment was started with recombinant GH (rGH). Prior to treatment, the patient's growth rate was 3 cm/year, rising to 9 cm/year with GH therapy. A low-dose (1 mcg) ACTH stimulation test was applied during follow-up, and a sufficient cortisol response was obtained (25.07 ng/dl). Molecular analysis revealed deletion mutation in the PROP-1 gene.

Case 2 (sister of the index patient)

A 1.9-year-old girl was referred to our pediatric endocrinology clinic due to failure to thrive and short stature that had first been noticed six months ago. She was born at term weighing 2800 g. The patient had one brother of normal height, and the one sister described above as

case 1. She was 73.5 cm tall (SDS:-3.20) and weighed 8.8 kg (SDS:-1.95) (BMI: 16.3, 0.18 SDS). This patient's basal hormone levels are shown in (Table-1). Na-L thyroxin therapy was initiated because of central hypothyroidism. Pituitary magnetic resonance imaging was normal.

While the patient was euthyroid, the GH stimulation test was applied with clonidine and glucagon and the responses to peak serum GH were found to be 0.56 ng/ml and 0.33 ng/ml, and the peak cortisol value was 22.6µg/dL. Adrenal insufficiency was excluded on the basis of these results, and GH deficiency was diagnosed. Treatment was initiated with rGH. Molecular analysis revealed deletion mutation in the PROP-1 gene.

Genetic data for the family are shown in (Figure-1).

Table-1. Hormonal evaluation of anterior pituitary function in the sister siblings.

Basal Hormone Levels (normal value)	Case-1	Case-2
TSH (0.77–5.64uIU/ml)	2.99	0.79
FT4 (0.74–1.26ng/dl))	0.58	0.29
Prolactin (3.34–26.72ng/ml)	8.28	10.32
ACTH (7.2-63.3pg/ml)	23.5	23.5
Cortisol (3.7–19.4µg/dl)	11.33	6.71
IGF-1 (51-303ng/ml)	25	18.1
IGFBP-3 (700-3600ng/ml)	500	780
Peak GH levels (ng/ml)		
L-Dopa	0.33	
Clonidine	0.56	1.93
Glucagon		1.75

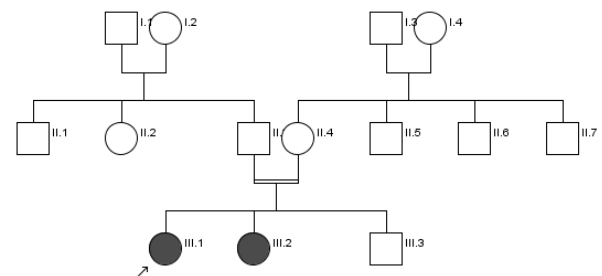


Figure-1. A pedigree of a family with individuals having PROP-1 gene mutation.

Genomic analysis

Genomic DNA was isolated from peripheral blood cells using standard procedures. The DNA samples were quantified with a NanoDrop. The exons encoding the *PROP1* gene were submitted for amplification using flanking primers and primer sequences. PCRs were validated using 2% agarose gel electrophoresis, which indicated no amplification of the gene. Thyroid hormone receptor beta (*THRB*) gene amplification was successfully performed as a reference amplification. No PCR product bands were observed for all exons of the *PROP1* gene when amplifying the genomic DNA samples from the siblings.

Discussion

A group of transcription factors are responsible for the development of the anterior pituitary gland in the embryonic period. A deficiency in the transcription factors can therefore result in impairment in pituitary development and endocrine functions. Mutations in pituitary transcription factors in pediatric patients are responsible for CPHD. Mutations in the *POU1F1*, *PROP1*, *HESX1*, *LHX3* and *LHX4* genes are responsible for >50% of familial CPHD (1). *PROP1* gene mutations encoding *PROP1* are the most prevalent cause of CPHD (6). Complete homozygous deletions of the *PROP1* gene are rare, and only approximately 40 cases have to date been reported (3).

Specific combinations of deficient pituitary hormones are associated with various transcription factor mutations (1). The *PROP1* gene is very important to the differentiation and function of somatotrophs, thyrotrophs, gonadotrophs and lactotrophs. In these gene mutations, GH deficiency is accompanied by deficiencies in one or more anterior pituitary hormones. Böttner et al. (1) reported adrenal insufficiency, including advanced impairment in pituitary functions, in cases with *PROP1* mutation.

In contrast to other CPHD patients, no symptoms of hypopituitarism are present at birth in cases with *PROP1* mutation, and length at birth is generally normal. The general characteristic of children with this mutation is retarded growth starting in early life, and diagnosis is often delayed until the age of 6-7 years (7). Hypothyroidism subsequently accompanies GH deficiency, but is generally mild (3). However, in the present cases with deletion mutation in the

PROP1 gene, height started to be affected at an earlier age, and hypothyroidism was detected at time of presentation. Studies have shown that pituitary hormone deficiencies may emerge at different times in patients with *PROP1* gene mutations, even if they possess the same mutation, and that there is therefore no clear genotype-phenotype correlation (8). Gorar et al. (9) reported that while ACTH deficiency was present in the youngest of three siblings with combined pituitary hormone deficiency and *PROP1* gene deletion, that no ACTH deficiency was present in the older sisters, and that different genotype-phenotype correlation may be found in cases with this mutation. In contrast to these studies, GH deficiency and clinical hypothyroidism findings occurred at an early age in both our cases with *PROP1* gene deletion, and genotype-phenotype correlation was consistent. Additional deficiencies in other hormones may occur in a time-dependent manner in patients with *PROP1* gene mutation. However, the time of emergence of hormone deficiencies cannot be predicted. The frequency and degree of gonadotropin deficiency is also variable. In some patients, pubertal development cannot be achieved, while in others, even if adolescence is entered, pubertal development cannot be completed or secondary hypogonadism gradually develops (6).

Adrenal insufficiency associated with ACTH deficiency is a component of CPHD that develops in association with *PROP1* mutation, but is seen less frequently (3). Adrenal insufficiency generally starts to produce clinical symptoms in adolescence and adulthood. In addition, even if basal cortisol and ACTH hormone levels are low, a sufficient cortisol response may be obtained in the hypoglycemia test in some patients (7). In the current cases, a sufficient cortisol response was obtained in low-dose ACTH and glucagon stimulating tests, and adrenal insufficiency was excluded.

Pituitary imaging studies have shown that the pituitary gland is normal in size or hypoplastic in the majority of cases of *PROP1* mutation. However, a case has been reported of a patient with an expanded sellar mass (10). Pituitary expansion is more frequent in young patients with *PROP1* mutation. Regression develops in the pituitary gland in later years. MRI examination of the cases in the current report, who presented early, revealed a normal pituitary size, consistent with the previous literature.

Conclusion

In conclusion, the identification of genetic defects in patients with CPHD is important in terms of prognosis and clinical management of the disease. PROP-1 mutation must be considered in patients with combined GH and TSH deficiencies, and when diagnosis is confirmed with genetic analysis, patients must be closely followed-up in

terms of development of adrenal insufficiency and hypogonadism.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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