Case Report
Central Eur J Paed 2023;19(2):147-151
DOI: 10.5457/p2005-114.350

Familial Combined Pituitary Hormone Deficiency by a Mutation in PROP1 – a Case Report

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Received: August 17 2023; **Accepted**: October 29 2023

Abstract

Objective This paper aimed to emphasize the importance of considering the diagnosis of *PROP1* mutation in all cases where multiple members of the same family are affected by combined pituitary hormone deficiencies (CPHD). **Case Report –** We describe two brothers of unrelated parents with a mutation in the *PROP1* gene. Both brothers presented with growth impairment - the older one at the age of 2.5 years, and the younger one at the age of 3.3 years. Central hypothyroidism and GH deficiency were established in both of them. Replacement therapy was started using levothyroxine and recombinant growth hormone. Pituitary magnetic resonance imaging was normal. Genetic analysis identified a pathogenic homozygous frameshift variant c.301_302delAG in the *PROP1* gene. **Conclusion –** Patients with *PROP1* mutation must be closely followed up to reveal other possible hormonal defects and to avoid possible life-threatening adrenal crisis in the future. *PROP1* mutation should be considered in all familial forms of CPHD and in all patients who have a deficiency of two or more pituitary hormones.

Key Words: Combined Pituitary Hormone Deficiency ▪ Growth Hormone Deficiency ▪ *PROP1.*

Introduction

Combined pituitary hormone deficiency (CPHD) is a rare disorder characterized by impaired production of two or more anterior and/or posterior pituitary hormones. Most commonly, CPHD presents as a combination of growth hormone (GH) deficiency and deficiency of one additional pituitary hormone. The majority of CPHD cases develop due to brain surgery, trauma, tumor, irradiation, infection, or autoimmune disease. In addition, this disorder can be caused by genetic mutations. So far, approximately 30 genes causing CPHD have been identified (1). However, about 84% of the patients with CPHD still have no genetic confirmation of the diagnosis, even though the familial history of this disorder suggests a genetic etiology (1).

Two groups of genes are involved in the etiology of CPHD. The first group of genes is involved in the early stages of the development of the pituitary gland, but they are also expressed in regions responsible for the formation of the forebrain and midline structures. Mutations in these genes are usually present as craniofacial abnormalities associated with pituitary dysfunction (syndromic CPHD) (1). The second group of genes are involved in the later stages of the development of the gland and cause nonsyndromic CPHD (1). Genetic forms of CPHD can be sporadic or familial, with familial forms accounting for 5% to 30% of cases (2). Of the known genetic mutations causing CPHD, pathogenic variants in *PROP1* are the most common both in sporadic (6.7%) and familial cases (48.5%) (1, 3).

We report a familial form of *PROP1* mutation in two brothers with CPHD to emphasize the importance of considering the diagnosis of *PROP*1

mutation in all cases where multiple members of the same family are affected by multiple pituitary hormone deficiencies.

Case Report

Both brothers were born at term by normal spontaneous vaginal delivery. They had no history of prolonged jaundice or hypoglycemia in the neonatal period. Their developmental milestones were normal and they had no dysmorphic features. They shared similar clinical features of proportionally short stature, as well as cherubic faces. They also had bilateral palpable testes and micropenis. Their parents were healthy and unrelated. The father's height was 176 cm, and the mother's height was 157 cm. Thus, the mid-parental height was 173 cm (-0.44 SDS).

An older brother was referred to a pediatric endocrinologist at the age of 2.5 years for clinical evaluation of short stature. His birth weight was 3.740 kg (+1.07 SDS), and his birth length was 49 cm (-0.3 SDS). Decreased linear growth was first observed at the age of 19 months. At 2.5 years, the infant's height was 80.0 cm (-3.17 SDS), and his weight was 11.0 kg (-1.93 SDS). Laboratory investigations excluded the presence of chronic systemic disorders. The hormonal profile showed low free thyroxine (FT4) and borderline low levels of insulin-like growth factor 1 (IGF-1). Prolactin level was initially elevated (Table 1).

His bone age was consistent with 15 months. Levothyroxine therapy was initiated because of central hypothyroidism. Pituitary magnetic resonance imaging (MRI) was evaluated as normal. After euthyroidism had been achieved, provocative (stimulation) GH testing was performed. A blunted peak GH response to the insulin-induced hypoglycemia test plus arginine was obtained, with a maximum peak of 3.60 mIU/L. GH deficiency was diagnosed on the basis of these results, and treatment was started with recombinant GH (rGH) at a dose of 0.03 mg/kg/day.

The anthropometric measurements of the younger brother were monitored by the primary pediatrician. He was referred to the pediatric endocrinologist at the age of 3.3 years. His birth weight was 3.85 kg (+1.29 SDS), and his birth length was 50 cm (+0.13 SDS). The hormonal analysis results are shown in Table 1. His bone age was consistent with 18 months and pituitary MRI was normal. The precise size of the pituitary gland was not reported in either of these patients. Due to central hypothyroidism, levothyroxine therapy was started. After euthyroidism had been achieved, provocative GH testing was performed. GH deficiency was diagnosed and treatment with rGH was initiated.

The older brother had a height gain of 8.6 cm (+0.67 SDS) in the first year and 5.5 cm (-1.64 SDS) in the second year of rGH therapy. Our patient is now 10.3 years old and his current height is 126.7 cm (-2.06 SDS). The younger brother had

Table 1. Hormonal Findings of the Affected Individuals

Age and hormonal findings at diagnosis	Older brother	Younger brother	Reference range
Age (years)	2.5	3.3	-
IGF1 (nmol/L)	1.8	3.0	1.7 – 13.1
IGFBP3 (nmol/L)	47	49.4	42 – 120
Peak GH levels (mIU/L)*	3.60	2.97	-
Cortisol (nmol/L)	528	558	171 – 536
ACTH (pmol/L)	6.8	1.81	1.6 – 13.9
TSH (mUI/L)	2.6	2.13	0.67 – 4.16
fT4 (pmol/L)	9.50	7.39	11.1 – 18.1
Prolactin (mIU/L)	721	611	50 – 650

*Insulin + Arginine.

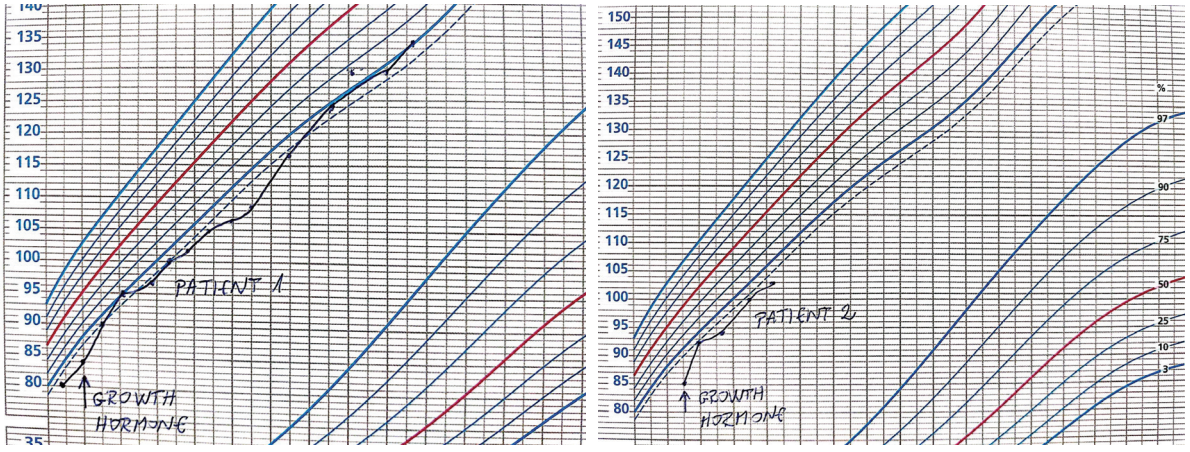

Fig. 1. *Growth of our patients after initiation of recombinant GH and levothyroxine therapy.*

a height velocity of 7.5 cm (+0.01 SD) in the first year and 6.3 cm (-0.39 SD) in the second year of rGH therapy. He is now 6.2 years old, and his current height is 107.7 cm (-2.72 SDS). The growth charts after the introduction of rGH and levothyroxine therapy in both brothers are shown on Fig. 1. During follow-up, IGF-1 levels are regularly measured in both patients and they are still continuously borderline low. Serum fT4 is monitored, and levothyroxine therapy is adjusted according to its level. We know for sure that in the older brother, levothyroxine was not administered for 6 months at the age of 7.

A familial form of impaired production of two pituitary hormones led us to the genetic cause of CPHD and genetic analysis of the *PROP1* gene. In both patients, sequencing of the entire exome was performed using the next-generation sequencing method (NGS). Genetic analysis identified a pathogenic homozygous frameshift variant c.301_302delAG in the *PROP1* gene. For now, no genetic analysis of the parents has been performed.

Discussion

Mutations in the *PROP1* gene are responsible for almost half of the cases of CPHD (4). *PROP1* (an acronym for 'prophet of Pit-1') is a transcription factor located in the long arm of chromosome 5 (5q35.3), and plays an important role in the differentiation of pluripotent anterior pituitary cells into distinct cell lines. The most prevalent mutations of the *PROP1* gene are the c.301_302delAG and c.150delA mutations (5). These mutations are most common in Eastern European, Russian, Brazilian, and Portuguese cohorts (6). The c.301_302delAG mutation is more frequent in familial than in sporadic cases, and parental consanguinity is a risk factor for the occurrence of this mutation (7). In familial cases, *PROP1* mutations have an autosomal recessive inheritance pattern (8). Phenotypic analysis of the Lithuanian cohort showed a higher proportion of ACTH deficiencies in affected individuals, which were already present in childhood and adolescence (9).

There is high variability in the time of onset, the clinical features, and the severity of hormone deficiencies among patients, even among siblings with the same homozygous mutation (10). This variability in clinical presentation is a result of variable expressivity, incomplete penetrance, and/or the involvement of other genetic or environmental factors. (1). The most striking phenotypic characteristic in patients with the *PROP1* mutation is growth impairment, usually due to combined GH and TSH deficiency. Compared to other genetic forms of CPHD, perinatal signs of hypopituitarism in patients with *PROP1* mutation are rare (4). Growth impairment becomes more prominent in early childhood. TSH deficiency can be present shortly after birth, but usually occurs together with or after the onset of GH deficiency. The spectrum

of gonadotropin deficiency is variable and ranges from early hypogonadism with micropenis and cryptorchidism in homozygous carriers of *PROP1* mutations to a complete lack of pubertal development or pubertal arrest requiring hormone replacement (4).

Prolactin levels in these patients are usually at lower levels than normal, although prolactin production differs between patients (4). The initially high level of prolactin in the older brother was unexpected and we cannot explain it. In repeated measurements during follow-up, prolactin levels were at the lower limit of normal values. ACTH deficiency usually occurs in the third decade of life. The underlying mechanism for cortisol deficiency has not yet been clarified since *PROP1* is not expressed in corticotroph cells. It is assumed that this deficiency results from a progressive lack of paracrine signals from dysfunctional cell lineages surrounding corticotroph cells, and due to the dysfunctional *PROP1* role in cell lineage maintenance and hormone expression (11). Since patients with *PROP1* mutation have the progressive disruption of the entire anterior pituitary axis, and have a high risk of developing adrenal failure with a life-threatening adrenal crisis, the pituitary function in these patients should be carefully followed-up.

Pituitary morphology also varies and is a subject of discussion. Most patients with *PROP1* mutation have normal-sized or small anterior pituitary glands. Pituitary enlargement has been reported in some patients, and is usually observed in early childhood and resolves spontaneously (5). The molecular diagnosis of patients with CPHD is important for clinical follow-up of patients, but also for genetic counseling.

Studies have shown that GH treatment enables near-normalized final height in patients with *PROP1* mutations (12, 13). Our patients do not have the expected growth velocity, probably due to poor adherence to GH therapy. This can be confirmed by the continuously borderline low levels of IGF 1 in both of our patients.

Conclusions

The diagnosis of CPHD should be suspected not only in patients who have a familial history of CPHD but also in all patients who have impaired production of two or more pituitary hormones. Identifying the exact genetic cause in these patients will provide further information about the clinical course of the disease. In patients with *PROP1* mutation, a careful long-term follow-up is crucial to reveal other possible hormonal defects and to avoid possible life-threatening adrenal crisis in the future.

Authors' Contributions: Conception and design: IBA, SS, IBČ; Drafting the article: IBA, MP; Revising it critically for important intellectual content: IBA, SS, MP, IBČ; Approved final version of the manuscript: IBA, SS, MP, IBČ.

Conflict of Interest: The authors declare that they have no conflict of interest.

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