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A Novel Clinical Presentation of PROP1-Associated Combined Pituitary Hormone Deficiency with Severe Thrombosis: A Case Report

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ABSTRACT

A 40-year-old woman with a clinical diagnosis of combined pituitary hormone deficiency (CPHD-2) (OMIM# #262600), and recurrent thrombosis underwent whole-exome sequencing, which identified a likely pathogenic variant in the PROP1 (Prophet of Pit1) gene and Variant of Unknown Significance (VUS) in the PROC gene. The PROP1 gene encodes as a “later acting transcription factor” in pituitary development and encodes a paired-like homeodomain transcription factor that is necessary for expression of the POUF domain transcription factor 1. The Protein C (PROC) gene encodes protein C, a vitamin K-dependent anticoagulant that regulates blood coagulation by inactivating coagulation factors Va and VIIIa.

Mutations in the PROP1 gene can cause CPHD-2, which may manifest as short stature, hypothyroidism, growth retardation, delayed and incomplete secondary sexual development with infertility. This is due to deficiencies in thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and growth hormone (GH). Pathogenic variants in PROC cause protein C deficiency, an inherited thrombophilia that predisposes affected individuals to venous thromboembolism.

We report a case where a lady presented with short stature, C-spine fusion, short and stiff neck, multiple

pituitary hormone deficiencies (LH, FSH, TSH, GH and Prolactin) and recurrent lower limb arterial thrombosis. She had primary amenorrhea, for which treatment was initiated at the age of 22 years. Genetic testing by exome sequencing enabled an accurate diagnosis of the underlying aetiology, with genotype – phenotype correlation which led to better disease management.

ABBREVIATIONS

PROP1- Prophet of Pit-1; CPHD-2 Combined Pituitary Hormone Deficiency-2; TSH- Thyroid Stimulating Hormone; LH- Luteinizing Hormone; FSH- Follicle Stimulating Hormone; GH- Growth Hormone; POU- Pit-1 (pituitary-specific factor) OMIM- online mendelian inheritance in man

INTRODUCTION

Combined pituitary hormone deficiency (CPHD) is a condition characterized by the deficiency of two or more pituitary hormones in the anterior pituitary gland. It is commonly caused by mutations in the Prophet of Pit1 (PROP1) gene, and this is termed Combined pituitary hormone deficiency 2 (CPHD-2). The mutation results in impaired differentiation of the pluripotent anterior pituitary cells into distinct cell lines, leading to insufficient pituitary gland development and multiple hormone deficiencies [thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and growth hormone (GH)]. Clinical manifestations typically become apparent during childhood.[1]

There is considerable variability observed in the age of onset, severity of hormone deficiencies, and associated structural abnormalities; even among affected individuals within the same family. While CPHD-2 presents later in infancy or childhood, the clinical course is often insidious, with progressive development of hormone deficiencies.[2,3,4] On magnetic resonance imaging (MRI), the anterior pituitary gland may appear normal or enlarged in the early phase of disease, followed by progressive involution as the condition advances.[5,6]

The PROP1 gene, located on the long arm of chromosome 5 (5q35.3), comprises three exons and encodes a 226-amino-acid paired-like homeodomain transcription factor that is essential for normal pituitary gland development.[7] It regulates cell differentiation by activating POUF1 and repressing HESX1, critical for lineage specification in the pituitary. PROP1 also helps in establishing pituitary stem cells pool and promoting their migration via epithelial to mesenchymal transition.[8]

PROP1 mutations are more prevalent in familial than in sporadic cases of CPHD-2. Owing to their autosomal recessive inheritance pattern, these mutations are also more common among individuals born to consanguineous parents, similar to other recessively inherited genetic disorders.[6,9] The PROP1 gene is transferred by autosomal recessive inheritance, each sibling of the patient has a 25% chance of being affected, 25% chance of being unaffected and 50% chance of being a carrier. Several studies have reported families with CPHD-2 caused by homozygous or compound heterozygous inactivating PROP1 mutations, further expanding the spectrum and clinical characterization of the disease.[1]

The clinical phenotype typically includes deficiencies of GH, TSH, FSH, LH, and prolactin, while adrenocorticotropic hormone (ACTH) deficiency occurs less frequently.[6,10] Growth hormone (GH) deficiency leads to impaired linear growth and short stature which is typically the first reported symptom. TSH deficiency may present early but is usually seen together with or after the onset of GH deficiency. FSH and LH are essential for normal gonadal development and fertility [11]. Their deficiency presents as absence of pubertal development. Some patients undergo spontaneous puberty with subsequent decline in gonadotropin function. ACTH deficiency may occur later in life; hence long-term surveillance is crucial. [Illustrations described in Figure 1]

Here, we present the case of a patient with Combined pituitary hormone deficiency-2 (CPHD-2) caused by a pathogenic variant in the PROP1 gene, highlighting the clinical presentation, diagnostic evaluation, genetic findings and management.

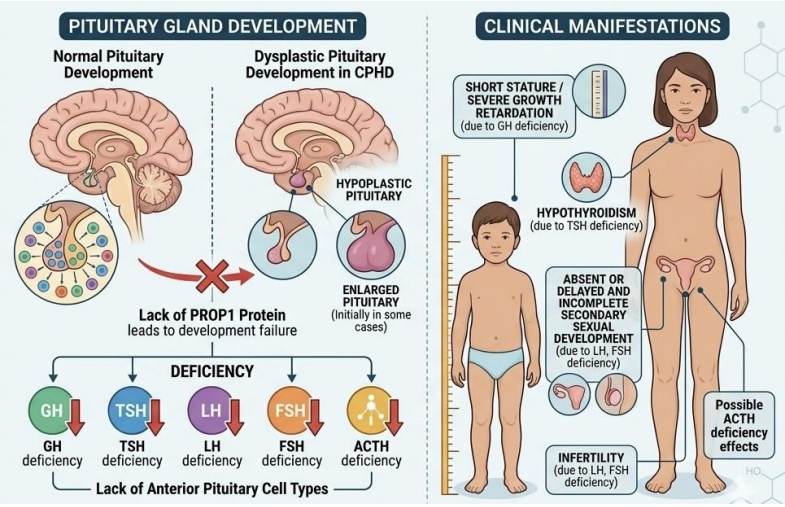

Figure 1: Schematic illustration of effects and clinical manifestations of PROP1 gene (original illustration created by authors)

CASE REPORT

Patient history: A 40-year-old woman presented with recurrent lower limb arterial thrombosis. She had a history of primary amenorrhea with delayed development of secondary sexual characteristics and had been on the combined oral contraceptive pill (OCP) since the age of 22 years. She had a successful pregnancy with in-vitro fertilisation. Later, she developed recurrent lower limb arterial thrombosis which was thought to be secondary to the OCPs (5). This was managed with unfractionated heparin, thrombectomy and aspirin therapy. OC pills were discontinued. Despite treatment, she had persistent right lower limb pain. After a decade, progression to worsening claudication was seen, requiring left to right femoral arterial bypass graft. She was managed with Rivaroxaban, clopidogrel and aspirin. Claudication persisted despite the patient being maintained on rivaroxaban (20mg daily) and aspirin.

Clinical investigation revealed a feeble right dorsalis pedis, short stature, short and stiff neck, wide chest, small hands and feet. X-Ray showed C2-C3 cervical spine fusion. MRI brain showed a flattened anterior pituitary with a normal central pituitary stalk, while the posterior pituitary bright spot was preserved. Laboratory investigations showed multiple pituitary hormone deficiencies with low LH (0.325 mIU/mL), FSH (0.664 mIU/mL) and prolactin (4.1 ng/mL). TSH (2.19 µIU/mL) was inappropriately normal for a low total T4 (3.95 µg/dL) and total T3 (78.3 ng/dL). Insulin-like growth factor-1 (IGF-1 30.4 ng/mL) was also low while ACTH and cortisol were found to be within the normal range. Ultrasound report displayed grade 1 fatty liver, normal uterus and ovaries.

Family history: Her brother also had short stature, delayed puberty and a history of orchidopexy at the age of four. This suggested a possible underlying genetic or endocrine disorder in the family, and she was advised to undergo exome sequencing.

The whole exome test of the patient revealed that she harboured two copies of a 'likely pathogenic' variant of in the PROP1 gene which is associated with CPHD-2 and a heterozygous VUS in the PROC gene with a possible association with an underlying thrombophilia due to deficiency in protein C. The variant (chr5:177422932C>G c.3G>C p.Met1?) was found to be homozygous with autosomal recessive inheritance. This variant (p.Met 1?) lies in exon 1 of PROP1 gene and alters the highly conserved residue of the protein and the translation initiation codon which might result in either loss of protein synthesis or the production of truncated polypeptide lacking end terminal region of the protein (UNIPROT). The next translation initiation site within the open reading frame of protein is predicted to be at position c.518A>T p.Lys173Met.

DISCUSSION

Combined pituitary hormone deficiency (CPHD) is a heterogeneous disorder characterized by impaired secretion of two or more anterior pituitary hormones. Both genetic and non-genetic factors contribute to its aetiology. Non-genetic causes include trauma, intracranial tumours, neurosurgical procedures, infections, autoimmune disorders, irradiation, and exposure to toxic agents such as heavy metals.[5] To date, approximately 30 genes have been implicated in the pathogenesis of CPHD, including GLI2, HESX1, LHX3, LHX4, OTX2, POU1F1, PROP1, and SOX2.[12-17] Among these, PROP1 represents the most frequently mutated gene and is recognized as the leading genetic cause of autosomal recessive CPHD-2.[18-19]

PROP1 is a pituitary-specific paired-like homeodomain transcription factor that plays a crucial role in pituitary organogenesis and cellular differentiation.[20] It functions upstream of several key developmental regulators, including HESX1 and POU1F1.[1,21,22,23] During pituitary development, PROP1 suppresses HESX1 expression, thereby permitting cellular differentiation, while simultaneously activating POU1F1, which is essential for the maturation of somatotrophs, lactotrophs, and thyrotrophs [24,25]. Disruption of PROP1 function results in impaired pituitary lineage specification and subsequent hormone deficiencies.[20] (Figure 2)

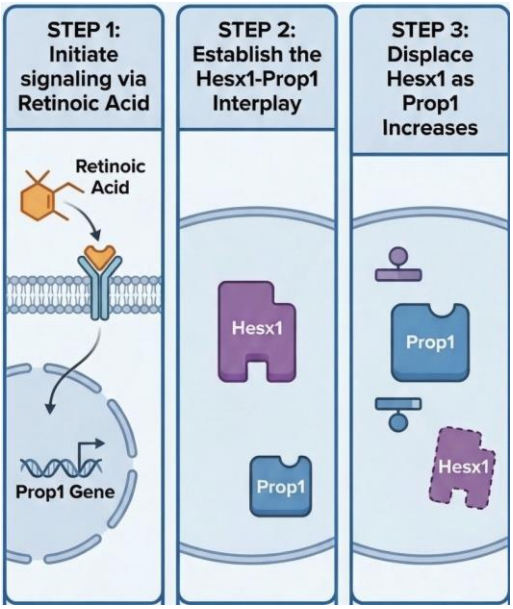

Figure 2: Schematic illustration of regulation of PROP1 gene (original illustration created by authors)

Pathogenic variants in PROP1 include whole-gene deletions, frameshift insertions or deletions, missense, nonsense, splice-site, and translation initiation codon variants.[19] The most frequently reported pathogenic variants are c.301_302delAG (p.Leu102CysfsTer8) and c.150delA (p.Arg53AspfsTer112), although their prevalence varies considerably among different ethnic populations. Studies from Eastern Europe have reported PROP1 mutations in up to 30–35% of familial CPHD-2 cases, whereas substantially lower frequencies have been observed in Asian and Western European populations.[19,26] Clinical manifestations are variable but commonly include growth hormone deficiency accompanied by deficiencies of other anterior pituitary hormones (FSH, LH, GH, prolactin, TSH and ACTH later in life). CPHD-2 results in variable clinical manifestations depending on the specific hormonal axes affected.[27] Hence, the genotype-phenotype correlation helps us understand the pathogenesis of the disease and accordingly plan appropriate treatment for the patient.

In the present case, a homozygous likely pathogenic PROP1 variant, c.3G>C (p.Met1?), was identified. This variant affects the translation initiation codon and is predicted to abolish or markedly reduce PROP1 protein synthesis, resulting in loss of transcriptional activity. The molecular findings correlate well with the patient's phenotype, which includes growth hormone deficiency manifested by short stature and reduced IGF-1 levels, hypogonadotropic hypogonadism presenting as primary amenorrhea with low LH and FSH concentrations, central hypothyroidism characterized by low thyroid hormone levels with inappropriately normal TSH, and hypoprolactinemia. Notably, the ACTH–cortisol axis remains preserved in this patient. This observation is consistent with the natural history of PROP1-related CPHD-2, in which ACTH deficiency presents late in life, emphasizing the importance of long-term endocrine surveillance.

An additional noteworthy finding in this patient is the history of recurrent arterial thrombosis and the identification of a heterozygous variant in the Protein C (PROC) gene. Although no biological interaction between PROP1 and PROC has been established, the PROC variant likely represents an independent genetic predisposition to thrombophilia in the present case. This coexistence highlights the importance of comprehensive genetic evaluation in patients presenting with complex or atypical clinical phenotypes. The PROC gene encodes protein C, a vitamin K-dependent anticoagulant that regulates blood coagulation by inactivating coagulation factors Va and VIIIa [28]. Pathogenic variants in PROC cause protein C deficiency, an inherited thrombophilia that predisposes affected individuals to venous thromboembolism. This PROC variant c518A>T (p.Lys173Met) was classified as Variant of unknown significance (VUS) by ACMG. The symptoms correlated with the clinical phenotype; hence this variant is proposed to be upgraded in the future based on the population statistics (<0.144% in the control population; Nomad) and clinical presentations of complicated thrombosis in the present patient.

The homozygous state of the variant, together with the presence of an affected sibling, strongly supports an autosomal recessive mode of inheritance. Hence, segregation analysis was recommended for the parents and brother on follow up.

Management of CPHD-2 primarily involves lifelong hormone replacement therapy tailored to the specific hormonal deficiencies. Treatment may include growth hormone replacement, levothyroxine, glucocorticoid replacement where indicated, and sex steroid therapy. Importantly, thyroid hormone replacement should only be initiated after adequate assessment of adrenal function to avoid precipitating adrenal insufficiency [29]. Fertility can be achieved through gonadotropin therapy or assisted reproductive technologies. In the present case, the patient received levothyroxine for central hypothyroidism, rivaroxaban and aspirin for recurrent arterial thrombosis, and subsequently underwent in vitro fertilization (IVF).

CONCLUSION

We report a patient with combined pituitary hormone deficiency harbouring a homozygous likely pathogenic PROP1 start-loss variant, c.3G>C (p.Met1?). The identified variant provides a clear molecular explanation for the patient's endocrine phenotype and further expands the mutational spectrum associated with PROP1-related CPHD-2. The coexistence of a heterozygous PROC variant and recurrent arterial thrombosis underscores the importance of considering multiple genetic diagnoses in patients with complex clinical presentations. Long-term endocrine follow-up, genetic counselling, familial segregation studies, and evaluation of at-risk relatives are recommended. A multidisciplinary approach involving endocrinologists, molecular pathologists, genetic counsellors, reproductive specialists, and other healthcare professionals is essential for optimizing patient care and improving long-term outcomes.

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