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Clinical case

Familial combined pituitary hormone deficiency by a mutation in PROP1: 4 of 7 brothers affected

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ABSTRACT

Introduction: PROP1 (Prophet of POUF1) mutations are the most frequent genetic cause of combined pituitary hormone deficiency, a condition associated with a deficiency or inadequate production of hormones of the anterior pituitary. The PROP1 gene encodes a transcription factor involved in the ontogeny, differentiation and function of somatotrophs, lactotrophs and thyrotrophs. These mutations are characterized by a remarkable clinical variability, including time of onset of hormonal deficiencies, hypophyseal dimensions and secretion of cortisol.
Case report: We describe a family of consanguineous parents (second-degree cousins), composed of 7 siblings, 4 with combined pituitary hormone deficiency. Two brothers, 41 and 45 years of age, had an initial diagnosis of dwarfism at ages 9 and 12 respectively. Subsequently, TSH, FSH/LH and prolactin deficiency was detected in both. The latter was also diagnosed with cortisol deficiency. The two sisters, aged 46 and 50-years-old, were diagnosed with combined pituitary hormone deficiency, namely of GH, TSH, FSH/LH, prolactin and ACTH, since the ages of 15 and 9, respectively. There was no previous family history of combined pituitary hormone deficiency. The genetic study was performed in the 4 brothers, detecting a homozygous mutation in the PROP1 gene (c.301–302delAG).
Conclusion: This case reflects the variability of clinical expression and the progressive functional impairment, including pituitary secretion of ACTH, in patients with PROP1 gene mutations.

Panhipopituitarismo familiar por mutação do gene PROP1: 4 de 7 irmãos afectados

Palavras-chave:
PROP1
Mutação
Insuficiência hormonal combinada

RESUMO

Introdução: As mutações no gene PROP1 (Prophet of POUF1) são a causa genética mais frequente de insuficiência hormonal combinada, uma condição associada à deficiência ou produção inadequada de hormonas da hipófise anterior. O gene PROP1 codifica um factor de transcrição envolvido na ontogênese, diferenciação e função dos somatotrófos, lactotrófos, e tireotrófos. Estas mutações caracterizam-se por uma notável variabilidade clínica, incluindo o início do aparecimento das deficiências hormonais, dimensões hipofisárias e secreção de cortisol.
Caso clínico: Família de pais consanguíneos (primos em segundo grau), composta por 7 irmãos, 4 com o diagnóstico de insuficiência hormonal combinada, seguidos em consulta de Endocrinologia. Dois irmãos do sexo masculino, 41 e 45 anos, com diagnóstico inicial de nanismo aos 9 e 12 anos de idade, respetivamente, tendo sido detetada posteriormente deficiência de TSH, FSH/LH e prolactina, em ambos e também de cortisol no último. As 2 irmãs, de 46 e 50 anos de idade, com insuficiência hormonal combinada por deficiência de GH, TSH, FSH/LH, prolactina e ACTH, confirmada aos 15 e aos 9 anos de idade, respetivamente. Sem história familiar prévia de insuficiência hormonal combinada. Foi efectuado o estudo genético, tendo sido possível detectar nos 4 irmãos uma mutação homozigótica no gene PROP1 (c.301–302delAG).

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Conclusão: Esta família demonstra a variabilidade da expressão clínica dos portadores de mutações do gene PROP1 e a progressiva alteração funcional hipofisária, nomeadamente da secreção de ACTH.

Introduction

The anterior pituitary development during the embryonic period is dependent on sequential and critical processes, from induction of Rathke's pouch to pituitary organogenesis and cell line proliferation, specification and differentiation. Deregulation of these steps can cause pituitary hypoplasia or dysfunction. Molecular analysis has allowed the identification of multiple genes involved in the coordination of this differentiation.[1] POUF1 gene encodes a transcriptional factor expressed during the differentiation of the anterior pituitary gland, which is responsible for the adequate production of growth hormone (GH), prolactin (PRL) and thyroid-stimulating hormone (TSH). A second transcription factor involved in pituitary development is the gene Prophet of POUF1 (PROP1).[2]

Mutations in PROP1 gene are the most frequent genetic cause of combined pituitary hormone deficiency, a condition associated with a deficiency or inadequate production of hormones of the anterior pituitary.[3] Prop1 gene (Prophet of POUF1, OMIM 601538) is located on chromosome 5q35.31 and encodes a 226-amino acid transcription factor.[4] PROP1 mutations have been firstly described in Ames dwarf mice.[5] Ames dwarf mutants carry a homozygous mutation that involves a serine-to-proline substitution of amino acid 83 (S83P), associated with multiple hormone deficiencies, namely GH, PRL, TSH and LH and FSH and with adult pituitary hypoplasia. Since then, several Prop1 mutations that structurally affect the 'paired-like' DNA-binding domain of the Prop-1 protein molecule have been described.[1]

Combined pituitary hormone deficiency by PROP1 mutations is an autosomal recessive disorder, and most of the patients do not present any family history of the disease. Thus, each sibling has 25% risk of being affected.[6] Since PROP1 gene encodes a transcription factor involved in the ontogeny, differentiation and function of somatotrophs, lactotrophs, gonadotrophs and thyrotrophs, patients with PROP1 mutations show combined pituitary hormone deficiency.[7] They are characterized by a remarkable clinical variability, including time of onset of hormonal deficiencies, hypophyseal dimensions and secretion of cortisol. In a multicentric study launched in Portugal to screen for mutations of the *PROP1* gene in patients with combined pituitary hormone deficiency, the most frequent mutation found was c.301–302delAG, also known as 296delGA. This 2-bp deletion in a dinucleotide repeat mutational hotspot is also the most prevalent mutation described in other studies.[6]

Case report

We describe a family of consanguineous parents (second-degree cousins), composed of 7 siblings, of which 4 present combined pituitary hormone deficiency and have been followed by the department of Endocrinology (family heredogram in Fig. 1). There was no previous family history of combined pituitary deficiency.

Patients' phenotype and diagnosis

Patient #1, the older sister, aged 50-years-old, had unremarkable neonatal period and psychomotor development. Failure to thrive was noticed when she was 9-years-old. Afterwards, documentation of GH, TSH, FSH/LH, prolactin and cortisol deficiency confirmed the diagnosis of combined pituitary hormone deficiency. She had initiated growth hormone therapeutic and, at adult age, she presented a final stature of 1.47 m and a body mass index of 32.9 kg/m^2. She is currently being supplemented with levotiroxine 250 mcg qd, hydrocortisone 25 mg qd and desogestrel/ethynil estradiol (0.15/0.02 mg).

Patient #2, female, aged 46, was also born by normal delivery, at term, and presented an unremarkable neonatal and psychomotor development. Growth retardation and lack of pubertal development were noticed when she was 15-years old. Documentation of GH, TSH, FSH/LH, prolactin and ACTH deficiency confirmed the diagnosis of combined pituitary hormone deficiency. She was treated with adequate complete hormone replacement therapy, acquiring an adult stature of 1.5 m (BMI of 35.97 m^2). She is currently under levotiroxine 250 mcg qd, hydrocortisone 20 mg qd and estradiol valerate/Norgestrel (2/0.5 mg).

Patient #3, male, 45-years-old, also did not show any complication during neonatal period or concerning psychomotor development. An initial diagnosis of dwarfism was performed at age 12. Subsequently, it was detected TSH, FSH/LH and prolactin deficiency, as well as cortisol deficiency. With adequate hormonal supplementation, including growth hormone therapeutic, at adult age he reached 1.68 m of stature (BMI of 30.67 kg/m^2). He is medicated with levothyroxine 200 mcg qd, hydrocortisone 25 mg qd and testosterone decanoate 4/4 weeks.

Patient #4, male, the youngest sibling, 41-years-old, was born by normal delivery, at term, with a normal birth length. His neuropsychomotor development was normal. Growth retardation was the first signal at 9-years old. Clinical data and standard stimulation tests allowed the detection of TSH, FSH/LH and prolactin deficiency,

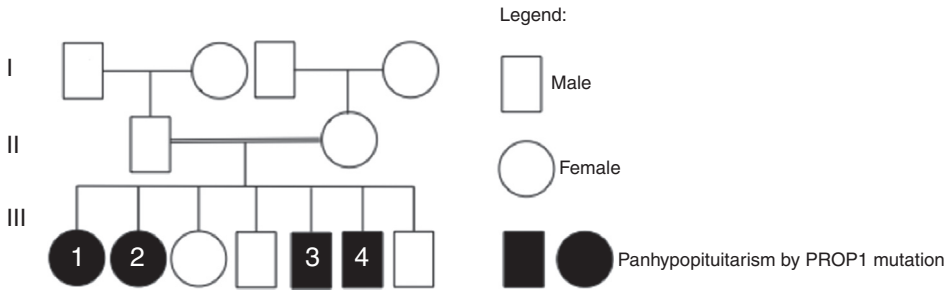

Fig. 1. Family heredogram. Number 1, 2, 3 and 4 inside de boxes represent the patients #1, #2, #3 and #4, described along the text.