Case Report

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A nonsense variant in *FGFR1*: a rare cause of combined pituitary hormone deficiency

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Abstract

Objectives: Variants in fibroblast growth factor receptor-1 (*FGFR1*) may either cause isolated hypogonadotropic hypogonadism (IHH) or Kallmann syndrome (KS). Although the relationship of genes classically involved in IHH with combined pituitary hormone deficiency (CPHD) is well established, variants in *FGFR1* have been presented as a rare cause of this phenotype recently.

Case presentation: Herein, we report an adopted 16-year-old male presented with delayed puberty and micropenis. He had undergone surgery for bilateral undescended testes in childhood. He was normosmic, and the pituitary imaging was normal. However, hypogonadotropic hypogonadism and growth hormone deficiency were detected, associated with a heterozygous nonsense variant (c.1864 C>T, p.R622X) in *FGFR1*.

Conclusions: *FGFR1* variants are among the causes of IHH and KS, which are inherited in an autosomal dominant manner and can be associated with midline defects. It should also be kept in mind that CPHD may be associated with *FGFR1* variants in a subject with normal olfactory function.

Keywords: *FGFR1*; hypopituitarism; pubertal delay; short stature.

Introduction

Fibroblast growth factor receptor-1 (*FGFR1*) is a tyrosine kinase receptor for the fibroblast growth factor (FGF). *FGFR1* is expressed mainly in Rathke's pouch and ventral diencephalon during the embryonic period. It is the primary receptor for FGF8, which is involved in formation and migration of neurons responsible for the production of gonadotropin-releasing hormones (GnRHs), as well as the olfactory system [1, 2]. Variants in *FGFR1* may either cause isolated hypogonadotropic hypogonadism (IHH) or Kallmann syndrome (KS), with a frequency of 7 and 10 % among all cases, respectively [3].

IHH, KS, combined pituitary hormone deficiency (CPHD), and septo-optic dysplasia (SOD) are clinical phenotypes which result from disruption of embryonic development of anterior midline in the forebrain. While majority of causative genes involved in abovementioned diseases are distinct, there is an overlap to some degree [4]. Recently, *FGFR1* variants were reported in 2.7 % of the cases with CPHD, supporting its essential role in the formation of pituitary cells [5].

Herein, we described an adolescent male case with a loss-of-function mutation in *FGFR1*, causing hypogonadotropic hypogonadism and growth hormone deficiency.

Case presentation

A 16-year-old male was referred to our clinic due to delayed puberty and micropenis. He had a history of surgery for bilateral undescended testes in childhood. Also, he had no

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complaints regarding disturbances of sense of smell. He was adopted in the neonatal period; therefore, his birth and family history were not available. His weight, height and body mass index were 41.2 kg (–2.62 standard deviation score [SDS]), 151.4 cm (–2.72 SDS) and 17.97 kg/m^2 (–1.12 SDS), respectively. He had a flat nasal root and Tanner stage 3 pubic hair. However, his testicular volumes were 2 mL on the left and 0.5 mL on the right. Stretched penile length was 2 cm.

His laboratory results were as follows: free T4 1.14 ng/dL (0.5–1.51 ng/dL), thyroid stimulating hormone 1.57 mIU/mL (0.38–5.33 mIU/mL), follicle-stimulating hormone (FSH) 0.71 mIU/mL (1.3–19.3 mIU/mL), luteinizing hormone (LH) 0.08 mIU/mL (N>0.3 mIU/mL), total testosterone 0.49 ng/mL (2.59–8.16 ng/mL). Bone age was consistent with 13 years of age. Peak LH level during LH-releasing hormone (LHRH) test was insufficient (4.75 IU/L, N>5 IU/L). Brain magnetic resonance imaging revealed a normal anterior pituitary and pituitary stalk. The posterior pituitary bright spot was normally located as well.

Monthly injections with a 100 mg of a mixed testosterone ester preparation (Sustanon®) were given for a period of six months, but it failed to induce pubertal development. Subsequently, testosterone replacement was initiated for hypogonadotropic hypogonadism. During one-year of follow-up, he grew only 2 cm, even though he was under testosterone treatment. Insulin-like growth factor (IGF)-1 and IGF binding protein-3 levels were 192 ng/mL (–1.94 SDS) and 4.81 mcg/mL (–1 SDS), respectively. Insulin tolerance test showed a low growth hormone (peak: 1.36 ng/mL, N>7 ng/mL), and a normal cortisol (peak: 22.3 mcg/dL, N>20) response to hypoglycemia. His prolactin level was also normal (9.7 ng/mL, N: 5–20 ng/mL). Thus, we started growth hormone treatment because of the documented growth hormone deficiency. On the 6th month of growth hormone treatment, his height was 161.9 cm (–1.92 SDS) and growth velocity was 6 cm/year. The smell test showed that his olfactory functions were normal and also his audiometry test showed no hearing loss. Abdominal ultrasonography was normal.

Following the diagnosis of CPHD, whole-exome sequencing was performed. A previously reported, heterozygous nonsense variant (c.1864 C>T, p.R622X) was found in *FGFR1* gene. No other pathogenic variant was present in remaining candidate genes. A written informed consent was obtained from the parents for publication of the case.

Discussion

Hypogonadotropic hypogonadism can be presented as IHH or CPHD with delayed puberty. It is a heterogeneous situation with various clinical and genetic features, mostly seen in boys rather than girls. It can be diagnosed with low gonadotropin levels during the time of puberty, causing low estradiol or testosterone levels. And also gonadotropin response to LHRH stimulation test is expected to be insufficient in these patients [6]. Our case had delayed puberty with prepubertal FSH, LH, and testosterone levels, and also his bone age was delayed. Thus, he was primarily diagnosed as IHH.

IHH can be seen as a component of KS in approximately 50 of patients, which is characterized with anosmia/hyposmia, absent puberty, lack of sexual maturity, infertility, renal agenesis, and midline deformities such as a cleft palate or dental agenesis [6]. Until today, several genes have been described in association with IHH or KS, which are responsible for the development of olfactory bulb or GnRH neurons. Most common variants were reported in *KAL1, FGFR1, FGF8, PROKR2, PROK2, GNRHR, GNRH1, CHD7, KISS1R, KISS1, WDR11, TAC3, TACR3,* and *HS6ST1* genes [3, 6]. Furthermore, SOD is described as CPHD, hypoplasia of the optic nerve and midline deformities like corpus callosum agenesis. This syndrome was shown to be associated with variants in *HESX1, SOX2, SOX3,* and *OTX2* [7]. A genetic and clinical overlap was defined between IHH, KS, SOD, and CPHD. Variants in genes generally associated with IHH/KS were also reported to be associated with CPHD/SOD, due to their same embryological origin [4]. These conditions are all caused by the similar developmental defects of anterior midline in the forebrain and associated with facial or cranial midline deformities [4] On the follow-up of our case, growth hormone deficiency was detected in addition to hypogonadotropic hypogonadism.

In our patient, whole-exome sequencing revealed a heterozygous nonsense variant (c.1864 C>T, p.R622X) in *FGFR1*. In vitro studies indicate that FGF-FGFR signaling is important for formation and proliferation of cells located in the anterior pituitary gland [8]. This role is supported by human data as well. Nearly 10 of 129 patients suffering from KS with concomitant abnormalities such as cleft palate, dental agenesis, synkinesia, corpus callosum agenesis, deafness, and syndactyly were found to have pathogenic variants in *FGFR1* [9]. Vermeulen et al. [10] reported the first CPHD case with an *FGFR1* variant in 2002. The male patient had sexual immaturity and anosmia; laboratory studies revealed low levels of gonadotropins and growth hormone [10]. In a cohort of patients with CPHD, *FGFR1* variants were found in 2.7% [5]. Growth hormone deficiency and hypogonadotropic hypogonadism were the most frequent endocrine features in patients with pathogenic *FGFR1* variants, causing micropenis and cryptorchidism like in our case [11]. In addition, trigonocephaly, coloboma, dental agenesis, and syndactyly were also reported as associated features [11]. Xu et al. [12] reported a family with normosmic IHH, who carried the same variant as our case. However, their patients had no other pituitary

hormone deficiencies [12]. In our case, we did not observe anosmia or any other anomalies related to KS. As described in the previous data and our case, the c.1864 C>T (p.R622X) variant in *FGFR1* seems to cause IHH or CPHD with a normal olfactory structure and function.

Conclusion

To date, several variants in *FGFR1* were associated with CPHD, inherited in an autosomal dominant manner. This reinforces the already reported genetic overlap between IHH, SOD, and CPHD. Therefore, it should be kept in mind that CPHD may be associated with *FGFR1* variants.

What is new?

We described a rare cause of combined pituitary hormone deficiency with normal olfactory function, associated with a heterozygous *FGFR1* variant.

Learning points

(1) A heterozygote variant of fibroblast growth factor receptor-1 (*FGFR1)* was identified in a case with combined pituitary hormone deficiency (CPHD).
(2) A review of the literature showed that *FGFR1* variants might cause CPHD, rarely.
(3) *FGFR1* variants should also be kept in mind in male patients with normosmic hypogonadotropic hypogonadism.

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