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Clinical case Seminar

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Combined pituitary hormone deficiency caused by a missense *de novo* variant in *FGFR1*

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Abstract

Heterozygous loss-of-function variants of fibroblast growth factor receptor 1 (*FGFR1*) are associated with Kallmann syndrome (KS) with anosmia/hyposmia, Congenital Hypogonadotropic Hypogonadism (CHH) with normosmia and Septo-Optic Dysplasia (SOD) and only occasionally with Combined Pituitary Hormone Deficiency (CPHD).

We report the case of a 14-year-old boy who came to our attention for short stature and pubertal delay.

The patient had a medical history of cleft lip and cryptorchidism, surgically corrected during childhood.

Endocrinological investigation, including endocrine dynamic function test, documented a growth hormone deficiency and hypogonadotropic hypogonadism (HH), while the other pituitary tropin hormones were within normal range. Brain magnetic resonance imaging revealed a complex malformation of the midline and maxillofacial bones, with hypoplastic olfactory sulci, caudal dislocation of the fronto-basal cortical gyri, impaired cranio-caudal development of the nasal pits, nasal septal deviation, defect of the alveolar process of the maxillary bone, maxillary and frontal sinuses hypoplasia and one palatalized supernumerary tooth. Nevertheless, pituitary gland was normal and the pituitary stalk was in axis. Despite, these radiological findings no anosmia was reported. Trio exome sequencing analysis identified a *de novo* heterozygous missense variant c.2002G>A in *FGFR1* gene, that determines the aminoacidic change p. Glu668Lys, confirming the diagnosis of CPHD.

Recombinant growth hormone and testosterone therapies were started, resulting in significant height recovery and in the development of secondary sexual characteristics.

In conclusion, the comprehensive study of pituitary function, brain MRI and genetic analysis are crucial in the diagnostic work-up of HH in order to clarify its etiology and any associated comorbidities.

Key-Words: combined pituitary hormone deficiency, FGFR1, malformation of maxillofacial bones

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Introduction

Hypopituitarism is defined as a reduction or absence of pituitary hormone secretion. Combined pituitary hormone deficiency is diagnosed in the case of a deficiency of two or more pituitary hormones. The phenotype is variable, although short stature, developmental delay and delayed puberty are the most common symptoms.

Hypopituitarism can be distinguished as congenital or acquired. Currently, approximately 16% of cases of congenital hypopituitarism (CH) are associated with genetic abnormalities. Mutations in genes involved in early pituitary development result in complex syndromes that include extra-pituitary defects and midline anomalies. On the contrary, mutations involved in later stages result in variable phenotypes without extra-hypophyseal defects (1).

In recent years, it was noted that heterozygous loss-of-function variants of *FGFR1*, previously

associated with Kallmann syndrome (KS) with anosmia/hyposmia, Congenital Hypogonadotropic Hypogonadism (CHH) with normosmia and Septo-Optic Dysplasia (SOD), occasionally can be responsible of a combined pituitary hormone deficiency (CPHD) (2).

This report presents the case of a male adolescent diagnosed with a combined pituitary hormone deficiency caused by a loss-of-function mutation in FGFR1.

Case Report

A 14-year-old Caucasian boy was referred to our pediatric endocrinology Outpatient Clinic for short stature and pubertal delay. The familial history was positive for constitutional growth retardation and puberty. His medical history was characterized by cleft lip and bilateral cryptorchidism, surgically corrected during childhood. On physical examination, no significant dysmorphic features were detected.

Height(139.7cm; -2.08 SDS) was below the lower normal limits for sex and age and slightly below the target height (-1.46 SDS); weight (35.50 Kg; -1.36 SDS) was adequate for sex and age as well as body mass index (18.19Kg/m2;-0.66SDS).

Pubertal evaluation, assessed by Tanner stages, documented a prepubertal testicular volume and the absence of pubarche (G1Ph1).

growth failure (growth velocity 1.24 cm/year; -6.82 SDS) and lack of spontaneous onset of puberty, despite the evidently pubertal bone age (14 years), were documented.

Based on the patient's medical history, clinical examination and physical measurements, due to suspected combined pituitary hormone deficiency (CPHD) with midline abnormalities, laboratory and instrumental investigation were carried out.

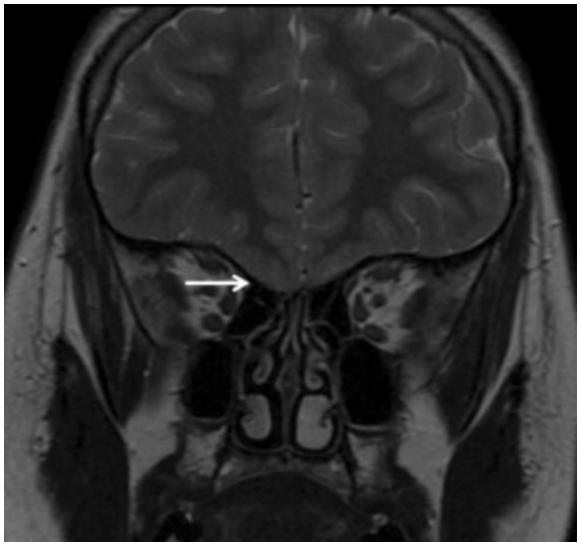
First level biochemical evaluations ruled out renal, liver and coeliac disease. The endocrinological investigation included both basal hormone secretion and dynamic function tests. Thyroid function and thyroid autoimmunity, morning ACTH and cortisol levels were within normal range. Prepubertal basal levels of gonadotropins and low levels of testosterone (12 ng/dl; normal pubertal values > 20 ng/dl) were demonstrated.

The luteinizing-hormone releasing hormone (LHRH) stimulation test, conducted by intravenous administration of gonadorelin acetate, documented a condition of hypogonadotropic hypogonadism, as evidenced by an LH peak of 2.70 mUI/ml one hour after the stimulus (normal pubertal values > 5 mUI/ml).

In addition, the patient was tested for growth hormone (GH) secretion using a standard stimulation test with clonidine and then with glucagon. The results indicated a GH deficiency with a GH peak of 2.050 ng/ml and of 0.069 ng/ml respectively (normal peak values > 8 ng/ml). Insulin-like growth factor-1 (IGF-1) was 203 ng/ml (-1.763 SDS). The patient underwent brain magnetic resonance imaging which

revealed a complex malformation of the midline and maxillofacial bones. Moreover, hypoplastic olfactory sulci (type II of Keros classification of the depth of olfactory fossa), caudal dislocation of the fronto-basal cortical gyri, impaired cranio-caudal development of the nasal pits, nasal septal deviation, defect of the alveolar process of the maxillary bone, maxillary and frontal sinuses hypoplasia and one palatalized supernumerary tooth were detected (Figure 1). Nevertheless, pituitary gland was normal (182 mm3), and the pituitary stalk was in axis. Despite, these radiological findings no anosmia and hyposmia was reported. Genetic analysis were perfomed. The patient underwent genetic analysis including array-CGH (negative for microduplications or microdeletions), and trio exome sequencing that identified a de novo heterozygous missense variant c.2002G>A in FGFR1 gene, that determines the aminoacidic change p.Glu668Lys. This missense variant is classified as pathogenic (class 5 according to the American College of Medical Genetics and Genomics Criteria), confirming the diagnosis of CPHD. In view of the diagnoses of GH deficiency and hypogonadotropic hypogonadism, since the age of 15, daily replacement therapy with recombinant GH and intramuscular testosterone therapy for the induction of puberty were started. These therapies resulted in significant height recovery (from -2.6 SDS to -1.15 SDS in two and a half years) and in the appearance and progression of secondary sexual characteristics

Figure 1 - Patient's Brain Magnetic Resonance Imaging
Hypoplastic olfactory sulci (type II of Keros classification of the depth of olfactory fossa) (white arrow)



Discussion

Fibroblast growth factor receptor 1 is a member of the tyrosine kinase receptor family and, along with its major ligand, fibroblast growth factor 8 (FGF8), constitutes one of the most widespread signaling pathways in biology. During the embryonic period, FGFR1 is primarily expressed in Rathke's pouch and ventral diencephalon. FGFR1 and FGF8 are essential for the development of the olfactory bulb and the migration of gonadotropin-releasing hormone neurons to the hypothalamus (3, 4) and they play a

crucial role in the formation of midline brain structures, including the pituitary, optic region, and septum pellucidum (2). Consequently, in view of the shared embryological origins, a wide range of phenotypic variations can be observed in diseases such as CHH, KS, SOD and CPHD which affect this anatomic region. Despite the distinct nature of the genetic factors associated with these conditions, a clinical and genetic overlap can be observed. Heterozygous loss-of-function variants of FGFR1 gene have been generally detected to be responsible for KS (10% of cases) and normosmic CHH (7% of cases), both of which are characterized by an autosomal dominant transmission (5, 6).

However, the use of next-generation sequencing and chromosomal microarray analysis has recently enabled the identification of alterations in the FGFR1-FGF8 couple in subjects with CPHD. Such FGFR1 variants are associated with variable expressivity and incomplete penetrance, both in KS and in CHH, as well as in CPHD. Nevertheless, while oligogenicity has been documented in KS and in CHH, this is not observed in CPHD (2, 7, 8). A limited number of cases of mutations in this gene have been documented, including missense, nonsense and deletions, characterized by wide phenotypic variability even within the same family nucleus (9-10). Considering the endocrine aspects, a common feature among these reported cases was the presence of HH, while growth hormone deficiency, even though frequent, was not found in all subjects. Concerning midline developmental abnormalities, a spectrum of severity has been observed, ranging from SOD to simple alterations in the development of the pituitary gland (9-11).

Conclusions

In conclusion, our case highlights the role of missense variants of FGFR1 in the development of CPHD associated with complex brain malformations, even in the absence of anosmia.

Comprehensive study of pituitary function, brain MRI and genetic analysis are crucial in the diagnostic work-up of hypogonadotropic hypogonadism in order to clarify its etiology and any associated comorbidities.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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