A NOVEL FGFR1 MUTATION IN KALLMANN SYNDROME WITH GROWTH HORMONE DEFICIENCY

TOPIC: GROWTH AND SYNDROMES 3

Tornese G[1], Pellegrin MC[1], Pavan M[1], Faleschini E[1], Barbi E[1,2]

1. Insitute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy
2. University of Trieste, Trieste, Italy

Authors have no financial support nor conflict of interest to declare

Address: Pellegrin Maria Chiara
IRCCS Burlo Garofolo,
Via dell'Istria 65/1, 34137 Trieste, Italy
Email: mariachiara.pellegrin@burlo.trieste.it

Background

Kallmann syndrome (KS) is a genetic disorder, mainly characterized by the association of anosmia (due to hypo/aplasia of the olfactory bulbs) and hypogonadotropic hypogonadism (due to GnRH deficiency). Both partial or complete forms are described. Other features (skeletal and renal malformations, deafness, bimanual synkinesis) can be variably associated. Behind this phenotypic heterogeneity, there is a considerable complexity of genetic mutations. KAL1, FGFR1, PROKR2, PROK2, CHD7, FGF8 are the principal genes involved, accounting up to 35% of KS cases.

Case presentation

A 4-years old boy presented to our Pediatric Endocrinology Unit for deceleration of linear growth in the previous two years (- 1.8 SD), with normal height (-0.1 SD, according to Cacciari's Italian growth charts), weight and body proportion. He was prepubertal, without micropenis or cryptorchidism. He was born at term from non-consanguineous parents. Birthweight was 2940 g (- 0.44 SD according to Bertino's neonatal growth charts). Past medical history was unremarkable. His father was affected by KS, clinically diagnosed at the age of 14 because of anosmia and pubertal delay. He did not presented short stature (final height 184 cm, +1.22 SD).

All standard blood tests performed for the assessment of child's poor growth resulted normal, including celiac disease and thyroid function tests. Conversely, a diagnosis of GH deficiency was confirmed by two stimulation tests (GH peak<8 ng/ml), associated to low level of IGF-1 (Table1). Bone age resulted 1 years delayed. Brain MRI showed no morphological alteration of pituitary gland but, unexpectedly, highlighted olfactory bulbs hypoplasia (Figure 1). Anosmia was further confirmed by the olfactory test. Alteration of kidneys, limbs movement and hearing were excluded.

Genetic investigation showed a heterozygous mutation in the FGFR1 gene (c.976C→G), already known for being involved in KS, in both the proband and his father. This mutation has neither been previously reported by literature, nor it is comprised by the Single Nucleotide Polymorphisms (SNPs) database. Therefore, it is a de novo mutation, who passed from the father to the child. The pathogenicity was evaluated with prediction software (positive predictive value 0.99 and 0.89 of Mutation Tester and PoliPhen2 respectively).

GH replacement therapy was started, at a dosage of 28 mcg/kg/day, with a good clinical response and no adverse events (Figure 2). At 9 years of age, he is still prepuberal.

Conclusions

Despite phenotypic variability, KS has been rarely associated to GH deficiency and short stature. KS is usually suspected in the pubertal period as a result of primary or secondary signs of hypogonadism, and not as a result of poor height growth. FGFR1 gene has been independently associated both to KS and to pituitary dysfunction, respectively. This novel mutation of FGFR1 might determine the concurrence of both these clinical situations.

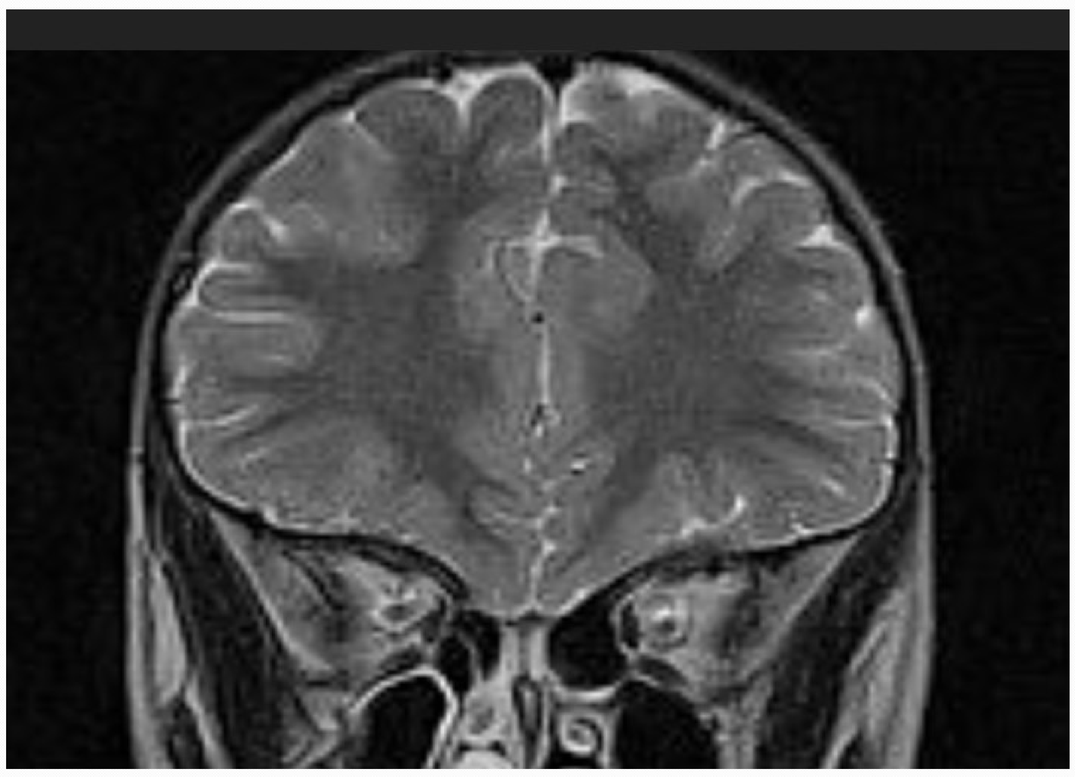

Figure 1. T2-weighted coronal MRI scan, showing olfactory bulbs hypoplasia

GH ng/ml	Basal	30° min	60° min	90° min	120° min
First test	0.84	5.74	2.29	1.19	6.80
Second test	2.15	7.60	4.90	2.62	2.45
IGF-1 ng/ml	25.7	(nv 50-286)			
IGF-BP3 mcg/ml	2.03	(nv 1.10-5.20)			

Table 1: Laboratory findings consistent with GH deficiency

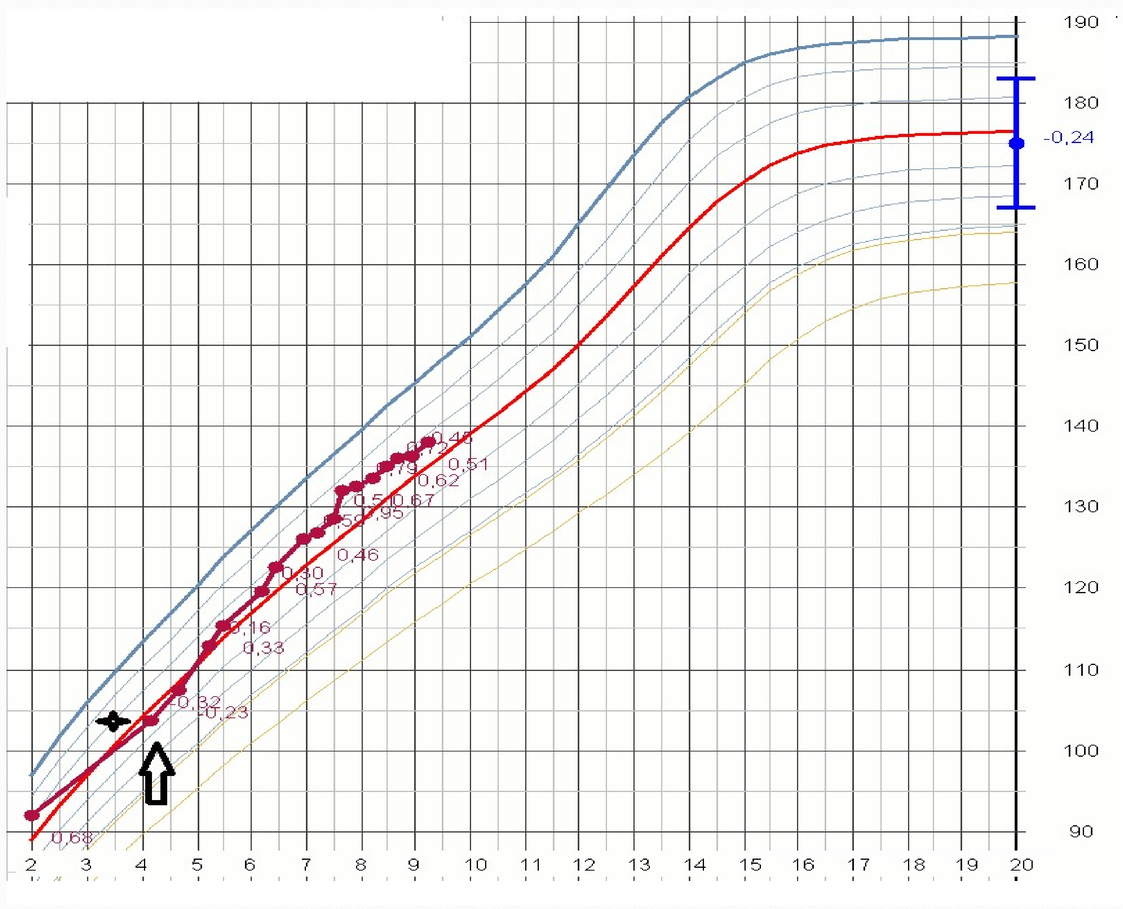

Figure 2 Growth chart of the patient before and after starting rhGH therapy (arrow), target height is -0.24 SD ± 8 cm (blue range).

References

-Dodé C, Hardelin JP. Kallmann syndrome. Eur J Hum Genet 2009;17:139-46.
-Subramanian N, Rajeswari S, Tamilvanan S. Rare cause for short stature-Kallmann's syndrome-a case report. Indian J Med Sci 2002;56:119-21.
-Tarique S, Iqbal MH, Riaz H, Abaidullah S, Murtaza Cheema T. Hypogonadotrophic Short Statured with Anosmia: Kallmann's Syndrome. J Coll Physicians Surg Pak 2011;21:113-4.
-Raivio T, Avbelj M, McCabe MJ, et al. Genetic overlap in Kallmann syndrome, combined pituitary hormone deficiency, and septo-optic dysplasia. J Clin Endocrinol Metab 2012;97:E694-9.