A Rare Cause of Hypogonadotropic Hypogonadism: *FGFR1* Mutation

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Introduction

- Mutations in FGFR1, which is involved in formation and migration of neurons responsible for the production of gonadotropin-releasing hormones, may either cause isolated hypogonadotropic hypogonadism (HH) or Kallmann syndrome (KS).
- In addition, FGFR1 mutations were reported in 2.7% of the cases with multiple pituitary hormone deficiency.

Case

- A 16-year-old male was referred to our clinic with absence of pubic hair and micropenis. He had a history of surgery for bilateral undescended testes. He was adopted in neonatal period, his birth and family history could not be reached.
- His weight was at -2.62 SDS, height -2.72 SDS, BMI -1.12 SDS. He had flat nasal root, Tanner Stage 3 pubic hair, testicular volumes were 2 ml on the left, 0.5 ml on the right, and stretched penile length was 2 cm.
- Laboratory results were as follow: fT4 1.14 ng/dL (0.5-1.51 ng/dL), TSH 1.57 mIU/mL (0.38-5.33 mIU/mL), FSH 0.71 mIU/mL (1.3-19.3 mIU/mL), 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 response during LHRH test was 4.75 IU/L (N, > 5 IU/L). Brain MRI was normal, no pituitary pathology was evident.
- There was no response to pubertal induction for two times, and low dose testosterone replacement was initiated. Growth velocity was low during the follow-up and insulin tolerance test showed low growth hormone (peak 1,36 ng/mL, N>7) and normal cortisol response to hypoglycemia. The smell test showed normal olfactory functions.
- Whole exome analysis revealed a previously reported, heterozygous **p.R622X** mutation in *FGFR1.*

Conclusion

- More than 25 genes have been identified to be associated with congenital HH. *FGFR1* mutations are among of the causes of congenital HH and KS, which are inherited autosomal dominantly and can be accompanied by cleft palate, tooth agenesis, and bimanual synkinesis. Also normosmic patients were reported with *FGFR1* variants.
- It should be kept in mind that multiple anterior pituitary hormone deficiencies may be associated with *FGFR1* mutations as well.

- **Keywords:** *FGFR1, Hypogonadotropic hypogonadism, Kallmann syndrome*