Neuroendocrine phenotype, genetics and hormonal treatment outcome in idiopathic normosmic hypogonadism and Kallmann syndrome patients: a multicenter Belgian study

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Aim: To study the clinical phenotype, the genetics and therapeutic responses in a series of 35 consecutive patients with hypogonadotropic hypogonadism and normosmia (HH) /hyposmia (KHS).

Methods: The study of the genes FGFR1 and KAL1 (anomalies), is performed in our center since 2013. Recently, a panel of genes is available for analysis of the following genes: KAL1, FGFR1, PROKR2, PROK2, GDNF, FGF8, KISS1, KISS1R, AFRS3, TACR3, GNRHR1, GNRHR1, NEFH, WDR11, HES6G71, SEMA3A.

Results: the series includes 35 patients (32 HH/18 ± 9 years) belonging to 31 families. We have identified by otoolfactometry 36 HH and 9 KHS. Brain MRI was performed in all patients: two patients had a malformation of Chiari I, two patients showed a partially empty sella, one patient had an cyst of the pouch of Rathke and another one had a cleft palate. Preliminary genetic analysis demonstrated a FGFR1 mutation in three patients and in a family. Identified mutations were: c.1983 + 1G > A, c.1026T > A (p.Luo342*) and c.937 - 1234C > T (new mutation: exon 8A of the isoform IIb). An acronym mutation was also identified in another patient: c.827.665 + 40delT, p.A168T (p.X286delins549ysyn). A last patient had a new mutation TAC3 c.238 + 1G > A, concerning fertility outcomes, an oligospermia was obtained in 6/12 men treated with HCG and FSH. Hormonal treatment allowed the development of secondary sexual characters in all patients. The patient with FGFR1 c.937 - 1234C > T showed a reversibility of hypogonadism, after 4 years of treatment.

Conclusions: Patients with HH FGFR1 mutation may also present with neuro developmental anomalies, which they should be screened for. The association of normosmic HH and Chiari malformation is intriguing; it was reported just once in the literature (Kulmer & al. Pituitary 2010). We demonstrated hypogonadism reversibility in a patient with one FGFR1 mutation. Finally, we report two novel TAC3 and FGFR1 mutations.

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