00029 Neuroendocrine phenotype, genetics and hormonal treatment outcome in idiopathic normosmic hypogonadism and Kallmann syndrome patients: a multicenter Belgian study

Hernan Valdes-Socin[1], Cécile Libioulle[1], François Guillaume Debray[1], Axelle Pintiaux[1], Anne-Simone Parent[1], Vinciane Corman[1], Karine Gellner[2], Vincent Geenen[1], Cristina Burlacu[4], C Jonas[1,4], Dominique Maiter[5], Guy T'Sjoen[6], Kris Poppe[7], Cécile Brachet[8], Vinciane Dideberg[1], Vincent Bours[1], Albert Beckers[1]

[1]CHU de Liège, Liège, Belgium, [2]CHR Citadelle, Liège, Belgium, [3]UCL, Louvain, Belgium, [4]CHU, Dinant Godine, Belgium, [5]Cliniques St LUC-UCL, Bruxelles, Belgium, [6]KUL, Ghent, Belgium, [7]CHU Erasme-ULB, Bruxelles, Belgium, [8]CHU Reine Fabiola, Bruxelles, Belgium

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

Methods: The study of the genes FGFR1 and KAL1 (anosmin), is performed in our center since 2013. Recently, a panel of genes is available for analysis of the following genes: KAL1, FGFR1, PROKR2, PROK2, CHD7, FGF8, KISS1, KISS1R, APR3, TACR3, GNRHR, GNRH1, NELF, WDR11, HS6ST1, SEMA3A.

Results: the series includes 35 patients (32 H/3F, 18 ± 9 years) belonging to 31 families. We have identified by olfactometry 26 nIHH and 9 KS. 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 a 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.1663 + 1 G > A, c.1025T > A (p.Leu342*) and c.937 - 1234C > T (new mutation: exon 8A of the isoform IIIb). An anosmin mutation was also identified in another patient: c.827_856 + 49delins, p.Ala276_asp286delinsGlyAsn. A last patient had a new mutation TAC3 c.238 + 1 G > 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 nIHH FGFR1 mutation may also present with neuro developmental anomalies, which they should be screened for. The association of normosmic IHH and Chiari malformation is intriguing: it was reported just once in the literature (Kulmar & al. Pituitary 2010). We demonstrated hypogonadism reversibility in a patient with one FGFR1 mutation. Finally, we report two novel TAC3 and FGFR1 mutations.