Male and female hypogonadotropic hypogonadism associated with two novel non sense heterozygous mutations of Klotho beta gene (KLB)

P 107

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Introduction: KLB encodes a transmembrane protein required for FGF21-FGFR1 linking and subsequent intracellular transduction signal through the Ras/MAP kinase pathway. Initially implicated in regulation of adipocytes metabolism, the FGF21/KLB/FGFR1 pathway was shown to have pleiotropic effects. Loss of function mutations in FGFR1 is the commonest cause of hypogonadotropic hypogonadism

CIlinical Case 1: A 15-year-old boy, with congenital deafness of the right ear, without olfaction disorders, consults for pubertal and growth retardation (1.59m, 47kg). Bone age of 14 years, GH: 6.4 ng/ml after Insulin tolerance test, LHRH-stimulable gonadotropins, testosterone-total 99ng/dl (28-1110 ng/dl). Pituitary MRI is normal. His father and sister had late puberty around the age of 16. The patient reaches 1.77m and 79 kg, under treatment with GH and Sustanon 250. At the age of 16, he develops multiple sclerosis, like his father. At 18 years, the gonadic balance is re-evaluated, normal (bilateral testicular volume: 14 ml).

Clinical case 2: A 30 years old woman (1.62m, 61 kg) consults in 2016 for secondary amenorrhea (LH:1.5U/L, FSH 2.3 U/L, estradiol 135 ng/l, progesterone 6.35 µg/L, testosterone <0.1 nmol/l) and infertility (chronic anovulation). Gynecological echography is normal. Clomiphene and FSHr stimulation tests are unsuccessful. After some left hypoesthesic symptomatology, a brain neuro inflammatory pathology was suspected on MRI (several frontal hyper intense T2 lesions) without a precise diagnosis. No pituitary lesions were identified. Interestingly, during follow up, a normal pregnancy was finally in obtained. She delivered a 3.3 kg girl in 2019.

Genetic analysis: A panel of 61 genes of hypogonadotropic hypogonadism found in case 1 an heterozygous variant KLB c.3092T>A, p.(Leu1031*). This new variant (likely pathogenic, class IV), causes the appearance of a premature stop codon in exon 5 of the KLB gene. In case 2, a novel mutation c.2230_2231insGGTT, p.(Ala744Glyfs*45) was confirmed, causing a frame shift and stop codon (since codon Ala744).

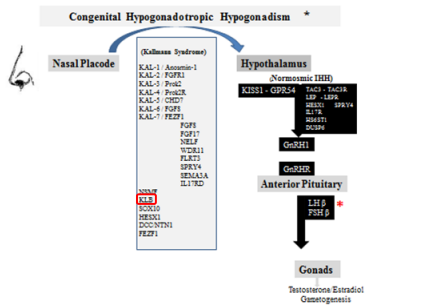

Figure: Schematic representation of the reproductive axis and the different genes, including KLB, participating in **Kallman syndrome** and **normosmic Isolated Hypogonadotropic Hypogonadism** (Valdes-Socin et al. Front Endocrinol 2014)

Case 1: A & B

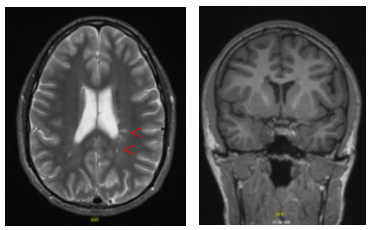

Figure A: Brain MRI with paraventricular white-matter lesions (SEP)

Figure B: Normal pituitary MRI

Case 2: C & D

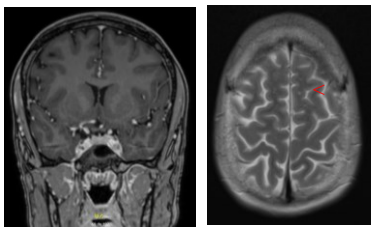

Figure C: Normal pituitary MRI

Figure D: Brain MRI with frontal white-matter lesions

Discussion: We describe two novel non sense KLB mutations and, for the first time, a reproductive phenotype in a female affected patient. In our series of 54 consecutive patients with congenital hypogonadotropic hypogonadism sequenced with a panel of 61 candidate genes, KLB mutations represents 3.7%. This prevalence is in line with the 4% finding of Xu. et al (EMBO Mol Med 2017). In the series of Xu et al, patients (n= 9/13) with missense KLB mutations had also a metabolic syndrome, unlike our patients carrying a nonsense mutation. In mice, the loss of the klb gene leads to delayed puberty, impaired estrogenic cycle, and subfertility. The association with multiple sclerosis/brain inflammatory lesions is intriguing: other family members will be studied.

References

* Valdes-Socin & al. *New England Journal of Medicine* 2004, * Valdes-Socin et al. *J Clin Endocrinol Metabol* 2009,Valdes-Socin & al. *Frontiers in Endocrinology* 2014
Xu et al. EMBO Mol Med 2017