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EVALUATION OF RELATIONSHIP BETWEEN OLFACTORY SYSTEM AND GONADAL FUNCTION IN PATIENTS WITH HYPOGONADOTROPHIC HYPOGONADISM AND CONGENITAL ANOSMIA

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Recently, the hypothalamic-pituitary-gonadal axis and the olfactory systems have been shown to be linked by a protein of the family of adhesion molecules, which controls the migration of Gn-RH neurons and olfactory axons from olfactory placode into the brain, across the lamina cribra. In Kallmann syndrome (KS) mutations of the gene encoding this protein induce hypo-anosmia and hypothalamic hypogonadism (HH). In idiopathic hypothalamic hypogonadism (IHH) a normal sense of smell is present and in congenital anosmia (CAN) a normal sexual function is reported. In order to better evaluate the relationship between olfactory apparatus and hypothalamic-pituitary axis we studied 25 patients (pts) (nine were affected with KS, 10 had IHH and 6 had CAN) by MRI-HR (thin, T1-weighted and coronal section) of olfactory and hypothalamic-pituitary regions and by olfactory tests (standard sniff-test and dilution test, with both pure olfactory substances and odorants stimulating the trigeminal nerve terminations in the nose). Serum LH and FSH levels were evaluated in basal conditions, after 3 consecutive Gn-RH boli (100 mcg iv every 2 hrs) and after busserelin injection (0.5 mg sc). In all pts MRI showed a normal hypothalamic-pituitary region. In KS MRI showed aplasia of olfactory bulbs and tracts in 7 pts and hypoplasia in 2 pts on the left side of the brain; on the right side aplasia was present in 6 and hypoplasia in 3 pts; olfactory sulci were absent in 1 pt, hypoplastic in 6 on the left and in 4 on the right side; normal sulci were observed in 1 pt on the left and in three pts on the right. In all pts with KS hypo-anosmia was present; however discrepancy between olfactory tests and MRI was noticed, as full anosmia associated with normal sulci and hypoplastic bulbs or hyposmia associated with lack of olfactory bulbs and sulci. Also in pts with CAN similar discrepancies were present. The 10 pts with IHH showed normal olfactory apparatus at the MRI and normal olfactory threshold for pure olfactory stimuli but reduced threshold for trigeminal stimulating odorants in 5 pts. Gonadotropin (Gn) basal levels (mean \pm SE) were normal in all pts with CAN (LH=4.8 \pm 0.4; FSH= 5.9 \pm 1.1) and very lowered in pts with KS (LH=0.2 \pm 0.03; FSH=0.4 \pm 0.05) and HHI (LH=0.7 \pm 0.2; FSH= 1.1 \pm 0.3). In KS basal Gn levels were significantly lower (P<0.05) than those found in IHH, suggesting a more relevant Gn-RH defect in KS. In CAN the Gn net increase after Gn-RH was normal (LH=20.5 \pm 3.7; FSH=9.3 \pm 1.7), while it was strongly reduced in KS (LH=2.2 \pm 0.4; FSH=3.2 \pm 0.6) and in IHH (LH= 3.7 \pm 0.6; FSH=3.7 \pm 0.4, not significant vs KS). After injection the LH and FSH increase in KS was similar to that observed after 3 consecutive Gn-RH boli injection, whereas in IHH only the LH increase (7.6 \pm 1.5 mIU/ml) was significantly higher (P<0.01) than that induced by GnRH boli and busserelin in KS.

In conclusion 1) MRI-HR and olfactory threshold are a valuable tools in evaluating olfactory system in HH; nevertheless discrepancies among clinical picture, MR imaging and olfactory threshold are still present; improved MR resolution's power, appropriate genetic studies and histological evaluation of olfactory epithelium will make possible better clarify phenotype's variability of HH and CAN; 2) the administration of consecutive Gn-RH boli and of busserelin induce a similar Gn increase; 3) the normal gonadal function in pts with CAN and the normal olfactory threshold in pts with HHI suggest the possibility of a correct migration into the brain of both GnRH and olfactory neurons, independently each from others.

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