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OLFACTORY THRESHOLD, BRAIN MRI AND GnRH TEST IN THE DIFFERENTIAL DIAGNOSIS OF HYPOTHALAMIC HYPOGONADISM AND IN CONGENITAL ANOSMIA.

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Olfactory and GnRH-secreting neurons originate in the olfactory placode and migrate across the lamina cribra of the ethmoid into the developing forebrain. In Kallmann syndrome (KS) mutations of genes encoding for neural cell adhesion molecule(s) (the most frequently involved gene is located on chromosome Xp22.3), prevent olfactory and GnRH secreting neurons to migrate into the brain. This results in alterations of olfactory bulbs, tracts and sulci, hypo-anosmia and hypothalamic hypogonadism (HH). However, most HH patients (pts) have a normal olfactory apparatus and pts with congenital anosmia (CAN) may develop normal sexual function. This prompted us to evaluate, in 16 pts with HH (3F and 13M) and in 3 with CAN (2F and 1M) and normal sexual function, the reliability of high resolution MRI (thin, T1-weighted and coronal sections), olfactory threshold (standard sniff-test and dilution test, with both pure olfactory substances and odorants stimulating the trigeminal nerve terminations) and LH-FSH levels (in basal condition and after 3 consecutive GnRH boli). Six pts (2F and 4M; age: 17-58 yrs) with HH and subjectively reported hypo-anosmia were clinically classified as KS; 10 pts (1F and 9M; age: 16-57 yrs) with HH and subjectively reported normal sense of smell were clinically classified as idiopathic HH (IHH). LH and FSH basal levels (range: 0.1-2.5 mIU/ml) and net increase after GnRH (range: 1-6.2 mIU/ml) were low in both pts with KS and IHH, while in pts with CAN basal LH-FSH levels and their response to GnRH were normal. MRI showed aplasia of olfactory tracts and bulbs in 2 pts with CAN and hypoplasia in the last one. In all pts with CAN sulci hypoplasia and anosmia for pure and trigeminal stimulating substances were found. This suggests the possibility of normal migration into the brain of GnRH secreting neurons also when olfactory neurons are laking or fail to migrate. In the six pts classified as KS, olfactory bulbs and tracts were laking in 4 and hypoplasic in 2; hypoplasia of olfactory sulci was also documented in all. Hypo-anosmia for both pure and trigeminal odorants was seen in all but one pts with a normal olfactory threshold despite MRI failed to show olfactory bulbs and tracts and the pts reported subjective hypo-anosmia. MRI showed normal bulbs, tracts and sulci in the 10 pts with IHH; olfactory threshold was normal for pure olfactory stimuli but strongly reduced for trigeminal stimulating odorants in 5 pts.

In conclusion our data highlight the current difficulties in the differential diagnosis of the various form of HH and in the correct evaluation of the relation between olfactory and GnRH secreting neurons. The discrepancies among the clinical picture, the brain MRI and the olfactory threshold, point to the necessity to includes also appropriate genetic studies and histological evaluation of olfactory epithelium in order to clarify the variable phenotypic apparence of HH and CAN

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