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Original article

Reconsidering olfactory bulb magnetic resonance patterns in Kallmann syndrome

La neuroradiologie des bulbes olfactifs dans le syndrome de Kallmann revisitée

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Abstract

Objective. – The aim of this retrospective study was to perform magnetic resonance imaging assessment of olfactory pathway and skull base abnormalities in Kallmann syndrome (KS) patients with hypogonadotropic hypogonadism and olfaction disorder. *Methods.* – Magnetic resonance brain patterns were retrospectively studied in 19 patients clinically classified as KS. Qualitative assessment of olfactory bulb region comprised bulb atrophy and rectus and medial orbital gyrus ptosis; quantitative assessment measured olfactory fossa depth and width, sulcus depth and ethmoid angle. Results were compared to an age- and sex-matched control population ($n = 19$) with no impairment in the region of interest. Sixteen of the 19 KS patients were genetically screened for mutations associated with KS. *Results.* – On the above qualitative criteria, 15 of the 19 patients presented either unilateral ($n = 2$) or bilateral ($n = 13$) olfactory bulb agenesis; 16 showed tract agenesis and 16 showed gyrus malformation (ptosis or absence). On the quantitative criteria, 18 of the 19 patients showed abnormal sulcus depth and/or olfactory fossa malformation and/or abnormal ethmoid angle. *Conclusion.* – The presence of malformation abnormalities in the olfactory fossae of 18 of the 19 patients appears to be a key factor for etiological diagnosis of hypogonadotropic hypogonadism, and should enable targeted study of genes involved in KS.

Keywords: Kallmann syndrome; Hypogonadism; Olfactory bulb; Olfaction Disorder; Magnetic resonance imaging

Résumé

Objectif. – L'objectif de cette étude rétrospective était d'évaluer par l'imagerie par résonance magnétique (IRM) les anomalies des voies olfactives et de la base du crâne chez les patients atteints d'hypogonadisme hypogonadotrope avec anosmie dans le cadre du syndrome de Kallmann. *Méthodes.* – Nous avons réalisé une relecture des IRM cérébrales de 19 patients atteints cliniquement d'un syndrome de Kallmann avec une évaluation qualitative (atrophie des bulbes, ptose de gyri-orbitaire médian et rectus) et quantitative (largeur et hauteur des fosses olfactives, angles ethmoïdaux, profondeur des sulci olfactifs) de la région des bulbes olfactifs en comparaison avec une population contrôle appariée pour l'âge et le sexe et sans atteinte de cette région ($n = 19$). Une étude génétique a pu être réalisée chez 16/19 des patients Kallmann. *Résultats.* – Sur les 19 patients,

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15 présentaient, selon les critères qualitatifs, une agénésie unilatérale ($n = 2$) ou bilatérale ($n = 13$) des bulbes olfactifs, 16 présentaient une agénésie des tractus et 16 présentaient une malformation des gyri (ptose ou absence). En complément, l'analyse quantitative a montré, des anomalies de la profondeur des sulci et/ou des anomalies malformatives des fosses olfactives et/ou des angles éthmoïdaux chez 18 des 19 patients. *Conclusion.* – La présence d'anomalies malformatives des fosses olfactives chez 18 des 19 patients de notre étude, semble un élément clé du diagnostic étiologique des hypogonadismes hypogonadotropes et devrait permettre l'orientation ciblée de la recherche des gènes associés au syndrome de Kallmann.

Mots clés : Syndrome de Kallmann ; Hypogonadisme ; Bulbe olfactif ; Anosmie ; Imagerie par résonnance magnétique

1. Introduction

Kallmann syndrome (KS), also known as De Morsier syndrome or olfactogenital dysplasia, is a rare form of congenital hypogonadotropic hypogonadism (CHH) involving impaired or absent sense of smell (anosmia).

In 1987, Klingmüller et al., using magnetic resonance imaging (MRI), identified olfactory abnormalities in four patients: olfactory sulci were either underdeveloped or absent [1]. In 1989, neuroanatomical studies showed that GnRH-secreting neurons of the hypothalamus originated in the olfactory placode and migrated into the brain along with olfactory, terminalis, and vomeronasal nerves [2,3]. The same year, Schwanzel-Fukuda et al. clearly described the embryologic mechanism of X-linked KS in a human fetus; they demonstrated that HH in KS is due to a migratory defect during embryonic development of the olfactory nerves, inducing lack of GnRH [4]. In 1993, three studies of imaging patterns in KS showed absence or hypoplasia of olfactory bulbs (OB), tracts and sulci [5–7].

Several genes were associated with the KS phenotype: *KAL1* (ANOS1), *KAL2/FGFR1*, *FEZF1*, *HESX1*, *IL17RD*, *SEMA3A*, *SOX10*, *AXL*, *CHD7*, *FGF8*, *FGF17*, *HS6ST1*, *NSMF*, *OL14RD*, *PROK2*, *PROKR2*, *SEMA7A* and *WDR11* [8]. Other genes were only associated with *CHH* without anosmia: *GNRH1*, *TAC3*, *TACR3*, *GnRHR*, *KISS1*, *KISS1R*, *LEP*, *LEPR*, *PCSK1*, *DMXL2*, *RNF216*, *OTUD4*, *PNPLA6*, *NR0B1*, *SPRY4*, *DUSP6*, *FLRT3*, *EBF2*, *NELF*, *DAX1* [8].

KS is usually diagnosed by clinical signs and symptoms [9], but misclassification may occur, as some KS patients may not be aware of their olfactory or gustatory disorders [10]. Neuroimaging may thus be a useful tool to detect relevant parenchymal rhinencephalic or ethmoid bone abnormalities. Recently, ethmoid bone abnormalities have been reported using computed tomography (CT) in KS patients [11], which raises the possibility of their being detected by MRI.

The aim of this observational retrospective study was to assess olfactory nerve MRI patterns and anterior cranial fossa abnormalities in a cohort of 19 KS patients with HH.

2. Methods

2.1. Patients

From 1993 to 2015, 32 patients initially diagnosed with KS were identified in the hospices civils de Lyon hospitals board database. KS was diagnosed on the association of olfactory deficit (hyposmia or anosmia) and HH. Ten patients were excluded due to missing data (some MR images were not available, and other images were centered on the pituitary gland and not on the olfactory region). Three other cases were excluded due to normosmia. The study population thus consisted of 19 patients.

Nineteen age- and sex-matched control subjects were also recruited: patients without impairment in the olfactory bulb region. Their brain MRI was considered normal by the referent neuroradiologist, although 6 presented some abnormalities: 4 with ophthalmic disease (optic neuritis, Grave's disease, uveitis), 1 with maxillary sinusitis and 1 with cavernous hemangioma.

2.2. Olfaction

Since no olfactory test was available for use in our institution hospices civils of Lyon between 1993 and 2015, the complete anosmia or hyposmia was assessed on a yes/no questionnaire: the patients were asked if they were able to smell several olfactory items such as fuel oil, smoke, bad smell, strong perfume, etc.

2.3. MR findings

MRI acquisitions had been performed with different MR systems (Philips, Siemens or GE), different field strengths (1.5 or 3 Tesla) and different sequences; only patients with high resolution T2-weighted coronal sequences (FIESTA, CISS, DRIVE) were included in the study.

MRI analysis in patients and control subjects consisted in olfactory region assessment on T2 coronal sequences, from orbital background to optic nerves when visible (Fig. 1). For each section, rectus and medial orbital gyrus position, sulcus and olfactory fossa depth and ethmoid angle (Fig. 1) were reported. Olfactory bulbs were carefully distinguished from the olfactory bulb artery. Bone contours of the anterior cranial fossa were delineated based on the contrast between the no signal in bone and hypersignal in cerebrospinal fluid, as shown in Fig. 1. Specific measurements [11,12] were made for each coronal T2-weighted sequence (Table 1) (Fig. 1a) as given below:

- olfactory fossa width: distance between midline and mid-part of the lamella lateralis;
- olfactory fossa height: distance between cribriform plate and fovea ethmoidalis plane;

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