

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.

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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. © 2017 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Syndrome de Kallmann ; Hypogonadisme ; Bulbe olfactif ; Anosmie ; Imagerie par résonance 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*, *ILI7RD*, *SEMA3A*, *SOX10*, *AXL*, *CHD7*, *FGF8*, *FGF17*, *HS6ST1*, *NSMF*, *OLI4RD*, *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;

Table 1
Clinical features (age at MRI and olfaction of the patients), qualitative evaluation of the olfactory bulbs, olfactory tracts and cortex (position of the gyri and depth of the olfactory sulci) and quantitative evaluation of olfactory fossae anatomy with MLA, FLA, and olfactory fossae height and width in the 19 patients (k).

	Age at MRI	Olfaction	R Gyri	R bulb	R tract	R sulcus (height) (mm)	R OF (height × width) (mm)	MLA D (°)	FLA D (°)	L gyri	L bulb	L tract	L OF (height × width) (in mm)	MLA G (°)	FLA G (°)	L sulcus (height) (mm)
K1	51	Anosmia	Ptosis	Agensis	Agensis	4	3.4 × 5	77	144	Ptosis	Agensis	Agensis	3 × 5	70	144	4
K2	39	Hyposmia	Normal	Hypoplasia	Agensis	6	4.2 × 4.7	46	140	Normal	Hypoplasia	Agensis	3.3 × 4.2	67	149	6
K3	36	Anosmia	Absent	Agensis	Agensis	0	0 × nm	90	180	Ptosis	Agensis	Agensis	2.4 × 2.9	78	142	6.3
K4	30	Anosmia	Normal	In T2 hypersignal	Present	8.6	7.1 × 4.1	40	127	Normal	In T2 hypersignal	Present	6.1 × 4.9	55	132	7.9
K5	28	Anosmia	Ptosis	Agensis	Agensis	5.6	1 × 2.7	79	152	Ptosis	Agensis	Agensis	1.3 × 4.5	71	159	5.4
K6	22	Anosmia	Ptosis	Agensis	Agensis	6.1	1 × 3.8	69	150	Ptosis	Agensis	Agensis	1 × 3.3	70	165	0
K7	47	Hyposmia	Normal	Biconvex and hypoplastic	Present	6.9	4.6 × 3.6	51	114	Normal	Biconvex and hypoplastic	Partially visible	4.6 × 4.1	59	165	7.1
K8	23	Anosmia	Ptosis	Agensis	Agensis	6.5	0 × nm	90	180	Ptosis	Agensis	Agensis	0 × nm	90	180	7.0
K9	17	Anosmia	Ptosis	Agensis	Agensis	9.7	0 × nm	90	180	Ptosis	Agensis	Agensis	2.8 × 2.3	70	180	6.5
K10	17	Anosmia	Absent	Agensis	Agensis	0	0 × nm	90	180	Ptosis	Agensis	Agensis	0 × nm	90	180	6.7
K11	17	Hyposmia	Ptosis	Agensis	Agensis	3.3	3.8 × 2.2	37	126	Ptosis	Hypoplasia	Agensis	5.9 × 3.4	48	112	7.0
K12	18	Anosmia	Ptosis	Agensis	Agensis	4.9	3.8 × 5.6	70	158	Ptosis	Agensis	Agensis	3.1 × 5	60	149	7.8
K13	20	Anosmia	Ptosis	Agensis	Agensis	4.2	0 × nm	90	180	Ptosis	Agensis	Agensis	0 × nm	90	180	5.9
K14	18	Hyposmia	Ptosis	Agensis	Agensis	7.0	4.3 × 5.6	51	160	Ptosis	Hypoplasia	Agensis	4.3 × 5.2	49	150	5.6
K15	31	Anosmia	Ptosis	Agensis	Agensis	2.6	2.2 × 3.5	60	157	Ptosis	Agensis	Agensis	1.8 × 2.4	52	146	1.9
K16	27	Anosmia	Ptosis	Agensis	Agensis	5.2	1.6 × 2.9	70	130	Ptosis	Agensis	Agensis	1.7 × 2.6	61	129	3.7
K17	14	Anosmia	Ptosis	Agensis	Agensis	nm	0 × nm	90	180	Ptosis	Agensis	Agensis	0 × nm	90	180	4.6
K18	15	Anosmia	Ptosis	Agensis	Agensis	8.2	2.1 × 3.2	72	128	Ptosis	Agensis	Agensis	1.0 × 2.6	72	184	4.8
K19	30	Hyposmia	Ptosis	Hypoplasia	Present	7.1	1.4 × 5.6	68	152	Ptosis	Hypoplasia	Present	1.4 × 6.3	69	172	6.5

FLA: foveolateral angle (angle between fovea ethmoidalis and lamella lateralis); L: left; MLA: mediolateral angle (angle between midline and junction between fovea ethmoidalis and lamella lateralis); OF: olfactory fossae; R: right.

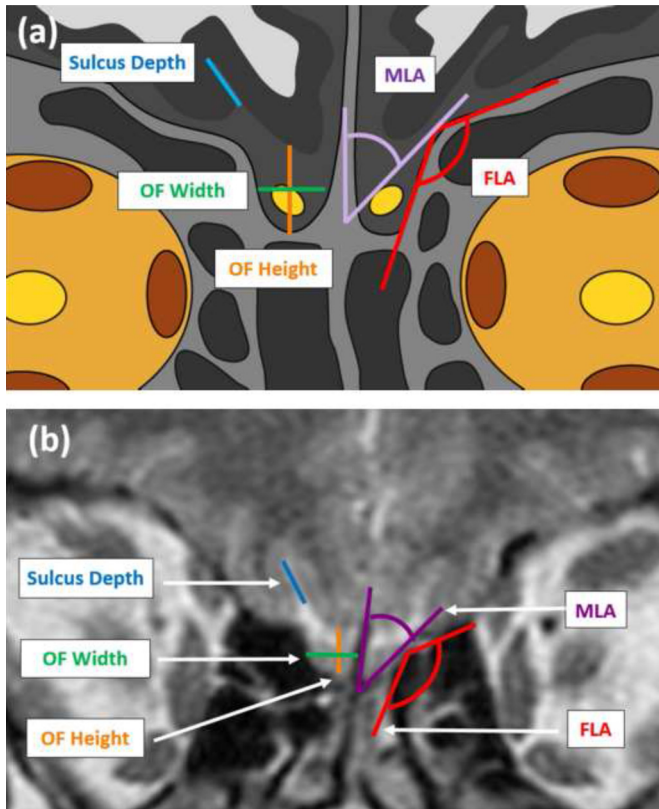


Fig. 1. a: coronal image of the olfactory region. This representation shows the MLA (angle between midline and junction between fovea ethmoidalis and lamella lateralis), FLA (angle between fovea ethmoidalis and lamella lateralis), OF height (distance between cribriform plate and fovea ethmoidalis plane), OF width (distance between midline and mid part of lamella lateralis) and sulcus depth (distance between gyrus rectus and orbital medial gyrus); b: coronal-T2-weighted MR image of a digital slice through the olfactory bulb. Representation shows the MLA (angle between midline and junction between fovea ethmoidalis and lamella lateralis), FLA (angle between fovea ethmoidalis and lamella lateralis), OF height (distance between cribriform plate and fovea ethmoidalis plane), OF width (distance between midline and mid part of lamella lateralis) and the sulcus depth (distance between gyrus rectus and orbital medial gyrus).

- sulcus depth: depth of groove between gyrus rectus and medial orbital gyrus, considered normal when > 8 mm;
- mediolateral angle (MLA): angle between midline and junction between fovea ethmoidalis and lamella lateralis;
- foveolateral angle (FLA): angle between fovea ethmoidalis and lamella lateralis

2.4. Genetics

Informed consent to screen for mutation *s* in KS and CHH genes was obtained from only 16 patients. Genomic DNA was extracted from peripheral blood or lymphoblastoid cell lines. Mutations were sought in coding exons and flanking splice sites of 5 KS genes (*KALI*, *FGFR1*, *FGF8*, *PROKR2*, and *PROK2*) using the PCR method before 2013, and of 10 KS genes (*KALI*, *FGFR1*, *FGF8*, *PROKR2*, *PROK2*, *WDR11*, *HS6ST1*, *CHD7*, *SEMA3A*, and *SOX10*) and 6 CHH genes (*GNRHR*, *GNRH1*, *KISS1R*, *KISS1*, *TAC3*, and *TACR3*) using the next-generation sequencing (NGS) technique after

2013 (Table 2). Primers were designed using Ampliseq designer software. Library preparation used the Ion Plus fragment library kit with 50 ng genomic DNA. Adapter ligation, nick repair and amplification were performed according to the Ion Torrent protocol (Life Technologies). Emulsion PCR and enrichment steps used the Ion One Touch template kit. Sequencing of the amplicon libraries used the Ion Torrent PGM system, with 316 chips and barcoding using the Ion Xpress barcode adapters kit. The Ion sequencing kit version 2 was used for all sequencing reactions, according to the recommended protocol. After sequencing, reads were mapped to the human genome 19 assembly using the Torrent mapping alignment program. Single-nucleotide variants and small insertions/deletions (indels) were identified using Torrent Variant Caller (Life Technologies) and Nextgene software. All mutations found by the NGS technique were confirmed by Sanger sequencing of new PCR products.

2.5. Statistical analysis

To ensure the reproducibility of the olfactory fossa and sulcus measurements, each of the 19 MR patterns was read first by a single medical student and then qualitatively confirmed and adjusted by a senior neuroradiologist. The resulting values were compared with those for the control group ($n=19$) using bilateral *t*-tests. Differences after Bonferroni correction were considered statistically significant at $P < 0.0125$. Statistical analyses were performed using Excel software, version 2013 (Microsoft Corporation, Redmond, Washington).

3. Results

The study included 15 male and 4 female KS patients, aged 14 to 51 years (mean \pm SD = 26 ± 11 years) and 15 male and 4 female control subjects, aged 17 to 50 years (27 ± 10 years).

The questionnaire revealed complete anosmia or hyposmia in all KS 19 patients.

Qualitative assessment of KS patients' MRI scans showed at least one non-specific abnormality in the bulb, olfactory tract or gyrus, detailed below.

3.1. Olfactory bulb

Olfactory bulb agenesis was observed bilaterally in 13 patients, and unilaterally in 2 (right agenesis with hypoplastic left olfactory bulb). Three patients had bilateral hypoplastic olfactory bulbs and 1 presented olfactory bulb T2 hypersignal (Table 1).

3.2. Olfactory tract

Olfactory tract agenesis was observed bilaterally in 16 patients, and was also seen in the right hemisphere of 1 patient but only partially visible (due to an artifact) in the left hemisphere (Table 1). The other 2 patients had normal olfactory tracts.

Table 2
Genetic results for the 19 patients of the cohort.

	Studied genes	Results
K1	<i>KALI</i> , <i>FGFR1</i> , <i>PROKR2</i> , <i>PROK2</i> , <i>FGF8</i>	<i>PROKR2</i> : c.254G > A, p.Arg85His/+
K2	Not determined	–
K3	<i>FGFR1</i> , <i>PROK2</i>	negative
K4	NGS panel	negative
K5	NGS panel	negative
K6	<i>KALI</i> , <i>FGFR1</i> , <i>PROKR2</i> , <i>PROK2</i> , <i>FGF8</i>	<i>FGFR1</i> : c.2164C > T, p.Pro772Ser/+
K7	Not determined	negative
K8	<i>KALI</i> , <i>FGFR1</i> , <i>PROKR2</i> , <i>PROK2</i> , <i>FGF8</i>	<i>PROK2</i> : c.302G > A, p.Arg101Gln/+
K9	NGS panel	negative
K10	<i>KALI</i> , <i>FGFR1</i> , <i>PROKR2</i> , <i>PROK2</i> , <i>FGF8</i>	<i>PROKR2</i> : c.518T > G, p.Leu173Arg/p.Leu173Arg
K11	<i>KALI</i> , <i>FGFR1</i> , <i>PROKR2</i>	negative
K12	NGS panel	<i>FGFR1</i> : c.1977 + 1G > A/+, <i>CHD7</i> : p.Arg2531Trp/+
K13	<i>KALI</i> , <i>FGFR1</i> , <i>PROKR2</i> , <i>PROK2</i> , <i>FGF8</i>	<i>KALI</i> : c.1270C > T, p.Arg424*
K14	NGS panel	<i>FGFR1</i> : c. 535G > C, p.Cys178Ser/+
K15	<i>FGFR1</i>	<i>FGFR1</i> : c.1862A > G, p.His621Arg/+
K16	NGS panel	negative
K17	<i>KALI</i> , <i>FGFR1</i> , <i>PROKR2</i> , <i>PROK2</i> , <i>FGF8</i>	<i>KALI</i> : c.226delT, p.Val75Valfs21*
K18	NGS panel	negative
K19	Not determined	–

3.3. Rectus and medial orbital gyrus

Bilateral ptosis of the gyri was observed in 14 patients. Left gyrus ptosis was observed in 2 patients. In 3 patients, the gyri were normal (Table 1).

3.4. Olfactory sulcus depth

MRI showed bilateral abnormal sulcus depth in 16 of the 19 patients: right sulcus depth 0–7.1 mm, mean 5.8 ± 3.4 mm; left sulcus depth, 0–7.8 mm and mean 4.9 ± 2.1 mm (Table 1). Olfactory sulcus depth was normal in 3 patients.

3.5. Olfactory fossa and ethmoid angle

Olfactory fossa (OF) and ethmoid angle abnormalities were observed in 18 of the 19 patients. The OF was absent bilaterally in 4 patients and unilaterally (right side) in 2. The right OF height was shallower (mean, 1.29 ± 1.5 mm) and thinner (3.83 ± 1.3 mm) than the left (1.56 ± 1.8 mm and 4.15 ± 1.5 mm, respectively). The differences in mean MLA and in mean FLA between the right and left sides were not significant ($79 \pm 18^\circ$ vs. $69 \pm 14^\circ$, and $154 \pm 22^\circ$ vs. $158 \pm 14^\circ$, respectively) (Table 1).

Compared to controls, mean OF depth was significantly smaller in KS patients (1.42 ± 1.64 mm versus 5.77 ± 1.07 mm; $P < 0.0001$), while width did not significantly differ (3.99 ± 1.41 mm and 4.10 ± 0.58 mm, respectively; $P > 0.7$).

Compared to controls, KS patients showed larger MLA ($69 \pm 16^\circ$ versus $45 \pm 8^\circ$; $P < 0.0001$) and FLA ($156 \pm 22^\circ$ versus $114 \pm 11^\circ$; $P < 0.0001$), while sulcus depth was significantly smaller (4.97 ± 2.8 mm versus 7.17 ± 1.22 mm, respectively; $P < 0.0125$).

One KS patient stood out from the others: a 30 year-old patient with HH and anosmia (Table 1) but no mutation in

known KS genes (patient K4, Table 2) showed normal anterior cranial fossa patterns on MRI, while clear olfactory bulb hypersignal was observed on T2 sequences, suggesting centro-bulbar necrosis (Fig. 2).

Genetic analysis identified *PROKR2* mutation (p.Arg85His/+ and p.Leu173Arg/p.Leu173Arg) in 2 patients, *PROK2* mutation (p.Arg101Gln/+) in 1 patient, *FGFR1* mutation (p.Pro772Ser/+, c.1977 + 1G > A/+, p.Cys178Ser/+ and p.His621Arg/+) in 4 patients, and *KALI* (p.Arg424* and p.Val75Valfs21*) in 2 patients (Table 2). One patient had 2 mutations: *FGFR1* (c.1977 + 1G > A/+) and *CHD7* (p.Arg2531Trp/+) (Table 2).

MR patterns were not specifically related to the identified mutations.

4. Discussion

KS is the clinical consequence of a defect in GnRH neuron migration within olfactory axon endings [4]. Many causative

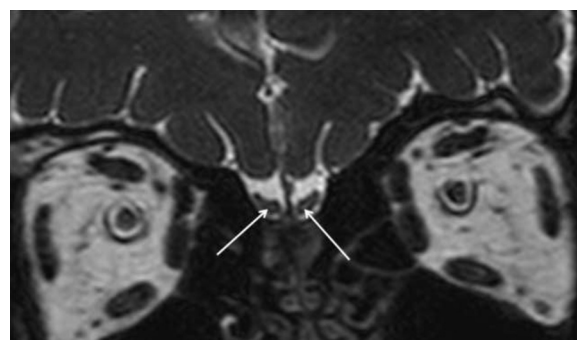


Fig. 2. Coronal T2-weighted MR image through the olfactory bulb of patient K5, a 30 year-old patient with hypogonadotropic hypogonadism and anosmia. Central hypersignal on T2 weighted images is visible in the olfactory bulbs (white arrow). Olfactory fossae and sulcus are wide and deep whereas ethmoid angles and rectus and orbital medial gyri are normal.

genes have been identified in the last decade and their mutations reported to be associated to a KS phenotype. This multigenetic aspect may contribute to the great heterogeneity in clinical presentation, with various degrees of gonadal dysfunction and olfactory deficit [13]. MRI has become crucial for the identification of atrophic olfactory systems and differentiation of central (hypogonadotropic) causes from other causes of hypogonadism [14].

In the present relatively small series of KS patients, we investigated ethmoid bone abnormalities and anatomic malformations of the olfactory region (bulb, tract). We also evaluated ptosis in the rectus and medial orbital gyri, height reductions in the sulci between gyri, anterior cranial fossae malformations, particularly in the roof of the ethmoid across the MLA and FLA angles, and OF height and width.

The results are in agreement with previously published radiological studies of the olfactory region in KS [1,5–7,15–18]. Olfactory bulb, tract and sulcus aplasia and gyrus ptosis were consistently the most commonly reported malformations in KS patients. Olfactory sulci depth is a useful clinical indicator in isolated anosmia in healthy patients [12], and here was shallower in KS than control patients, and may therefore be a useful tool for the diagnosis of olfactory deficit in KS.

The results of quantitative MRI analysis are also in agreement with previous CT analyses of skeletal abnormalities [11]. There was absence of the OF absence, which is present in normal subjects, resulting in a “flattening” of the ethmoid floor in all KS patients except one. Because the anterior cranial fossa is clearly outlined by the high CSF signal on T2-weighted images, contrasting with the lack of signal (black) from compact bone [19], MRI demonstrates abnormalities of the OF bone that are quite similar to CT findings, as previously reported by Maione et al. [11]. Therefore, the present data suggest that, in hypogonadotropic hypogonadism, MRI, being a non-irradiating technique, should be the first radiological step for investigating the pituitary gland as well as abnormalities of the ethmoid, olfactory bulb and tract.

A correlation was previously reported between olfactory bulb volume and olfactory function in healthy patients, regardless of age [20]. An association was also demonstrated between MRI findings and olfactory function in KS patients; the authors suggested that analyzing olfactory bulb volume according to olfactory function might be helpful in differential and early diagnosis of KS [21].

No clear correlation of genotype with phenotype was established in the present study: many patients had mutations on the same gene, but the mutations differed (not the same locus, etc.), hence the different phenotypes.

This point deserves to be investigated prospectively, screening all KS patients on NGS: the type of mutation on KS genes may play a major role.

However, other unknown factors, such as rescue genes, may be involved in the complexity of phenotypic expression of KS gene mutation.

The present study had some limitations: sample size was small, and different MRI protocols and systems were used due to the long period of observation (1993–2015).

Interestingly, in one KS patient with normal initial MRI, typical malformations of the anterior cranial fossae (olfactory sulci, gyri and ethmoid angles) were identified on second assessment (patient K2, Table 2).

5. Conclusions

Our study suggests that the olfactory bulb and tract and also anterior cranial fossa should be systematically rigorously analyzed on MRI in any patient with congenital HH. If abnormalities are found, screening for a molecular mutation of a gene associated with KS should be considered.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

We would like to thank the staff of the University's Department of Anatomy, Rockefeller, Lyon Est, for providing facilities needed for party of the study. We also thank Florence Christiany, Dr Marie Barbesier and Pr Jean-Pierre Pracros for their valuable assistance.

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