Kallmann Syndrome: MR Evaluation of Olfactory System

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PURPOSE: To describe the MR appearance of the olfactory bulbs and tracts and temporal lobes in patients with Kallmann syndrome, a disorder characterized by hypogonadotropic hypogonadism and anosmia. **METHODS:** High-resolution MR scans with a surface coil placed over the nasion were performed in two patients with Kallmann syndrome. Coronal 3-mm thick contiguous sections were obtained through the olfactory bulbs and tracts. MR scans included volumetric analysis of the bulbs, tracts, temporal lobes, and hippocampi. **RESULTS:** No olfactory bulbs or tracts could be identified in patients with Kallmann syndrome. In comparison, the olfactory bulbs and tracts were identifiable in seven healthy volunteers. The temporal lobe and hippocampal volumes were comparable between control subjects and Kallmann patients. **CONCLUSIONS:** High-resolution surface-coil MR can identify the absence of olfactory bulbs and tracts in patients with Kallmann syndrome. Normal olfactory bulbs and tracts are easily discerned with surface-coil imaging.

Index terms: Kallmann syndrome; Nervous system, disease; Olfactory lobe; Brain, magnetic resonance; Brain, growth and development

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In 1944, Kallmann described a syndrome of primary eunuchoidism secondary to hypogonadotropic hypogonadism associated with congenital anosmia with presumed absence of the olfactory bulbs and tracts (1). Additional associations included color blindness and synkinesis. Patients with Kallmann syndrome present with eunuchoidal habitus and delayed puberty, gynecomastia, and microphalli. The syndrome has recently been isolated to the Xp22.3 portion of the short arm of the X chromosome (2).

The olfactory bulbs and tracts of healthy patients have been visualized on magnetic resonance (MR) by Suzuki et al (3), but we do not know of any examination of the olfactory bulb and tract region in patients with Kallmann syndrome. Pathologically, absence of the olfactory bulbs and tracts with Kallmann syndrome has been described; however, there may be a variable degree of rudimentary olfactory apparatus present (4, 5). In this study, we sought to evaluate, using high-resolution surface coil MR two patients with Kallmann syndrome as part of a broader assessment of the olfactory bulbs and tracts in various pathologic entities. Because the olfactory bulb projects to regions of the amygdala and has tertiary projections to the hippocampus, we also analyzed the temporal lobe for volumetric changes.

Materials and Methods

Two patients with hypogonadotropic hypogonadism and congenital anosmia fulfilling the criteria of Kallmann syndrome were evaluated by the Smell and Taste Center of the Hospital and the University of Pennsylvania. These patients were administered the University of Pennsylvania Smell Identification Test and phenylethyl alcohol odor detection threshold tests to confirm anosmia (6). One patient was a 31-year-old black man with delayed puberty and oligospermia; the second patient was a 29-year-old white man with impotence and delayed puberty. The two patients were referred for MR scans to attempt to identify the olfactory bulbs and tracts, as well as to analyze the volume of the olfactory apparatus, the hippocampi, and

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the temporal lobes. In addition, seven healthy volunteers were studied in this protocol.

A 5-inch round general-purpose surface coil was positioned over the bridge of each patient's nose. The patients were then placed in a 1.5-T Signa GE (Milwaukee, WI) scanner for analysis of the olfactory bulbs and tracts. After a sagittal 500/20 localizing scan, coronal images 500/14/2 (repetition time/echo time/excitations) were taken at 3-mm contiguous intervals (Fig. 1). The field of view was 12 cm, and the matrix size was 256 × 256. The scans were prescribed from the frontal sinus to the sella turcica. Additionally, fast spin-echo 2000/18, 90/1 scans through the olfactory bulbs and tracts were performed with 3-mm contiguous sections and a 256 × 256 matrix.

The 5-inch round general-purpose coil was then removed from the patient's forehead, and scanning was performed with a standard quadrature head coil to evaluate the temporal lobes. After an initial sagittal 500/11/1 localizing image, coronal 600/11/1 scans through the temporal lobes were performed at 3-mm contiguous sections with a 256 × 256 matrix size. After this scan, a fast spin-echo 3000/90/1 axial scan through the entire brain was performed.

The T1-weighted 3-mm contiguous sections through the olfactory bulbs and tracts were analyzed in a quantitative volumetric analysis designed in-house (7). A tape of the study was loaded onto a SunSparc workstation, and the area of the olfactory bulbs and tracts was outlined on sequential sections using a track-ball system. The outlined anatomy was then subjected to a threshholding algorithm, so that only the olfactory bulbs and tracts and not the surrounding paranasal sinus air or cerebrospinal fluid were included. The binary data were interpolated by the computer program assuming a smooth surface of the bulbs and tracts. The volume of the outlined anatomy was then calculated by the computer assuming a geometric configuration. Anteriorly, the margin of the olfactory apparatus was identified superior to the ethmoid air cells; posteriorly, the tract eventually became indistinguishable from the gyrus rectus as it became the olfactory striae in the subcallosal gray matter.

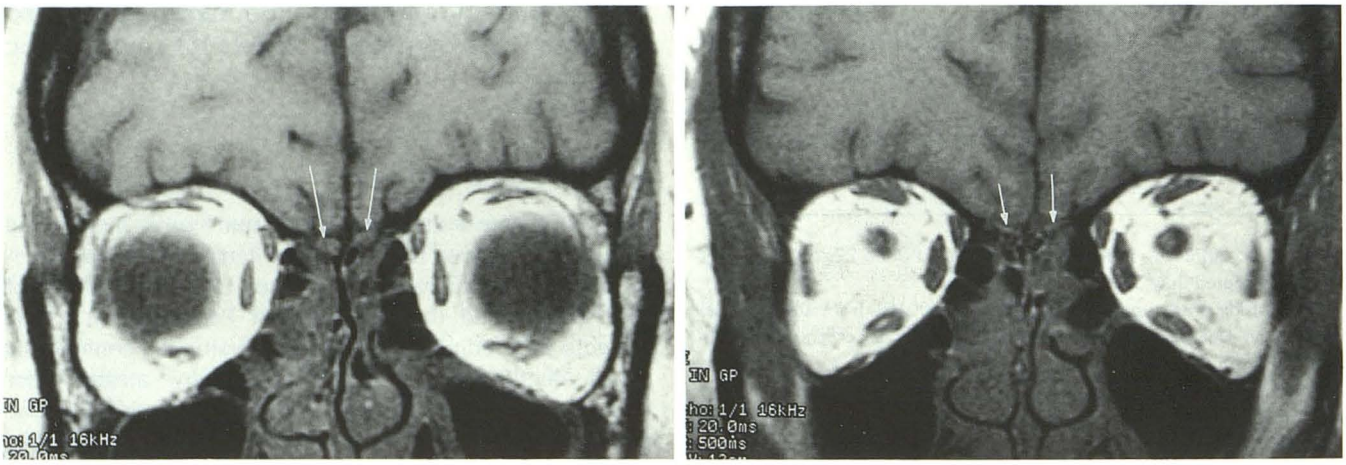
The 3-mm thick sections through the temporal lobes were also evaluated by similar steps to obtain the volume of the hippocampi and the temporal lobes. The posterior margin of the temporal lobe was identified as that point where the sylvian fissure was no longer distinguishable from the neighboring sulci in size, and the anterior border was the sphenoid wing. The superior margin used was the sylvian fissure; medially, the margin included the parahippocampus, but not deep gray matter, ventricle, or capsular white matter. The hippocampus was encircled by defining the choroidal fissure and/or ventricle superolaterally and the sulcus between the parahippocampus and hippocampus inferiorly. The medial border was the cerebrospinal fluid around the brain stem. The amygdala was included in the measurement, as it was not easily distinguishable from hippocampal gray matter.

Two physicians (W.J.D.T. and D.M.Y.) analyzed the data for volumes of the olfactory bulbs and tracts and temporal lobes. Interobserver error was calculated. On subsequent days, both investigators performed volumetric data analysis on the same structures to obtain intraobserver data.

Results

MR Findings

There was no readily discernible olfactory bulb or tract tissue in either case of Kallmann syndrome. In contrast, the seven healthy volunteers had readily identifiable olfactory bulbs and tracts; and mean bulb-tract values of 0.330 ± 0.076 cc. The signal intensity of the olfactory bulbs and tracts was normal in the volunteer subjects.



A B

Fig. 1. *A*, Coronal 500/14/2 scan through a healthy volunteer demonstrates the olfactory bulbs (*arrows*) situated along the cribriform plate.

B, A coronal scan further posteriorly in the control subject demonstrates the olfactory tracts (*arrows*). Incidental ethmoid sinusitis is present.

The olfactory sulcus lateral to the gyrus rectus of the brain was absent unilaterally in one patient (Fig. 2) with Kallmann syndrome and bilaterally (Fig. 3) in the other patient. In the seven volunteers, the gyrus rectus-olfactory sulcus regions were readily identifiable and well formed.

Quantitative analysis of the temporal lobes of the patients with Kallmann syndrome demonstrated no significant difference in the temporal lobe volume (228 ± 5.6 cc) compared with that in the healthy patients (233.47 ± 36.5 cc). These findings were duplicated in the hippocampal volumes (27.0 ± 0.9 cc vs 29.27 ± 4.0 cc).

Intraobserver error for defining temporal lobe volumes was 3% in one observer and 4.5% in the second reviewer. For the olfactory bulbs and tracts, the intraobserver variability was 10% and 23% for the two reviewers. Interobserver variance was 3% for temporal lobe volumes, but was 30% for olfactory bulbs and tracts. This is not unexpected with such small volumed structures as the bulbs and tracts.

No signal intensity abnormalities were visualized in the temporal lobes or hippocampi in the Kallmann syndrome patients.

Discussion

Kallmann described a familial occurrence of patients who failed to reach sexual maturity and had a lack of the sense of smell (1). Testicular biopsies have subsequently shown an arrest of spermatogenesis with fibrotic infiltration (5). The patients are completely anosmic by olfactory

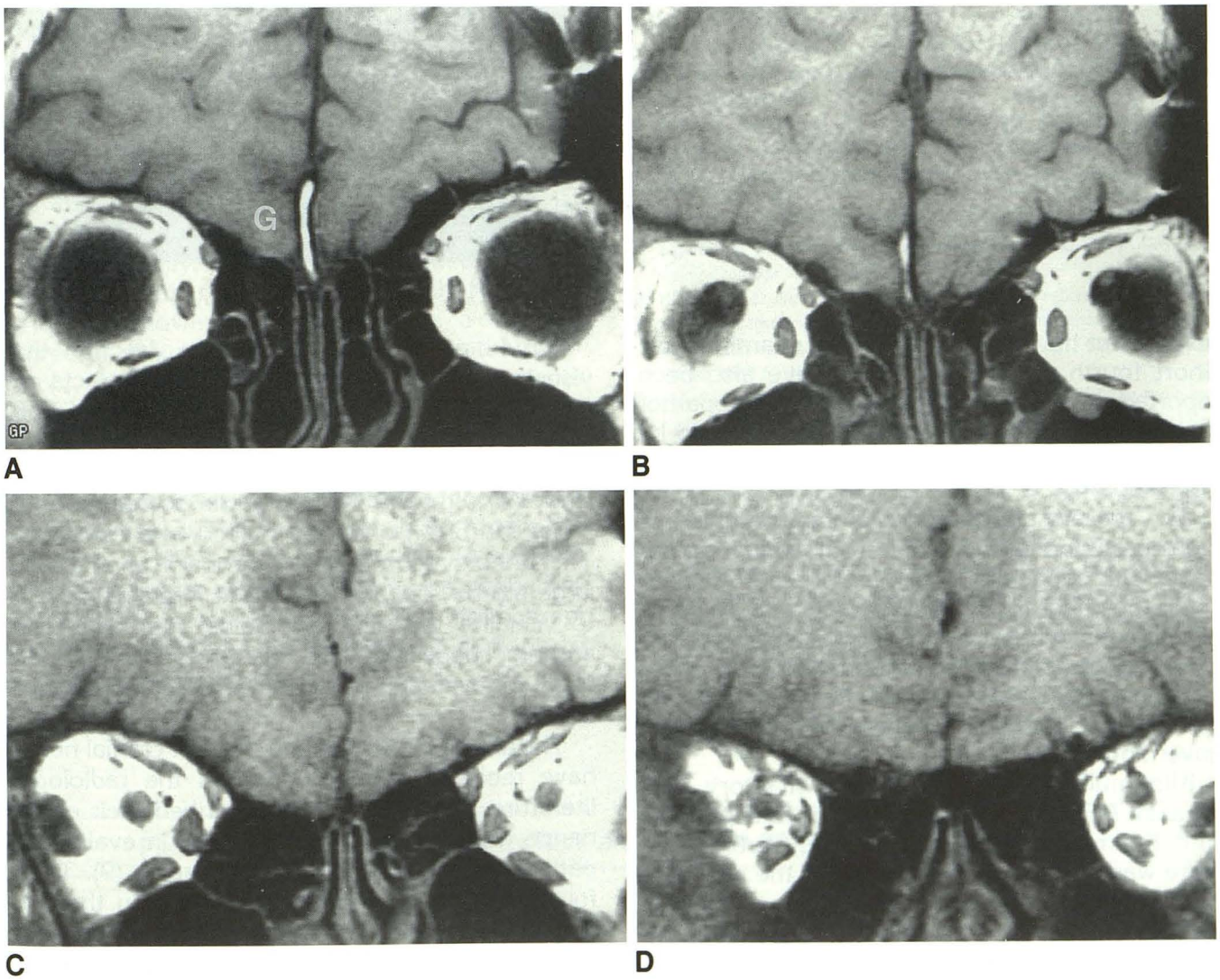


Fig. 2. *A–D*, Patient with Kallmann syndrome demonstrates absence of the olfactory bulbs and tracts with a flattened gyrus rectus (*G*) and no olfactory sulcus on the right side, but a normal-appearing gyrus rectus on the left side. (Figures proceed from anterior to posterior from *A* to *D*; 500/14.)

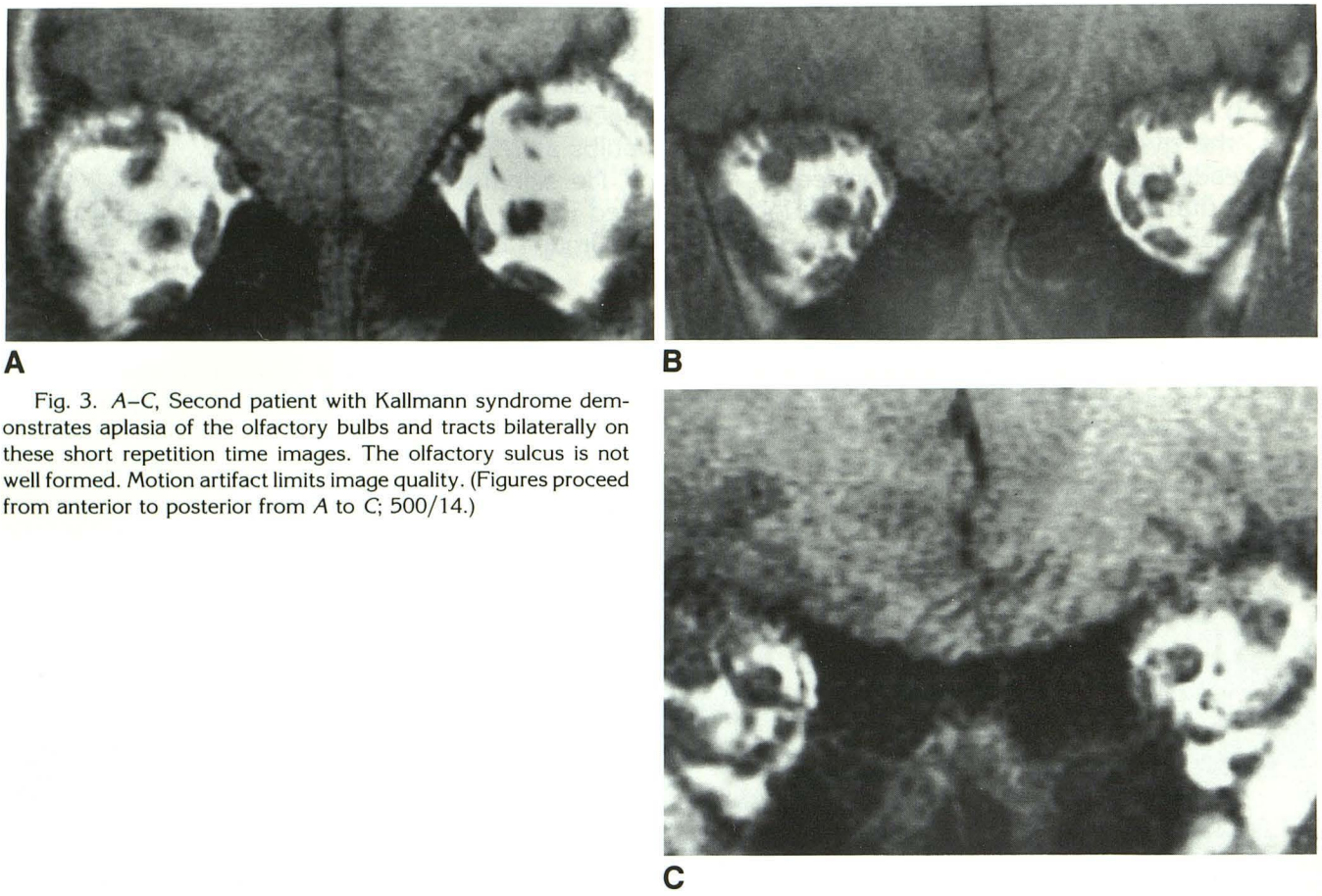


Fig. 3. *A–C*, Second patient with Kallmann syndrome demonstrates aplasia of the olfactory bulbs and tracts bilaterally on these short repetition time images. The olfactory sulcus is not well formed. Motion artifact limits image quality. (Figures proceed from anterior to posterior from *A* to *C*; 500/14.)

testing, but have normal intranasal examinations. Short fourth metacarpal bones have also been reported in Kallmann syndrome (5). Histopathologically, the pituitary glands are reported to be normal although the hypothalamus may be hypoplastic (4).

The present study demonstrates the utility of high-resolution surface-coil MR in evaluating patients with congenital anosmia. MR showed aplasia of the olfactory bulbs and tracts in both cases of Kallmann syndrome and showed normal olfactory structures in control volunteers. The olfactory nerve can be readily studied with MR and can yield a complete analysis of the anatomy governing olfaction.

Klingmuller et al evaluated the olfactory sulci on axial MR images of the brain in four patients with Kallmann syndrome (8). They found that there was absence or hypoplasia of the olfactory sulci of the frontal lobes, as seen on axial MR. However, they did not evaluate the patients' olfactory bulbs or tracts, possibly because of the low spatial resolution of the MR scanner. A surface coil was not employed to visualize the olfactory bulbs and tracts.

Suzuki et al were the first to describe the visualization of the olfactory bulbs and tracts on MR scans (3). They found that with 256 × 256 matrix scanning, visualization of the olfactory bulb was possible in 70 of 80 instances (87.5%). However with 256 × 128 matrix scanning, only 34 of 50 (68%) olfactory bulbs were visualized. The authors recommended coronal scanning with large matrix size and decreased intersection gap to visualize the olfactory bulbs optimally. The authors suggested that this protocol could be used to evaluate patients with Kallmann syndrome.

The olfactory system and the first cranial nerve have received little attention in the radiologic literature. Schellinger et al described their experience with computed tomography in evaluating patients with smell and taste disorders (9). They found that encephalomalacic change in the low frontal/gyrus rectus region and the temporal lobes was the most common finding in patients with olfactory deficits. These changes were most common in patients with posttraumatic (53% of patients) hyposmia. The yield by computed to-

mography in patients with congenital causes was very low.

The olfactory nerve has been largely ignored in imaging literature despite the association of numerous neurologic diseases with smell dysfunction, including Alzheimer disease, Parkinson disease, schizophrenia, Huntington chorea, and Korsakoff syndrome (10). Although there are a number of causes of anosmia, including posttraumatic, postinflammatory, degenerative disorders, neoplasms (olfactory groove meningiomas, olfactory neuroblastomas), and congenital etiologies (11), total aplasia of the olfactory bulbs and tracts is typically associated with Kallmann syndrome. There are other congenital disorders associated with decreased olfaction (12, 13), including holoprosencephaly, Down syndrome, Turner syndrome, and Riley-Day syndrome; however, complete absence of the olfactory bulbs and tracts has been well-documented only in Kallmann syndrome. These lists of disease entities associated with smell dysfunction are only partial; as smell and taste testing has become more widespread, the prevalence of lesions associated with hyposmia has increased. Smell is one of the least studied senses.

Pathologically, absence of the olfactory bulbs and tracts has been described with Kallmann syndrome; however, there may be a variable degree of rudimentary olfactory apparatus present (4, 5). Since the olfactory system projects fibers to the amygdala and hippocampus, we analyzed the temporal lobe for volumetric changes. Theoretically, without stimuli from the olfactory apparatus peripherally, hypoplasia of the hippocampus or temporal lobes might be expected. In fact, we found this not to be true, although a larger sample size may be needed to establish this point definitively. The hippocampi and temporal lobe volumes were analogous to those of control patients.

With a surface coil placed over the bridge of the nose and contiguous thin sections with large matrix sizes, the olfactory bulbs and tracts should always be seen in healthy patients. The absence thereof in association with congenital anosmia and hypothalamic hypogonadism supports the diagnosis of Kallmann syndrome.

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