Kallmann Syndrome: MR Findings

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PURPOSE: To evaluate patients with known hypogonadotropic hypogonadism, some with known anosmia, for defective rhinocephalon development that resulted in olfactory tract abnormalities, an affliction known as Kallmann syndrome. METHODS: Six patients who clinically had hypogonadotropic hypogonadism were examined by MR. Thin coronal images of the interior frontal region were used to determine presence or absence of olfactory tract and to evaluate the olfactory sulci. RESULTS: Olfactory tracts were not seen in three of the six cases; two of which had hypoplastic olfactory sulci. CONCLUSIONS: T1-weighted MR examination of the inferior frontal region in the coronal plane can help determine whether a patient with hypogonadotropic hypogonadism, with or without clinically evident anosmia, is afflicted with Kallmann syndrome.

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

Kallman syndrome is a form of congenital hypogonadotropic hypogonadism with accompanying hyposomia or anosmia (1). Its reported incidence is on the order of 1 in 10,000 men and 1 in 50,000 women (2). This disease is believed to be due to defective rhinocephalon development, which results in hypoplasia or absence of olfactory tract development (3). We used magnetic resonance (MR) imaging to visualize the olfactory tracts and to evaluate the olfactory sulci in patients with this abnormality.

Materials and Methods

We examined six patients who appeared clinically to have hypogonadotropic hypogonadism and anosmia, and had a family history of Kallmann syndrome. The standard examination included sagittal T1-weighted and axial double-echo T2-weighted images (for example, conventional spin-echo CSE 400/11 (repetition time/echo time) and 2500/30 and 80, respectively). However, an additional sequence was performed on each patient to evaluate the olfactory sulcus region further and to determine the presence of the olfactory tract. Three-millimeter section thickness with T1-weighted technique (for example CSE 800/12) images were obtained through the frontal lobe region (see Fig. 1). Scans were performed on a 1.5-T system. The images were evaluated by two neuroradiologists for the appearance of the olfactory sulci as well as visualization of the olfactory tracts (see Fig. 1). The coronal plane was chosen for evaluation because the structures of interest are well seen in this plane, and volume averaging, even with 3-mm section thickness, could not obscure them. As the authors were unaware of a standard of depth for the olfactory sulci, olfactory sulcus depth was compared with that of other sulci visualized in the same patient.

Results

The clinical and radiologic findings are displayed in Table 1.

Case 1

The patient presented at age 16 years with short stature and delayed puberty. He was the product of a difficult delivery and clinically had severe neonatal asphyxia. He also had severe hydrops and hyperbilirubinemia, presumed to be due to Rh incompatibility, requiring three exchange transfusions. As a child, he had delayed milestones, such as not walking or talking until 2 years of age, although it was not immediately clear whether this was related to his neonatal illnesses.
On presentation, his height was below the fifth percentile, and weight was between the tenth and twenty-fifth percentiles. His penis was small, and his scrotum undervirilized. He remained cryptorchid, although small testes (5 mm) were thought palpable in the inguinal canals. He was unable to perceive the odor of peppermint or lemon oil.

The patient was placed on monthly testosterone and synthetic thyroid hormone therapy and achieved full puberty after 4 years.

An MR examination of the brain was tailored to the inferior frontal lobes (Fig. 2). Hypoplastic and small olfactory sulci were noted. The olfactory tracts and bulbs were not seen. The pituitary gland was normal.

Case 2

The patient presented at 18 years of age with short stature and delayed puberty. His family history was notable for a maternal grandmother who had anosmia, which she thought due to chronic "sore throat." A maternal great uncle never developed puberty and had no children. A maternal aunt had a son with retardation, hypogonadism, anosmia, and an undefined renal affliction. Another maternal aunt bore a son with cryptorchism, hypogonadism, and mental retardation.

The patient's height and weight were below the fifth percentile for his age. His penis was
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

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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.)
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 $256 \times 256$ matrix scanning, visualization of the olfactory bulb was possible in 70 of 80 instances (87.5%). However with $256 \times 128$ 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.

References
in normal patients, visualization of the olfactory tracts. Hypoplasia of the olfactory sulci or non-visualization of the olfactory tracts along with the clinical findings of hypogonadotropic hypogonadism, anosmia, or heredity (family history of Kallmann syndrome) is consistent with the presence of Kallmann syndrome.

Acknowledgments

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