MR Evaluation of Patients with Congenital Hyposmia or Anosmia

OBJECTIVE. The purpose of this study was to evaluate patients with reduced or no sense of smell since birth for sites of abnormality by MR imaging.

MATERIALS AND METHODS. Twenty-five patients who reported no olfactory function since birth were evaluated by olfactory testing, sinonasal endoscopy, and MR imaging. Surface coil and head coil images of the olfactory bulbs, olfactory tracts, subfrontal cortex, and temporal lobes in contiguous 3-mm sections were obtained. Two reviewers determined unilateral olfactory bulb and tract volumes and temporal lobe volumes in two separate sessions. Qualitative grading for olfactory bulb, olfactory tract, olfactory sulcus, subfrontal region, hippocampus, and temporal lobe damage also was performed.

RESULTS. The absence of olfactory bulbs and tracts (68–84%) or the presence of hypoplasia (16–32%) was noted in all cases. Eight individuals had Kallmann’s syndrome (hypogonadotropic hypogonadism with anosmia). Temporal and/or frontal lobe volume loss was noted in five individuals and was mild in all but one individual.

CONCLUSION. Congenital anosmia or hyposmia appears to be an olfactory bulb–olfactory tract phenomenon rather than a cerebral process.

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Congenital anosmia is said to exist when a patient has no recall of smell sensation dating from early childhood. Some patients report a reduced sense of smell since birth (congenital hyposmia); others who claim to have no sense of smell may show some residual function on laboratory testing. Although the causes of early anosmia or hyposmia may include viral infections, posttraumatic injury to the olfactory epithelium, choanal atresia, or Kallmann’s syndrome (hypogonadotropic hypogonadism with anosmia) [1], studies conducted by Jafek et al. [2] and Leopold et al. [3] suggest that congenital anosmia usually does not occur in association with other anomalies.

Imaging of patients who have congenital anosmia has been limited to a few series of patients with Kallmann’s syndrome [4–8]. These studies usually were performed with CT scanning or head coil MR imaging. Others included a smaller field of view and surface coil MR imaging to optimally visualize the olfactory bulbs and tracts [8].

We evaluated 25 patients who reported no recollection of smell sensation. Using both surface coil and head coil MR images, we examined the olfactory bulbs, olfactory tracts, temporal lobes, frontal lobes, and hippocampal regions both quantitatively and qualitatively for sites of abnormalities. These structures of the brain have been shown to modulate the sense of smell in animal and human models. Our goal was to determine whether patients with congenital hyposmia or anosmia lack the morphologic apparatus for smell or whether the problem is a functional abnormality resulting from damaged, nonfunctional tissue.
Materials and Methods

Twenty-five patients with complaints of no sense of smell since childhood were referred to the University of Pennsylvania Smell and Taste Center. These patients underwent extensive review of their clinical histories to exclude the possibility of childhood head trauma or major respiratory tract infections (requiring hospitalization). Intracranial infections, including meningitis and encephalitis, also were considered as possible etiologies for the congenital anosmia. Only patients who had no definite etiology for their smell dysfunction were included in this study. Patients who reported no ability to smell in their daily life but who did show residual olfactory function on smell testing were included and are referred to as congenitally "hyposmic."

The 25 patients included 14 men and 11 women who were 11–68 years old (mean, 29.8 years old). All patients underwent bilateral smell testing with occlusive tape on the nares opposite from the tested side. The olfactory tests included the following: (1) the University of Pennsylvania Smell Identification Test (UPSIT) (20 items for each side), (2) a 16-item odor discrimination test, (3) a 12-item odor memory test (with retention intervals of 0, 30, and 60 sec), and (4) a single-staircase odor detection threshold test with the odorant phe- nylethyl alcohol [9–12]. We administered the 40-item Picture Identification Test (PIT) and the 30-item Mini-Mental Status Examination to ensure that the patients had the cognitive capacity to perform the smell tests reliably [13, 14]. The pictures used in the PIT are of the sources of the smells that are used in the scratch-and-sniff UPSIT (i.e., on the PIT a picture of a peanut is shown to ensure that the patient knows the word "peanut" for when the peanut odor is presented on the UPSIT).

The patients also underwent sinonasal endoscopy to exclude obstructive (e.g., polyps or choanal atresia) or inflammatory (e.g., active sinusitis or polyposis) causes for the smell dysfunction. All patients included in this study passed the Mini-Mental Status Examination, PIT, and sinonasal endoscopy examination; no significant abnormalities were found.

All individuals also signed an informed-consent form regarding this study, which was approved by our institutional review board.

The MR examination consisted of a surface coil evaluation (with a 5-inch [-13-cm] round general-purpose coil) of the olfactory bulbs and tracts and the coil centered on the nasion. After a sagittal localizing scan, coronal T1-weighted images with a TR of 500 msec, a TE of 15 msec, and two excitations were obtained with 3-mm interleaved scans (no interslice gaps), a 12-mm field of view, and a matrix of 256 × 256. These coronal T1-weighted scans were used in the quantitative evaluation of the olfactory bulbs and tracts. Three-millimeter interleaved coronal fast spin-echo T2-weighted scans through the olfactory bulbs and tracts were performed with a long TR (2000/ 84/2), a matrix of 256 × 192, and a 12-mm field of view. These coronal fast spin-echo T2-weighted scans were used to assess signal intensity abnormalities within the olfactory bulbs and tracts.

A head coil examination of the brain also was performed. The head coil examination included a sagittal localizing scan and 3-mm interleaved coronal T1-weighted scans (600/11/1) with a 25-cm field of view and a matrix of 256 × 256. These scans were followed by 5-mm interleaved axial fast spin-echo T2-weighted scans (4000/80/1) of the entire brain. The coronal T1-weighted scans through the temporal lobes were used for volumetric assessment of the temporal lobes.

Volumetric analyses of the right and left olfactory bulbs and tracts and of the temporal lobes were performed by two independent evaluators using coronal T1-weighted images on two occasions at least 1 week apart. The volumetric analyses were performed on an ISG Technologies (Toronto, Ontario, Canada) workstation and required threshold determinations, tracing, and three-dimensional volumetric processing. To assess inter- and intraobserver reliabilities, intraclass correlation coefficients were determined for pairs of readings by individual readers and between readers for right and left temporal lobe volumes and for right and left olfactory bulb and tract volumes.

The most experienced reviewer performed a qualitative grading of the right and left olfactory bulbs, right and left olfactory tracts, right and left olfactory sulci, right and left temporal lobes, and right and left parahippocampal regions using a scale from 0 to 4: 0 was assigned when no volume loss or damage to the aforementioned structures was present; 1, 2, and 3, respectively, were used for minimal, moderate, and marked volume losses or damage to the olfactory structures; and 4 was assigned when these structures were absent. This analysis was performed on two occasions 3 months apart for intraobserver variability. The grading of these regions of the anatomy was based on an analysis of both T1- and T2-weighted scans through the anatomy. During this review, an assessment of the possibility that material at the olfactory placode had not differentiated or migrated was made.

A phantom was used to confirm the accuracy of the volumetric technique. This model was scanned on four separate occasions with the same scan sequences and four different slice locations. The MR images of this phantom were evaluated by two individuals on two occasions to assess inter- and intraobserver variabilities. The true volumes of the phantom contents were measured by use of a water displacement technique with a graduated cylinder designed for this purpose.

Results

Smell Testing

On the basis of norms provided by previous work on normal individuals [10], 22 of 25 patients were anosmic, having scored 19 or less out of 40 items (20 for each side) on the UPSIT. Three patients demonstrated borderline function. In one instance of a craniofacial anomaly, the UPSIT scoring indicated borderline function on the right side but anosmia on the left side. The other two individuals who were able to smell did not have asymmetry in their olfactory function but had severe deficits (UPSIT score <23/40).

Imaging Findings

The most common MR finding for the 25 individuals with congenital anosmia or hyposmia was complete absence of the olfactory bulbs (n = 21, 84%), which occurred bilaterally in all instances. The olfactory tract was absent on the right side in 19 patients (76%) and on the left side in 18 patients (72%) (Fig. 1). In five cases, there was evidence of a tract without a bulb (two on the right and three on the left), but in no case was a bulb present without a tract. In four patients, both the olfactory bulbs and the olfactory tracts were visible, although the bulbs and/or tracts were hypoplastic (Fig. 2). Olfactory sulci were absent bilaterally in nine patients, unilaterally on the right in four patients, and unilaterally on the left in one patient. In 18 instances (out of 50 possible), a bulb was absent but an olfactory sulcus was present, and in no instance was an olfactory sulcus absent but a bulb present.

In the individual who had borderline function on the right side and anosmia on the left side, the olfactory tracts were normal, but moderate volume loss in the right olfactory bulb and marked volume loss in the left olfactory bulb were noted.


In the two remaining individuals with residual olfactory function, the olfactory bulbs were absent bilaterally; one individual had no olfactory tracts, and the other had moderate volume loss in the olfactory tracts.

Of the 25 patients, eight (32%) had definite Kallmann's syndrome (diagnosed based on endocrinologic and genetic testing); in all eight, the olfactory bulbs and tracts were absent. Olfactory sulci were absent bilaterally in two and unilaterally in two of these patients with Kallmann's syndrome. No abnormalities in T2-weighted signal intensity were identified in the anatomic regions evaluated in the patients with Kallmann's syndrome and in the other patients. Mild to moderate volume loss was noted in the temporal lobes in five patients, the frontal lobes in three patients, and the hippocampi in four patients.

The regions around the cribriform plate were assessed for the possibility that neuronal tissue had not differentiated to form the olfactory bulbs (a neuronal migrational anomaly). Some soft tissue in the cribriform plate regions was present in three of 25 individuals, but it was unclear what this tissue represented.

Reliability Data

The intraclass correlation values determined for the volumes of each structure by the two readers and the two sets of double readings made by each reader fell between 0.86 and 0.96, signifying outstanding agreement (same scale as
that used as for kappa tests). The mean left and right temporo-labral lobe volumes were 68,892 (standard deviation = 10,107) and 68,273 (standard deviation = 9,117) mm³, respectively, for all patients. The mean olfactory bulb and tract volumes were dominated by the large number of completely absent bulbs and tracts (18 patients). For patients with hypoplastic bulbs and tracts, the mean volumes were 18.6 mm³ on the right and 11.6 mm³ on the left.

With regard to qualitative grading of the olfactory regions, there was complete agreement on the presence or absence of the bulbs, tracts, and sulci. In two of 150 gradings of the olfactory bulbs, tracts, and sulci, the reader assigned different grades on the first and second readings; in both cases, this difference involved mild versus moderate volume losses. In 23 of 150 gradings, there was a disagreement in the grades of volume loss in the inferior frontal, temporal, or hippocampal regions; all of these were variations in one grade (i.e., none to mild, mild to moderate, or moderate to severe volume loss). Overall, the agreement rate was 275/300 gradings, or 92%.

**Phantom Data**

The maximum variations in volume measured at four different slice locations ranged from 0.9% to 4.8% for the three structures measured in the phantom. The interobserver variability between the two reviewers of the phantom ranged from 0.1% to 3.7%. The volumes calculated from ISG Technologies data differed from those determined by the water displacement method by 6.3–7.0% for the three items in the phantom.

**Discussion**

The questions central to the imaging of patients with congenital hyposmia or anosmia are the presence or absence of the olfactory apparatus and/or the presence or absence of other craniofacial abnormalities. Smell testing, physical examination, and nasal endoscopy cannot completely determine the anatomic cause of congenital olfactory loss. Imaging of the olfactory system initially was done with CT [15]. Most of these CT examinations were studies of patients with a history of head trauma or postinflammatory loss of sense of smell. Unfortunately, because of beam-hardening artifacts at the skull base, visualization of the olfactory bulbs and tracts is limited with CT.

In contrast, MR imaging is not affected by beam-hardening artifacts and provides an excellent view of the olfactory bulbs and tracts as well as the rest of the olfactory system within the brain. The olfactory system can best be evaluated for abnormalities through the use of both a T1-weighted sequence for volumetric analysis and a T2-weighted sequence for identification of areas of damage to the olfactory system.

Vogt et al. [7] documented the ability of MR imaging to demonstrate abnormalities of the olfactory pathway in patients with congenital anosmia. They were able to identify normal anatomy in their control group of six subjects. Eighteen patients diagnosed with Kallmann's syndrome and 10 patients diagnosed with idiopathic hypogonadotropic hypogonadism were included in that study, which was done with a head coil. In 17 of the 18 patients with Kallmann's syndrome, the olfactory bulbs and tracts were absent; eight of these 18 individuals had normal olfactory sulci. Olfactory bulbs and tracts were present in the 10 patients with idiopathic hypogonadotropic hypogonadism, although some degree of hypoplasia was noted in three patients. In other studies of patients with Kallmann's syndrome, complete absence or hypoplasia of the olfactory bulbs and tracts was the predominant finding [4–8]. The olfactory sulci were variably aplastic, hypoplastic, or normal [4–8]. The hypothalamus and pituitary gland were normal [5, 8]. An MR imaging assessment of patients who have congenital anosmia but who do not have Kallmann's syndrome has not been performed until this study.

We found either complete absence or hypoplasia of the olfactory bulbs and/or tracts in our patient population, suggesting that various degrees of differentiation of tissue from the olfactory placode through the cribriform plate could account for the variable amounts of olfactory bulbs and/or tracts identified. In no individual did we identify an abnormal signal intensity suggesting damage or demyelination of olfactory system structures.

Most patients with congenital anosmia have the finding as an isolated abnormality. In a study by Leopold et al. [3] of 22 individuals who had no recollection of smelling anything, two patients had choanal narrowing and one had Kallmann's syndrome, but most were normal clinically, except for the anosmia. Intracranial CT scans were unremarkable.

Kallmann's syndrome was first described in 1944 [1] and has been the focus of a number of clinical, genetic, and pathologic studies. The disorder appears to be found most commonly as an X-linked disorder but can be inherited through autosomal transmission as well [16]. Patients are eunuchoid and may have coexistent renal anomalies, cleft lips or palates, infertility, spastic paraplegia, cerebellar dysfunction, nystagmus, or hearing loss [16, 17]. Although most initial reports noted the absence of demonstrable olfactory bulbs and tracts in Kallmann's syndrome macroscopically [1, 18], the presence or absence of olfactory neuroepithelium in patients with congenital anosmia and/or Kallmann's syndrome is still being debated. Gauthier [18] and Moran et al. [19] have reported complete absence of olfactory epithelium in Kallmann's syndrome patients; others have claimed that these series suffered from sampling error. Sparse deranged olfactory epithelium seems to be present in at least some of these patients. Schwob et al. [20] and Leopold et al. [3] found olfactory neurons that had lost their cilia, had reduced numbers of axons, and had disordered neuroromatous collections within the epithelium in patients with Kallmann's syndrome. Thus, two camps have developed—those that believe that Kallmann's syndrome patients have no epithelium and those that believe that the olfactory axons simply fail to reach the prosencephalon and hence do not connect intracranially. The hypogonadism of Kallmann's syndrome is thought to be attributable either to a lack of cells that can express luteinizing hormone-releasing hormone or to abnormal migration of the luteinizing hormone-releasing hormone neurons from the olfactory placode in the nose to the hypothalamus [3, 21]. Truwit et al. [6] support the neuronal migrational anomaly theory. They
believe that soft tissue revealed by MR imaging in the region below the expected location of the olfactory bulbs represents arrested neurons. We saw suspicious tissue in this region in only three of our 25 patients and do not believe that this is a common finding, if it is valid at all.

In terms of patient management, there is little to offer the patient who has congenital hyposmia or anosmia. MR imaging usually can definitively answer questions regarding possible restoration of the sense of smell by revealing a complete absence of the means to regain olfaction, but even in individuals who have hypoplastic olfactory bulbs and tracts, the likelihood of restoration of function is slight. In our extensive experience with normal controls [8], none had hypoplastic or absent olfactory bulbs or tracts.

MR imaging may provide information that can save the patient from spending time and resources searching for possible treatment options. In addition, MR imaging may be able to detect alternative causes for olfactory dysfunction, including meningiomas along the cribiform plate, posttraumatic injury, extraaxial collections, and other sinonasal masses that may affect olfactory function.

REFERENCES
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