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# MR Imaging of Kallmann Syndrome, a Genetic Disorder of Neuronal Migration Affecting the Olfactory and Genital Systems

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**PURPOSE:** We report the MR findings in nine patients with clinical and laboratory evidence of Kallmann syndrome (KS), a genetic disorder of olfactory and gonadal development. In patients with KS, cells that normally express luteinizing hormone-releasing hormone fail to migrate from the medial olfactory placode along the terminalis nerves into the forebrain. In addition, failed neuronal migration from the lateral olfactory placode along the olfactory fila to the forebrain results in aplasia or hypoplasia of the olfactory bulbs and tracts. Patients with KS, therefore, suffer both reproductive and olfactory dysfunction. **METHODS:** Nine patients with KS underwent direct coronal MR of their olfactory regions in order to assess the olfactory sulci, bulbs, and tracts. A 10th patient had MR findings of KS, although the diagnosis is not yet confirmed by laboratory tests. **RESULTS:** Abnormalities of the olfactory system were identified in all patients. In particular, the anterior portions of the olfactory sulci were uniformly hypoplastic. The olfactory bulbs and tracts appeared hypoplastic or aplastic in all patients in whom the bulb/tract region was satisfactorily imaged. In two (possibly three) patients, prominent soft tissue in the region of the bulbs suggests radiographic evidence of neurons that have been arrested before migration. **CONCLUSIONS:** Previous investigators of patients with KS used axial MR images to demonstrate hypoplasia of the olfactory sulci but offered no assessment of the olfactory bulbs. In the present study we used coronal images to show hypoplasia of both olfactory sulci and bulbs. In addition, we found what we believe to be the radiologic correlate of arrested neuronal migration in KS.

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

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Kallmann syndrome (KS) is a genetic disorder of neuronal migration in which cells that normally express luteinizing hormone-releasing hormone (LHRH) fail to migrate from the medial olfactory placode into the forebrain (1). In addition, projections from the lateral olfactory placode to the

forebrain are insufficient to induce formation of the olfactory bulbs adequately. KS is clinically characterized by isolated hypogonadotropic hypogonadism and anosmia or hyposmia (1, 2). Although most commonly seen in men, occasional cases in women have been reported (3). Transmission of KS can occur according to autosomal dominant, autosomal recessive, or X-linked patterns (1). Moreover, a specific gene on the X-chromosome recently has been isolated and appears to involve not only neuronal migration of the olfactory placode but also specific "proteins involved in neural cell adhesion and axonal path-finding" (4).

Before the era of magnetic resonance (MR), the diagnosis of KS required clinical and laboratory verification. With the extraordinary anatomic resolution afforded by MR, however, the olfactory system and, in particular, abnormalities of KS now can be successfully shown (3, 5, 6). Previous investigators of MR imaging in KS have used

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axial images to demonstrate hypoplasia of the olfactory sulci. Volume averaging in the axial plane, however, may potentially result in over- or underestimation of the olfactory sulci. In addition, assessment of the olfactory bulbs is difficult with axial images (6). We report the use of coronal images to evaluate both the olfactory sulci and bulbs in nine patients with clinical and laboratory evidence of KS.

## Materials and Methods

### *Clinical and Laboratory Assessment*

Nine patients, 3 to 28 years of age, were included in the study. All patients had complete clinical and laboratory studies. Eight patients had been evaluated before MR imaging (7) and satisfied accepted criteria for the diagnosis of KS (7). All eight were reportedly anosmic at the time of their original evaluations. Because more current smell testing has not been performed on these patients, it is possible that subtle degrees of hyposmia might be revealed. Several of the patients have been previously reported in endocrinologic studies of KS (7). The ninth patient was studied separately from the first eight patients. That patient is remarkable for asymmetric hyposmia, as tested by Pennsylvania smell test. On the left, the patient was moderately hyposmic; mild hyposmia was noted on the right. Complete endocrinologic studies and genetic analysis were performed. At birth, hypospadias was noted; KS was diagnosed 29 years later. A 10th patient, 3 weeks of age, is also included; at birth, physical examination revealed arhinia, microphthalmia, micrognathia, microphallus, and unidentifiable testes. MR was obtained to check for other midline abnormalities and to evaluate the hypothalamus and pituitary. (KS was not suspected.) Although that patient's diagnosis of KS is not yet confirmed, the clinical and MR findings are very suggestive of KS. We include this case because it may represent a prospectively diagnosed case of KS.

### *Radiologic Assessment*

MR imaging was performed at 1.5 T in eight patients and at 0.35 T in two patients. All studies included coronal T1-weighted images (600/30/1–2, repetition time/echo time/excitations) from the back of the frontal sinus through the hypothalamus. Spin-echo images were obtained at 3-mm thickness with 0.5-mm intersection gap in all cases except one, in which contiguous, 3-mm radiofrequency-spoiled gradient-recalled echo images were obtained. In addition, sagittal T1-weighted images (600/20–30) were obtained on all patients. Images were interpreted with knowledge of the diagnosis of KS, except in the 3-week-old infant. The olfactory sulci, tracts, and bulbs were assessed as normal, hypoplastic, or aplastic. The sulci were subjectively divided into anterior and posterior portions. Unfortunately, as slight differences in the angulation of the

scans were apparent, it was impossible to identify systematically a transition point from anterior to posterior. The first few sections posterior to the crista galli were considered anterior, and the sections toward the posterior portion of the subfrontal region were considered posterior. The tracts and bulbs could not be reliably distinguished from each other. As a result, the bulb/tract complex was assessed. Because the olfactory nerves themselves cannot be identified consistently in the healthy patient, we were unable to identify them reliably in the patients with KS. (The olfactory nerve is the true cranial nerve portion of the olfactory complex, extending from the bulbs to the olfactory neuroepithelium in the infracribriform region.) The hypothalamus and pituitary gland were assessed as normal or abnormal (that is, hypoplastic). The images of four healthy patients (imaged for reasons unrelated to the olfactory or hypothalamic-pituitary regions) were reviewed for comparison (Fig 1). MR sequences were similar to those used in the patients with KS, and the same structures were evaluated in the healthy patients. In addition, anatomic human fetal specimens of 57 mm, 100 mm, and 137 mm crown-rump length, with ages estimated to be 10, 14, and 16 weeks gestation, respectively, were imaged using three-dimensional radiofrequency-spoiled gradient-recalled echo sequences (35/5, 30° flip angle) at 0.9 to 1.1 mm thickness.

## Results

All images obtained at 1.5 T were adequate for review. In one patient (case 4), however, we inadvertently failed to include the anterior olfactory sulci, bulbs, and tracts in the coronal images. In one (case 5) of the two patients imaged at 0.35 T, the sulci could be evaluated, although the tracts and bulbs were not properly resolved.

As noted in Table 1, abnormalities of the olfactory sulci were apparent in all nine patients, in whom the diagnosis of KS was known. Specifically, three patients with KS demonstrated bilateral aplasia of the anterior olfactory sulci (Fig 2). Rudimentary anterior sulci were detected in four patients. In five patients, the posterior olfactory sulci appeared hypoplastic, and in three patients the posterior sulci appeared normal. The olfactory bulbs and tracts appeared hypoplastic in five patients (Fig 3) and absent in one. In two patients, prominent soft tissue masses were noted where the bulb/tract complex should have been (Figs 2 and 4). No tracts were seen posterior to these masses. In patient 9 (Fig 4) there was remarkable asymmetry. On the left, the olfactory sulcus was absent anteriorly and hypoplastic posteriorly. On the right, the sulcus was hypoplastic anteriorly, yet normal posteriorly. A hypoplastic olfactory bulb/tract complex was seen on the right. On the left, neither the bulb nor the tract could be identified. There was a suggestion of a soft tissue mass in the cribriform and immediate supracribriform region, although it was not as distinct as in the other two cases. In the 3-week-old child (Fig 5), the posterior olfactory sulci appeared normal, whereas the anterior olfactory sulci and the olfactory bulbs and tracts were not present.

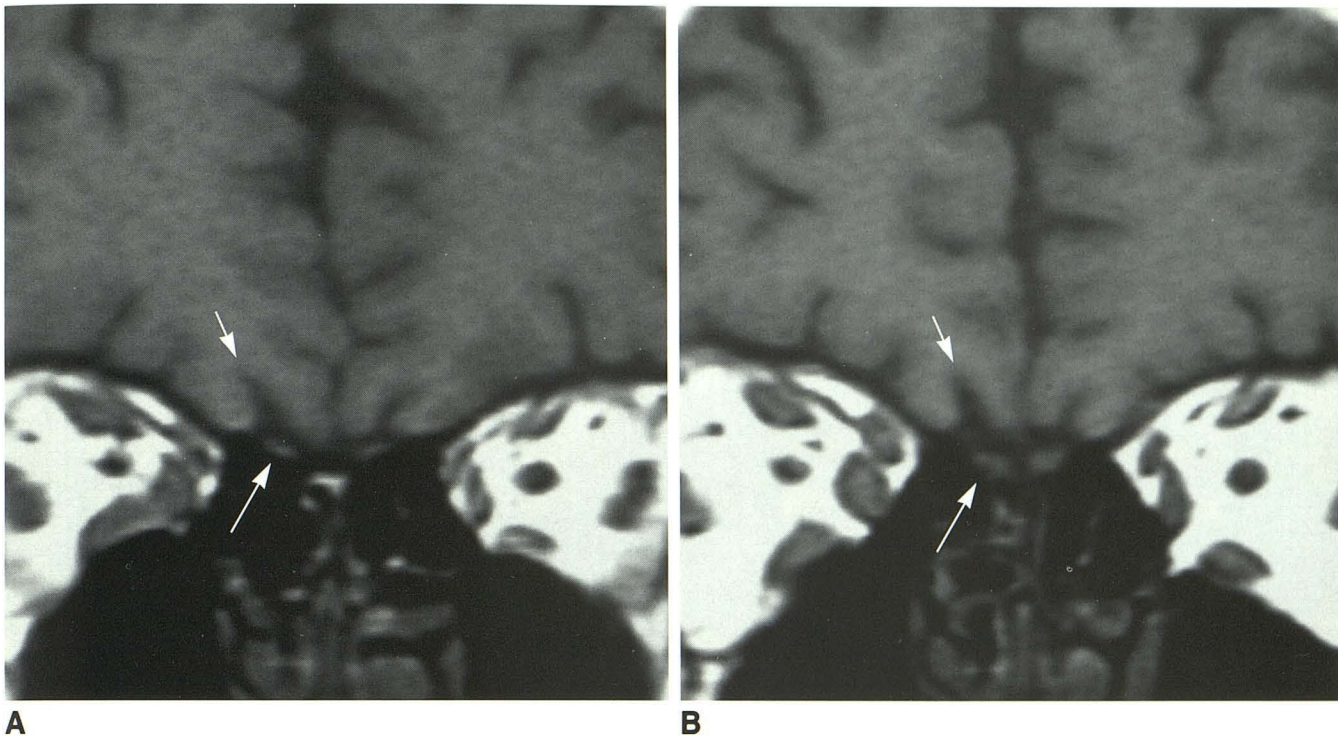


Fig. 1. Coronal T1-weighted images (600/12) in a normal patient without olfactory or endocrine disturbances show normal olfactory sulci (*small arrows*) and olfactory tract/bulb complexes (*arrows*). Although tracts (A) can be distinguished from bulbs (B) in this patient, this is not consistently defined in all patients.

TABLE 1: MR findings of patients with KS

Patient	Age (years)	Sex	Olfactory Sulci		Olfactory Bulbs/Tracts	Hypothalamus	Anterior Pituitary	Other
			Anterior	Posterior				
1	29	M	Hypoplastic	Normal	Hypoplastic	Normal	Normal	
2	18	M	Absent	Hypoplastic	Absent	Normal	Normal	Dysplastic tangles
3	18	M	Absent	Hypoplastic	Hypoplastic	Normal	Normal	
4	17	M	Not visualized	Normal	Not visualized	Normal	Normal	
5	19	M <sup>a</sup>	Hypoplastic	Normal	Not visualized	Normal	Normal	
6	3	M <sup>b</sup>	Absent	Hypoplastic	Hypoplastic	Normal	Small	
7	8	M <sup>a</sup>	Hypoplastic	Hypoplastic	Hypoplastic	Normal	Normal	
8	20	M	Hypoplastic	Hypoplastic	Hypoplastic	Normal	Normal	Dysplastic tangles
9	29	M	Absent left	Hypoplastic left	Absent left	Normal	Normal	? Dysplastic tangle on left
10	3 weeks	M	Hypoplastic right	Normal right	Hypoplastic right	Normal	Small	
			Absent	Hypoplastic	Absent	Normal	Small	

<sup>a</sup> X-Linked by pedigree analysis; patients 5 and 7 are second and third boys in family of four boys, all affected with KS. Imaging declined by oldest child and not performed in youngest child.

<sup>b</sup> X-Linked by pedigree analysis; on mother's side, one second cousin (male) and two second cousins (brothers).

The hypothalamus appeared normal in all patients. The pituitary gland appeared normal in all patients except one. In that patient, the adenohypophysis appeared hypoplastic, as it did in the 3-week-old infant.

The olfactory systems appeared normal in the four patients imaged for reasons unrelated to the olfactory or hypothalamic and pituitary systems (Fig 1). Specifically, the olfactory sulci and bulbs and tracts were easily seen. The sulci appeared symmetrical and well formed. The bulbs and tracts were consistently identified, starting one or two images posterior to the crista galli and extending the length

of the optic nerves. The developing olfactory system was well visualized in the three fetal specimens (Fig 6).

## Discussion

The association of olfactory and genital abnormalities was noted in postmortem studies by Maestre de San Juan in 1856 and again by Weidenreich in 1914 (8). In 1944, Kallmann et al described a syndrome in 11 patients in three

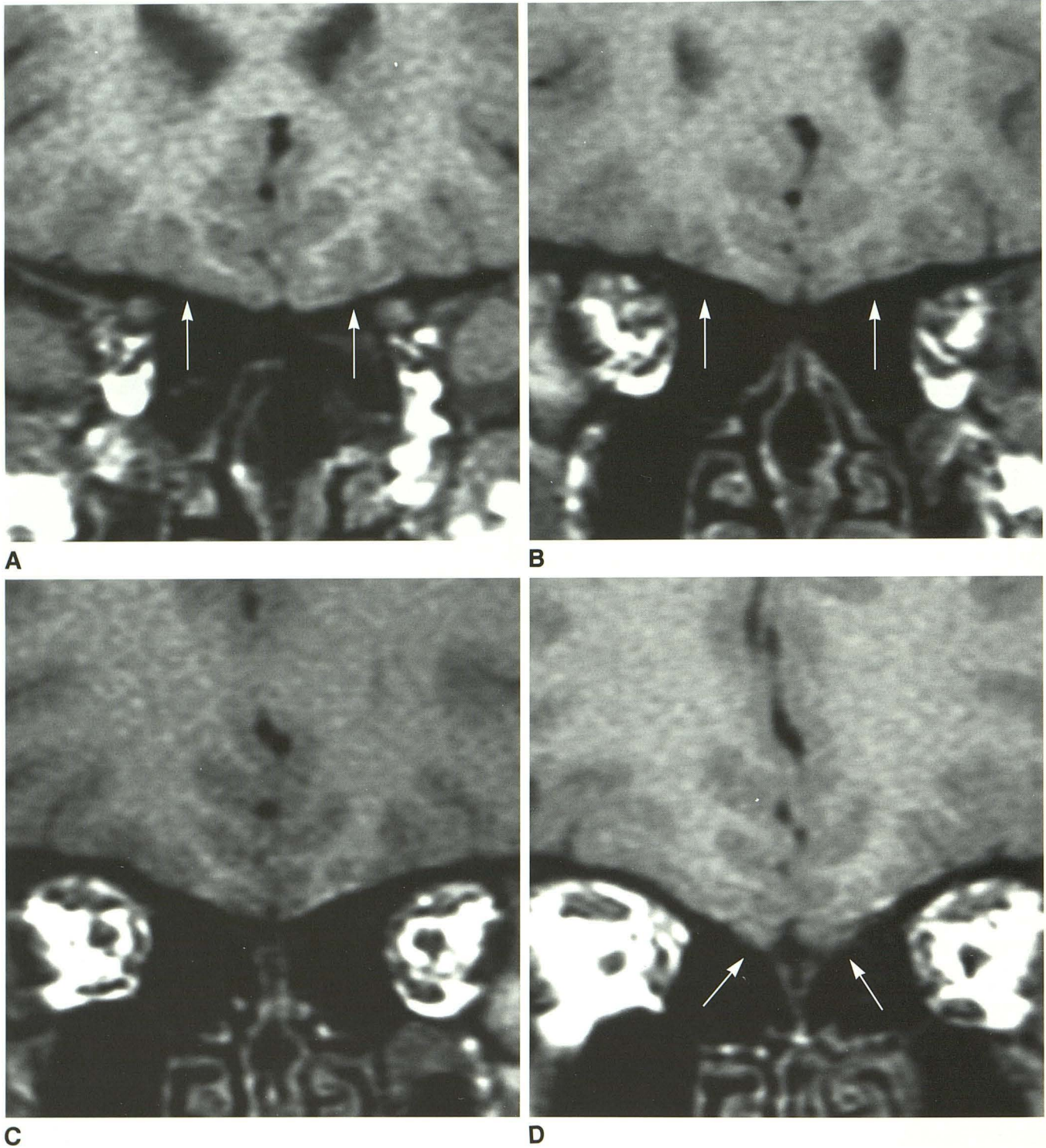


Fig. 2. Coronal T1-weighted images (600/12) from posterior to anterior in patient with KS show hypoplasia of posterior olfactory sulci (*arrows in A and B*), absence of olfactory tracts, aplasia of anterior olfactory sulci (*C and D*), and prominent soft tissue beneath forebrain, embedded in cribriform plate (*arrows in D*). These soft-tissue nodules may represent disordered neuronal migration from olfactory placodes.

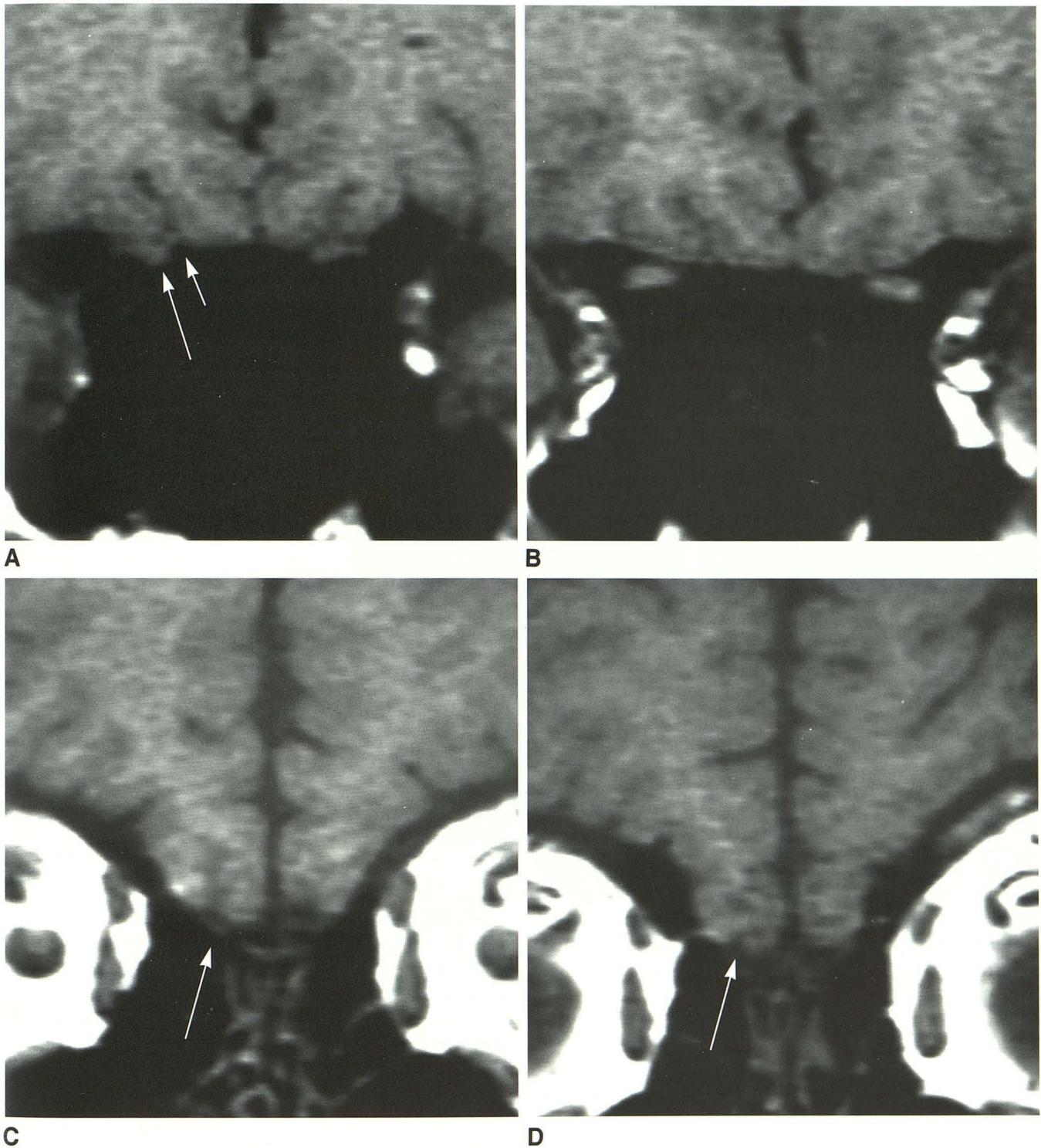


Fig. 3. Coronal T1-weighted images (750/12) of a 29-year-old man with KS reveal essentially normal posterior olfactory sulci (A and B) and mildly hypoplastic anterior olfactory sulci (C). The right olfactory tract is barely visualized (*small arrow*) at the base of the olfactory sulcus and just above the right optic nerve (*large arrow*). More anteriorly, no bulbs or tracts were seen on the left, whereas a small bulb/tract complex was noted on the right (*arrow* in C). The patient is hyposmic and, with hormone replacement, has fathered a child.

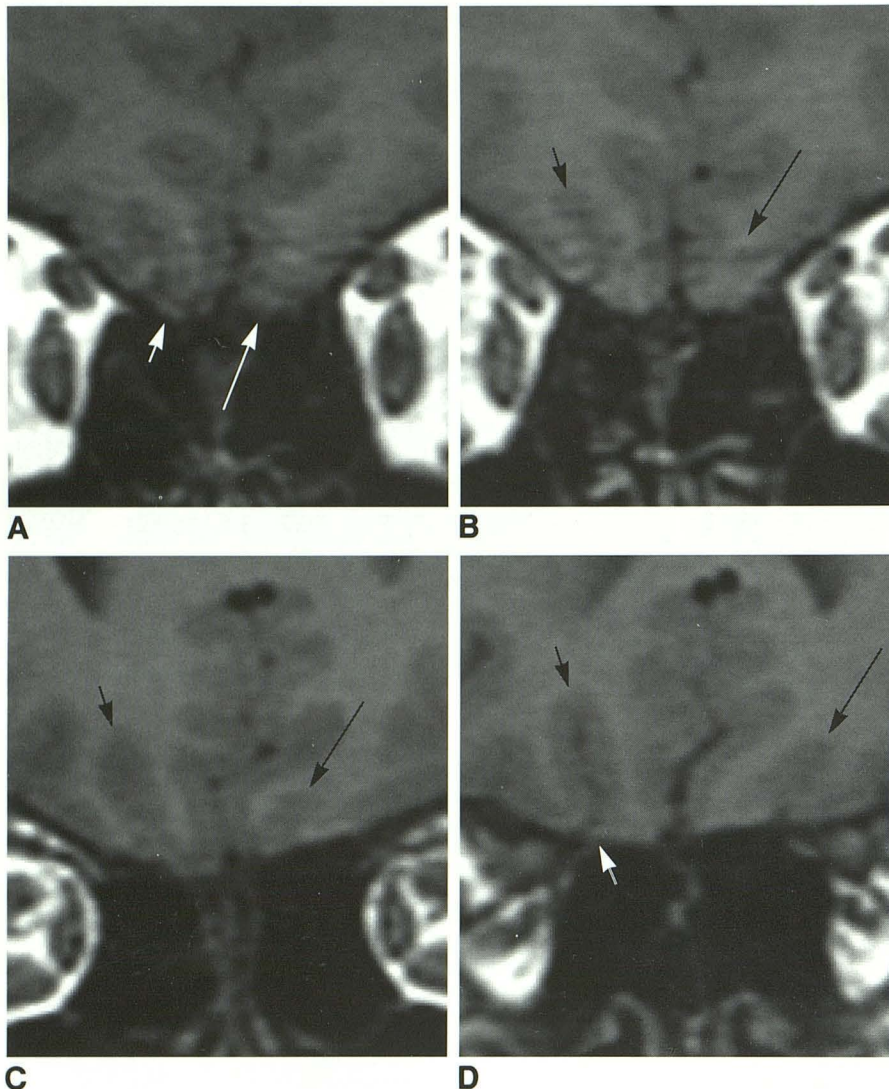


Fig. 4. Coronal T1-weighted images (549/12) of a 29-year-old man with KS reveal significant asymmetry of right and left olfactory structures. On the patient's right, a hypoplastic right olfactory bulb/tract complex is seen (*short arrow in A*). On the left, a dysplastic tangle of olfactory tissue (neuroma) is seen (*long arrow in A*). Anteriorly, olfactory sulci are mildly hypoplastic on the right (*small arrow in B*) and absent on the left (*long arrow in B*). Posteriorly, olfactory sulci are normal on the right (*short black arrows in C and D*), yet hypoplastic on the left (*long black arrows in C and D*). The olfactory tract is barely seen within the right olfactory sulcus (*short white arrow in D*).

families (9). Since then, the disorder has become known as Kallmann syndrome, perhaps inappropriately crediting Kallmann with the first description.

#### Clinical Features

KS is an inherited disorder characterized by hypogonadotropic hypogonadism and anosmia or hyposmia (7, 8, 10). The primary disturbance in KS has recently been linked (in the X-linked disease) to a failure of genetic expression of cell markers (proteins) that guide migrating neurons (4). The result is abnormal neuronal migration of LHRH-expressing cells from the olfactory placode to the hypothalamic and septal regions resulting in failure of adeno-hyphyseal stimulation to synthesize and secrete luteinizing hormone and follicle-stimulating hormone (1). Clinically, this is

manifested by (hypogonadotropic) hypogonadism. The abnormal development of the olfactory placode also results in improper development of the olfactory bulbs, gyri, and sulci, manifested clinically as anosmia or hyposmia.

Unlike many developmental anomalies, KS is a partially treatable disorder. Although the olfactory deficiencies cannot be corrected, hormone injections have succeeded at restoring reproductive function (case 1) and relatively normal lifestyles in patients with KS.

#### Embryology

Unlike much of neuroembryology, the development of the olfactory system has been, until recently, both poorly defined and poorly understood. In recent years, however, advanced immunohistochemical studies have revealed much

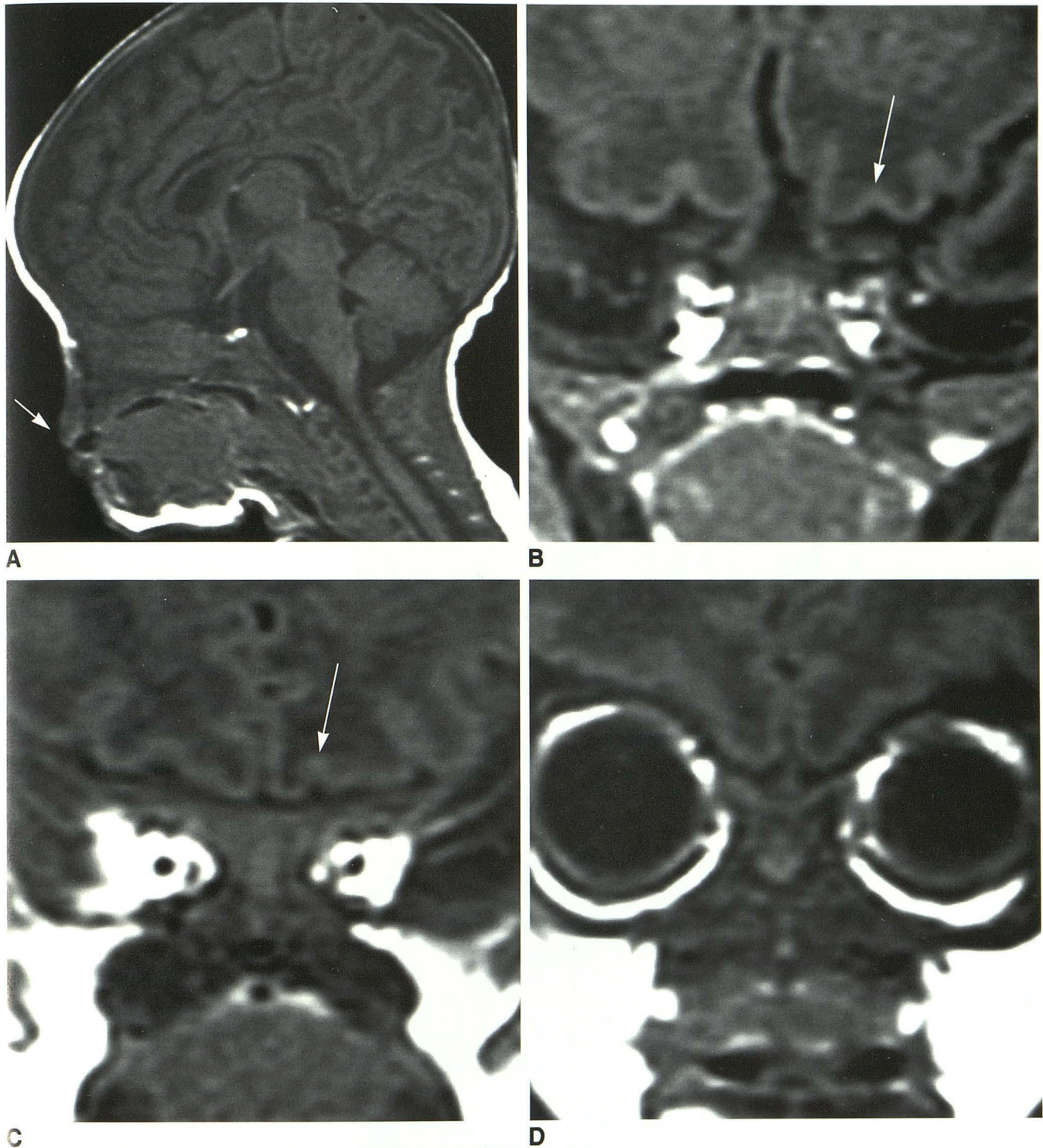


Fig. 5. Sagittal (500/11) and coronal (600/11) T1-weighted images of 3-week-old boy with KS demonstrate hypoplastic anterior lobe of pituitary gland and posterior olfactory sulci (*long arrows* in *B* and *C*). Neither anterior olfactory sulci nor olfactory bulbs or tracts were seen. Note arhinia (*short arrow* in *A* points to upper lip).

about olfactory embryology and development (1, 11–13). Simply stated, the olfactory placode in the most cephalad nasal fossa gives rise to fibers and cells that migrate superiorly and *anteriorly*

toward the overlying telencephalic vesicles (11, 14–17). This migration results in the formation of olfactory fila, which stretch obliquely forward and, in the aggregate, are considered the olfactory



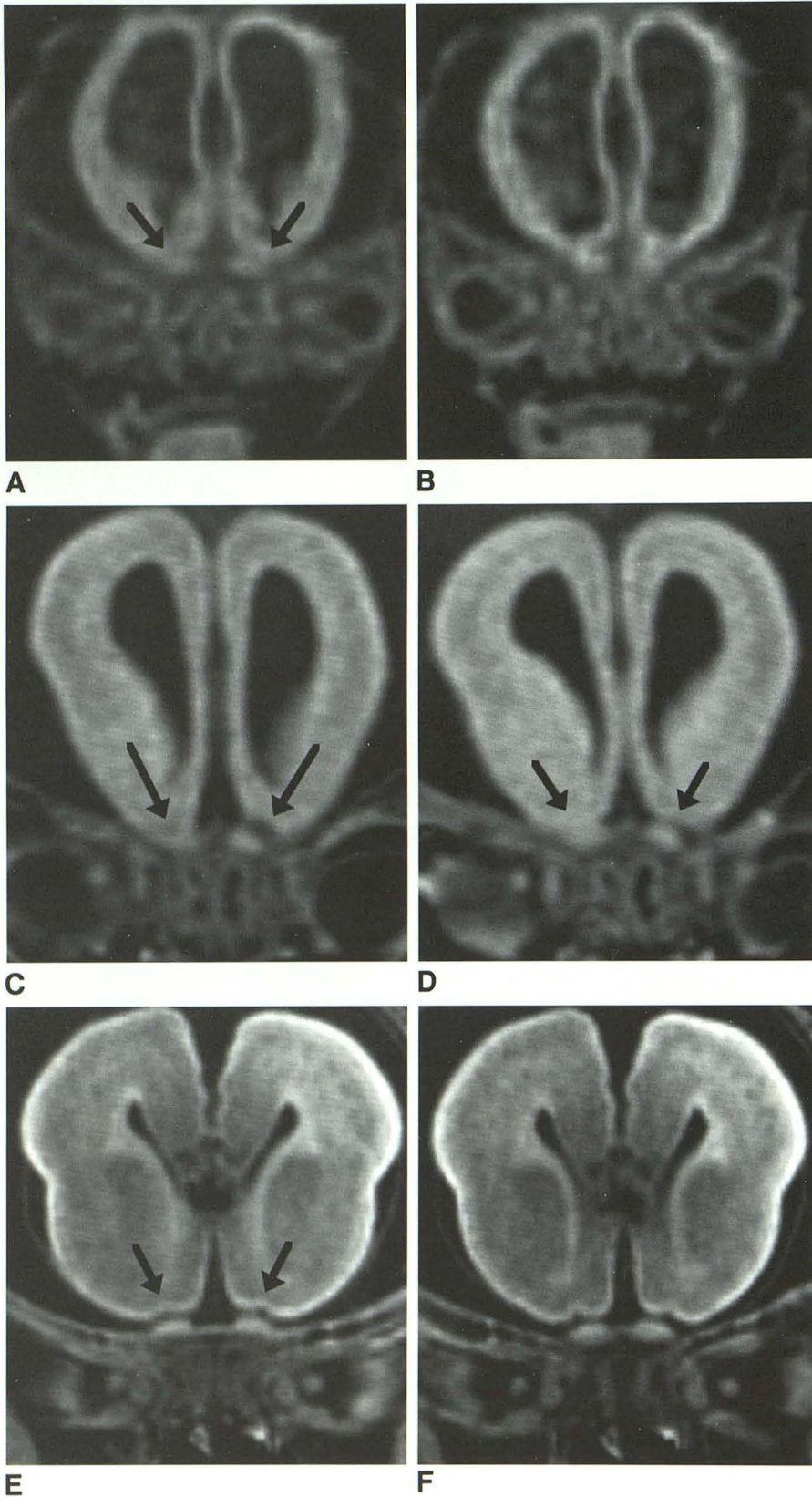


Fig. 6. Coronal radio frequency-spoiled gradient-recalled echo images (35/7, 35°) of abortuses at approximately 10 (A and B), 14 (C and D), and 16 (E and F) weeks gestation (by crown-rump length) reveal normal development of the olfactory bulb/tract complex and early induction of olfactory sulci (arrows). Note germinal matrix along ventricular margin (arrowheads) as well as waves of neuronal migration within hemispheric parenchyma. Arrested migration in KS is thought to result in dysplastic nodules of olfactory fila above, within, and below a dysplastic cribriform plate.

nerves (Carnegie stage 17, approximately 41 days) (11, 12). Medially, and indistinctly, the terminalis and vomeronasal nerves are included in these bundles of olfactory fila (Fig 7). Once communication with overlying brain is established, and nerve fibers grow into the brain, the olfactory bulb is induced to develop (Carnegie stage 18, approximately 44 days) (11, 12, 18).

Contrary to the adult configuration, the olfactory bulbs initially take a downward and *posterior* course. The bulbs are essentially ventricular diverticuli, although the cellular constituents of the bulbs differ from those of the rest of the telencephalii. The bulbs are capped distally by the olfactory nerves and are lined internally by ependyma, as would be expected of ventricular diverticuli. With progressive growth of the bulbs and overlying telencephalii, the bulbs are reoriented to assume a vertical course and, ultimately, a downward and anterior direction, as in the adult. With further growth, the olfactory ventricle is pinched off from the telencephalic ventricle; ultimately the olfactory ventricle is obliterated, although rarely it may persist (19). Finally, at the end of the embryonic period, a cartilaginous crib-

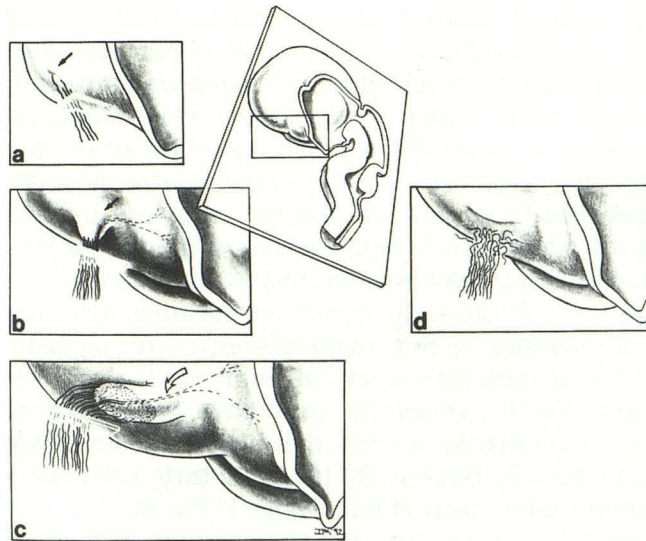


Fig. 7. Schematic representation of normal olfactory embryology (A–C) and aberrant neuronal migration (D) in KS. Perspective (center, unlabeled) is from below, anterior, and left looking up, posteriorly, and to the right. Early in development (A), note course of olfactory fila. With further telencephalic growth, orientation becomes more vertical (B) and, finally, posterior (C). Note terminalis nerve medial and posterior along bundle of olfactory fila and extending along primitive forebrain toward future septal and hypothalamic regions (curved, *open arrow* in C). The vomeronasal nerve is not shown. The dysplastic tangle of olfactory fila and terminalis nerve are shown in D. Note normal olfactory bulb development (*arrows* in A and B) versus failed induction of olfactory bulb (D).

iform plate starts to develop. With it, the olfactory fila are aggregated more clearly into bundles, comprising the olfactory nerve more laterally (and the terminalis and vomeronasal nerves more medially) (11, 16, 17, 20).

Thus, like the optic nerves, which are diencephalic outgrowths, the olfactory bulbs and ventricles are telencephalic outgrowths. However, development of the olfactory nerves from the olfactory placodes precedes and is prerequisite to the initiation of olfactory bulb, ventricle, and tract development (11, 17).

More specifically, the ingrowth of olfactory axons is preceded by the migration of cells that are immunoreactive for neuronal cell adhesion molecule from the epithelium of the olfactory pit. These cells form a cellular aggregate within the mesenchyme between the olfactory pit and the overlying forebrain. Once this has occurred, central processes of the olfactory, vomeronasal, and terminalis nerves climb toward the forebrain to induce the olfactory bulbs. These axons, also neuronal cell adhesion molecule immunoreactive, form an embryonic scaffolding along which LHRH-immunoreactive neurons ultimately will migrate (21–23).

At least in the X-linked cases, this migration appears to be genetically determined, and recently, the *KALIG-1* gene has been identified (4). Specifically, two of three domains of this gene were found to have significant homology with neural cell-cell adhesion and axonal path-finding molecules. Accordingly, this gene is hypothesized to have a “direct influence on axonal outgrowth, or alternatively might be involved in recognition mechanisms between . . . neurons, allowing coordinated migration” (4).

In addition to the migration of cells from the olfactory placodes to the future olfactory bulbs, cellular migration from the medial placodes to the future hypothalamus and septal regions is an integral consequence of olfactory development (11, 13). In particular, along the medial aspect of the olfactory nerve complex are fibers that comprise the terminalis and vomeronasal nerves. During Carnegie stages 20–21, the ganglion of the nervus terminalis appears (16, 20).

It is along the embryologic scaffolding of the terminalis and possibly the vomeronasal nerves that LHRH-releasing cells migrate into the forebrain to the medial septal nucleus and hypothalamus (13). Moreover, Schwanzel-Fukuda has demonstrated the failure of such migration as the underlying anomaly in KS (Fig 8) (1). As a result

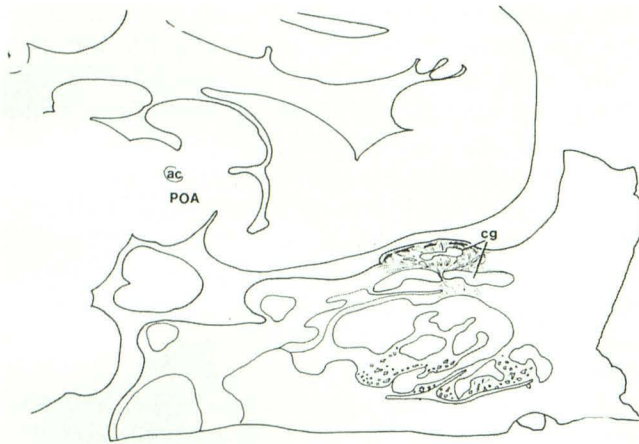


Fig. 8. Microprojection drawing of a sagittal 8- $\mu$ m paraffin section through the brain and nasal cavity of a 19-week-old fetus with KS, showing the distribution of LHRH-expressing neurons and fibers (*thick lines* represent an LHRH fiber bundle). On the right side of the cribriform plate, lateral to midline, the tangle formed by the central processes of the olfactory nerves encompasses a part of the cartilage of the crista galli (cg). A few LHRH-containing nerve fibers are seen on the medial surface of this structure. LHRH-expressing cells were seen on other sections through the cribriform plate and nasal cavity (not shown), but no LHRH immunoreactivity was seen in either the median eminence of the hypothalamus or in the organum vasculosum of the lamina terminalis. AC, Anterior commissure; POA, preoptic area. (Reprinted with permission from Ref 1.)

of this migratory failure, LHRH-releasing cells are arrested in their migration and are found not in the hypothalamus and septal regions but in a "tangle beneath the forebrain, with the dural layers of the meninges, on the dorsal surface of the cribriform plate of the ethmoid bone" (1). *In KS, therefore, the olfactory, terminalis, and vomeronasal axons either never reach the brain or do reach the brain and initiate olfactory induction but somehow fail to maintain proper communication, resulting in failed neuronal migration and olfactory hypogenesis or agenesis (21–24). Biochemically, the result is an inability to drive the adenohypophysis to synthesize and release follicle-stimulating hormone and luteinizing hormone. Clinically, the result is a (reversible) failure of reproductive hormones to drive the gonads.*

### Radiologic Findings

Based on this limited review of olfactory embryology and of the failure of neuronal migration in KS, it is possible to correlate (and predict) the radiologic findings in KS. Given the primary failure of olfactory nerve development, a primary deficiency of olfactory bulb and tract development is expected, as is an associated failure of

olfactory sulcal induction. Depending on the degree of failure of olfactory nerve development, the olfactory bulbs and tracts will be either hypoplastic or aplastic. In addition, as noted above, failure of normal development of the terminalis and vomeronasal nerves is associated with cellular deficits within the hypothalamus and septal regions, although it is unlikely that such (small) deficits would significantly affect the ultimate morphology of the hypothalamus and septum. Finally, although the embryologic olfactory placodes regress, the consequence of failed neuronal migration of the LHRH-releasing cells may be seen in the cribriform and immediate supracribriform region, beneath the forebrain, both histopathologically (Fig 8) (21) and potentially in vivo on MR, as we have suggested.

In the present study, as in prior studies, deficiency of the olfactory sulci was noted in patients with KS (3, 5). In most patients, hypoplasia of the olfactory sulci was most pronounced anteriorly. According to the normal reorientation of the bulbs and ventricles as outlined above, initial development of the olfactory bulbs and ventricles would take place in what ultimately becomes the *posterior* olfactory region. Hence, secondary development of the *posterior* olfactory sulci would be most likely. With further forebrain development, the more anterior structures would further develop, if properly induced by the underlying olfactory nerves. In fact, in the present study, the anterior olfactory sulci were abnormal in the eight patients in whom the anterior olfactory regions were adequately visualized. The anterior olfactory sulci were absent in three and rudimentary in four patients. Posteriorly, however, the sulci appeared rudimentary in five (with absent or hypoplastic anterior olfactory sulci) and normal in three patients (with hypoplastic anterior sulci in both of the patients in whom the anterior sulci were imaged). In patient 9, the olfactory sulci were asymmetric, as noted in Table 1 (Fig 4). Remarkably, this asymmetry suggested the possibility of asymmetric smell test results. In fact, this proved to be the case.

Visualization of the olfactory bulbs and tracts may be difficult, even with dedicated coronal images. Nevertheless, in the present study, excluding the two studies at lower field strength and the one patient in whom the anterior olfactory regions were not imaged, the olfactory bulbs and tracts appeared rudimentary in four patients and absent in one. In patient 9, a hypoplastic olfactory bulb/tract complex was seen on the mildly hy-

posmic right side; on the moderately hyposmic left side, no tract was seen. It appears that this patient has an asymmetric form of KS; although distinctly uncommon, this has been reported (25, 26).

In addition to the abnormalities of the olfactory bulbs, tracts, and sulci, in two (possibly three) patients abnormal soft tissue was present in the region between the upper nasal vault and the forebrain. (In patient 9, the abnormal soft tissue was seen only on the left side.) This soft tissue most likely represents the dysplastic "tangle" noted by Schwanzel-Fukuda (1). Although pathologic correlation of this suggestion is not available, we suspect that the soft-tissue neuromas seen in these patients represent the residua of abnormal neurons in patients with KS. In support of this speculation, we noted prominent olfactory tissue and early sulcal formation in the fetal specimens; the similarities between the fetal specimens and the three patients with abnormal supracribriform tissue nodules is striking. Because the specimens are from the early fetal period, at which time neuronal migration is underway, it is likely that an arrest of neuronal migration affecting the olfactory neurons could result in a prominent soft tissue mass underneath the frontal lobes, as seen in two (or three) of our patients.

Current limitations on resolution do not afford information about the terminalis and vomeronasal nerves. Failure of their development, therefore, can only be inferred by the failure of olfactory development and the known association of the migration of olfactory cells and LHRH-releasing cells along the terminalis and vomeronasal nerves (1, 4, 11, 13, 21).

Finally, the hypothalamus and pituitary gland were examined in all patients. Not surprisingly, the hypothalamus was normal in all patients. Because the LHRH-releasing cells make up only a small contribution to the hypothalamus, no morphologic changes would be expected in cases in which such cell nests are absent. With regards to the pituitary gland, the neurohypophysis would be expected to be morphologically normal in patients with KS, and the adenohypophysis would be expected to be normal or hypoplastic in such patients (27, 28). In the present study, one patient's scan revealed mild hypoplasia of the adenohypophysis.

In addition to the findings described above regarding the nine patients with known KS, the findings in the 3-week-old boy are remarkable in that the diagnosis is not yet confirmed, and we

suggested the diagnosis based on our findings in the present study. In that case, only posterior olfactory sulci were noted. Neither anterior olfactory sulci, bulbs, nor tracts were detected. The hypothalamus appeared normal, but the adenohypophysis was diminished in size.

In summary, based on an appreciation of the embryology of the human olfactory system, the radiologic findings of patients with Kallmann syndrome can be predicted. In the present study, with the use of coronal images, such findings were observed. In addition, we have identified what we believe represents the dysplastic tangle of disordered olfactory nerves beneath the forebrain in two, and possibly three, patients, consistent with the concept of KS as an anomaly of neuronal migration.

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### References

- Schwanzel-Fukuda M, Bick D, Pfaff DW. Luteinizing hormone-releasing hormone (LHRH)-expressing cells do not migrate normally in an inherited hypogonadal (Kallmann) syndrome. *Mol Brain Res* 1989;6:311-326
- Bick D, Ballabio A. Chromosome abnormalities in and pathogenesis of Kallmann syndrome. *Am J Med Genet* 1990;37:298
- Klingmüller D, Dewes W, Krahe T, Brecht G, Schweikert H-U. Magnetic resonance imaging of the brain in patients with anosmia and hypothalamic hypogonadism (Kallmann's syndrome). *J Clin Endocrinol Metab* 1987;65:581-584
- Franco B, Guioli S, Pragliola A, et al. A gene deleted in Kallmann's syndrome shares homology with neural cell adhesion and axonal path-finding molecules. *Nature* 1991;353:529-536
- Dewes VW, Krahe T, Klingmüller D, Harder T. MR-Tomographie beim Kallmann-syndrom. *Fortschr Röntgenstr* 1987;147:400-402
- Suzuki M, Takashima T, Kadoya M, Takahashi S, Miyayama S, Taira S. MR imaging of olfactory bulbs and tracts. *AJNR: Am J Neuroradiol* 1989;10:955-957
- VanDop C, Burstein S, Conte FA, Grumbach MM. Isolated gonadotropin deficiency in boys: clinical characteristics and growth. *J Pediatr* 1987;111:684-692
- Lightman S. Kallmann's syndrome. *J R Soc Med* 1988;81:315-316
- Kallmann FJ, Schoenfeld WA, Barrera SE. The genetic aspects of primary eunuchoidism. *Am J Ment Defic* 1944;48:203-206
- White BJ, Rogol AD, Brown KS, Lieblisch JM, Rosen SW. The syndrome of anosmia with hypogonadotropic hypogonadism: a genetic study of 18 new families and a review. *Am J Med Genet* 1983;15:417-435
- Bossy J. Development of olfactory and related structures in staged human embryos. *Anat Embryol* 1980;161:225-236

12. Müller F, O'Rahilly R. The human brain at stage 17, including the appearance of the future olfactory bulb and the first amygdaloid nuclei. *Anat Embryol* 1989;180:353-369
13. Schwanzel-Fukuda M, Pfaff DW. Origin of luteinizing hormone-releasing hormone neurons. *Nature* 1989;338:161-164
14. Humphrey T. The development of the olfactory and the accessory olfactory formations in human embryos and fetuses. *J Comp Neurol* 1940;73:431-468
15. Humphrey T. The development of the anterior olfactory nucleus of human fetuses. *Prog Brain Res* 1963;3:170-190
16. Pearson AA. The development of the nervus terminalis in man. *J Comp Neurol* 1941;75:39-66
17. Pearson AA. The development of the olfactory nerve in man. *J Comp Neurol* 1941;75:199-217
18. Müller F, O'Rahilly R. The human brain at stages 18-20, including the choroid plexuses and the amygdaloid and septal nuclei. *Anat Embryol* 1990;182:285-306
19. Roy EP III, Frost JL, Schochet SS Jr. Persistent olfactory bulb ventricle. *Clin Neuropathol* 1987;6:86-87
20. Müller F, O'Rahilly R. The human brain at stages 21-23, with particular reference to the cerebral cortical plate and to the development of the cerebellum. *Anat Embryol* 1990;182:375-400
21. Schwanzel-Fukuda M, Abraham S, Crossin KL, Edelman GM, Pfaff DW. Immunocytochemical demonstration of neural cell adhesion molecule (NCAM) along the migration route of luteinizing hormone-releasing hormone (LHRH) neurons in mice. *J Comp Neurol* 1992;321:1-18
22. delCastillo I, Cohen-Salmon M, Blanchard S, Lutfalla G, Petit C. Structure of the X-linked Kallmann syndrome gene and its homologous pseudogene on the Y chromosome. *Nature Genet* 1992;2:305-310
23. Incerti B, Guioli S, Pragliola A, et al. Kallmann syndrome gene on the X and Y chromosomes: implications for evolutionary divergence of human sex chromosomes. *Nature Genet* 1992;2:311-314
24. Rugarli EJ, Lutz B, Kuratani SC, et al. Expression pattern of the Kallmann syndrome gene in the olfactory system suggests a role in neuronal targeting. *Nature Genet* (in press)
25. deMorsier G. Median cranioencephalic dysraphias and olfactogenital dysplasia. *World Neurol* 1962;3:485-504
26. Males JL, Townsend JL, Schneider RA. Hypogonadotropic hypogonadism with anosmia-Kallmann's syndrome: a disorder of olfactory and hypothalamic function. *Arch Intern Med* 1973;131:501-507
27. Cacciari E, Zucchini S, Carlà G, et al. Endocrine function and morphological findings in patients with disorders of the hypothalamo-pituitary area: a study with magnetic resonance. *Arch Dis Child* 1990;65:1199-1202
28. Kovacs K, Sheehan HL. Pituitary changes in Kallmann's syndrome: a histologic, immunocytologic, ultrastructural, and electron microscopic study. *Fertil Steril* 1982;37:83-89

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