Evaluation of Olfactory Deficits by Structural Medical Imaging

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I. INTRODUCTION

Olfactory dysfunction can generally be classified into (1) conductive disorders caused by interference with the access of odorants to the olfactory receptors, (2) peripheral sensorineural disorders resulting from injury to the olfactory receptors (within the olfactory mucosa), and (3) central neural disorders of the olfactory bulb or tract or related parts of the central nervous system such as the prefrontal lobe, septal nuclei, amygdala, and temporal lobe. For medical imaging and the anatomical approach, we categorize olfactory dysfunction into two major groups: peripheral causes—sinonasal tract disorders—and central causes—intracranial disorders. It is important to relate olfactory deficits to the appropriate anatomical and pathological changes. Unfortunately, clinical olfactory testing, whether psychophysical or electrophysiological, is rarely capable of localizing the source (aside from determining whether it is on the right or left) or identifying the specific cause of decreased smell function.

Modern medical imaging techniques offer a valuable means for assessing the basis of some disorders of olfaction. Although revolutionary changes in medical imaging techniques have occurred in the last few decades, only a few articles have dealt with imaging studies related to chemosensory disorders (Doty et al., 1999; Goodspeed et al., 1987; Kimmelman, 1991; Klingmuller et al., 1987; Li et al., 1994; Schellingher et al., 1983; Yousem et al., 1996, 1997, 1998, 1999). In this chapter we comprehensively review the pertinent medical literature on this general topic and detail our own experience.

II. IMAGING MODALITIES AND TECHNIQUES

Major advances in pinpointing the anatomical and pathological changes of many disorders of the sinonasal cavity and brain have become possible as a result of the development and refinement of imaging techniques (Carter and Runge, 1988; Healy, 1992; Jagust and Eberling, 1991; Jolles et al., 1989; Reiman and Mintun, 1990; Shapiro and Som, 1989; Vogl, 1990; Yousem et al. 1996a, 1997b, 1998). Even though the imaging evaluation is not the diagnostic equivalent to histological study, anatomical imaging, such as high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), can not only map regional lesions, but may also suggest a differential diagnosis (Carter and Runge, 1988; Shapiro and Son, 1989; Som and Shapiro, 1988). On the other hand, functional imaging (PET, SPECT, fMRI), which is reviewed in Chapter 12, affords one the potential to explore regional pathophysiological changes in the living brain (Healy, 1992; Jagust and Eberling, 1991; Jolles et al., 1989; Reiman and Mintun, 1990; Yousem et al., 1997b, 1999b, c). The relevant imaging modalities which may be helpful in the evaluation of common causes of olfactory deficits are reviewed in this section.
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Recent studies have suggested that functional imaging is more sensitive than anatomical imaging in detecting airflow to the olfactory receptors. Besides the obstructive
follow the course of the nerve and can expand skull base foramina through which they travel. The signal intensity of schwannomas varies according to the content of the dense Antoni A tissue or loose Antoni B tissue, the latter being brighter on T2W scans. Schwannomas enhance avidly, although they may have inhomogeneity to the enhancement.

Finally, one has the juvenile angiofibroma, a fascinating benign neoplasm, which appears to arise in the region of the sphenopalatine foramen and/or the pterygopalatine fossa. The lesion accounts for 0.5% of head and neck masses and is typically seen in adolescent males who present with epistaxis and/or a nasal mass (Mehra, 1989). The lesion is highly vascular as exemplified on MRI by the signal flow voids within the lesion and its marked contrast enhancement. Because of its propensity for spreading via the canals and foramina at the skull base, MRI is probably the study of choice for the evaluation of this neoplasm. Embolization of these lesions will assist the surgeon in limiting blood loss if resection is considered.

3. Malignant Neoplasms

CT and MRI probably play complementary roles in the evaluation of sinonasal malignancies because of CT’s superiority in defining bony margins and MRI’s superior soft tissue resolution and ability to define intracranial or intraorbital spread. One of the advantages of MRI is the ability to distinguish sinus neoplasm from postobstructive secretions. This may be difficult by CT if the secretions are isodense to the mass and if the malignancy does not enhance dramatically. If one was forced to study the patient with a single modality, the literature supports MRI as the best study for the staging of sinonasal malignancies (Hunink et al., 1990; Kraus et al., 1992; Paling et al., 1987; Sisson et al., 1989).

Som et al. (1991) noted that squamous cell carcinoma (low in T2 intensity) could be distinguished from inflammation (high in T2 intensity). They compared CT to MRI for mapping sinonasal tumors. They found that MRI and CT were equivalent in 23 of 53 patients in defining tumor extent and that MRI was superior to CT in 26 patients. Of the 4 cases in which CT was superior, subtle bony erosion (2) and osteo-cartilaginous (1) lesions accounted for the “misses” on MRI. Of 60 inflammatory lesions, MRI was superior (Bonte et al., 1993) or equivalent (Everall et al., 1991) to CT in all cases. Inflammation (bright) and neoplasm (intermediate) could be distinguished in 95% of cases based on T2W signal intensity. Even when the sinus secretions become increasingly inspissated and the signal intensity on T2W scans decreases, the neoplasm can be distinguished from the obstructed secretions by its typical heterogeneity as opposed to the smooth homogenous...
appearance of sinus secretions. This is also true in the cases of mucoceles, which may occur after or in association with sinus neoplasms. Additionally, MRI has shown that most squamous cell carcinomas of the sinonasal cavity enhance with gadolinium in a solid fashion as opposed to a peripheral rim of enhancement in sinus secretions and/or mucoceles. Unfortunately, lymphomas, undifferentiated carcinomas, inverted papillomas, and some sarcomas may have identical signal intensity and enhancement characteristics as squamous cell carcinoma.

Gadolinium is particularly useful for demonstrating epidermal or meningeal invasion of neoplasms. Often, postcontrast scans must be combined with fat suppression techniques in order to identify enhancement amidst the abundant skull base fat. In one series, 75% of patients with intracranial extension of sinonasal malignancies had additional information about tumor extent demonstrated with postcontrast MRI studies (van Tassel et al., 1991). Subtraction MRI of pregadolinium scans from postgadolinium scans may improve visibility of such subtle enhancement (Lloyd and Barker, 1991). It should be noted that meningeval enhancement need not necessarily imply neoplastic invasion; just as in cases of meningioma, the dura may enhance because of reactive fibrovascular changes alone.

When one encounters a sinonasal mass that is eroding intracranially, one must consider carcinoma, olfactory neuroblastoma, sarcomas, lymphomas, sinonasal polyposis, and inverted papillomas. Twelve percent of patients with polyposis and mucoceles eventually erode the skull base (Som et al., 1991). The pattern of bone destruction may be similar between malignant and benign lesions at the non–sinus bearing skull base. Bone remodeling in this location is a rarity; a permeative pattern is the norm for all lesions. Som et al. (1988) have suggested that a lesion with homogeneous signal intensity invading intracranially is more likely to be a malignancy, whereas heterogeneity suggests an inflammatory cause. Unfortunately, necrosis, hemorrhage, or calcification in carcinomas, olfactory neuroblastomas, or sarcomas may cause signal heterogeneity. Polyps generally enhance in a peripheral pattern; true neoplasms enhance solidly. Malignancies have a broad flat base of skull erosion; benign conditions have a rounded polypoid intracranial excrescence.

Squamous cell carcinomas account for 80% of the malignancies to affect the paranasal sinuses and 80% in the maxillary sinus. The hallmark of malignancies of the sinonasal cavity is bony destruction, seen in approximately 80% of CT scans of sinonasal squamous cells carcinoma at initial presentation. The lesion is confined to the maxillary antrum in only 25% of cases at presentation (Lyons and Donald, 1991). In most series documenting sinonasal squamous cell carcinoma signal intensity characteristics on MRI, the lesion is characterized by a low signal intensity on T2W scans. This is why differentiation with obstructed secretions which are typically bright in signal intensity on T2W scans is so easy on MRI.

Because of Som et al.'s early work depicting sinonasal malignancies as hypointense on T2W scans, people have come to rely on this pulse sequence for mapping cancers (Som et al., 1990). Unfortunately, low intensity on T2W scans is an inconstant finding in sinonasal malignancies in general. Hunick et al. found that over 50% of head and neck malignancies had signal intensity on T2W scans that was brighter than muscle and isoointense to brain (Hunick et al., 1990). Approximately 25% of benign tumors had the same intensity pattern. Lanzeri et al. (1991) also reported that the signal intensities of tumors, mucoceles, schwannomas, and obstructed secretions may show some overlap. Som et al. (1991) have found that minor salivary gland masses and schwannomas may have T2W signal intensity similar to that of inflammatory lesions. Minor salivary gland tumors and melanoma are the next most common malignancies to affect the sinonasal cavity after squamous cell carcinoma (van Tassel et al., 1991). The minor salivary gland tumors represent a wide variety of histological types including adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, and undifferentiated carcinoma. Of these tumors, adenoid cystic carcinoma is the most common variety. Its signal intensity may be high or low on T2W scans, possibly related to the degree of tubular or cribriform histological pattern as well as cystic spaces, necrosis, and tumor cell density. Tissue specificity is not readily achievable with MRI or CT. Gadolinium is of particular use with adenoid cystic carcinomas, which have a propensity for perineural spread (Graamans and Slootweg, 1989). With sinonasal cavity malignancies one should always attempt to trace back the branches of the fifth cranial nerve via the pterygopalatine fossa, foramen rotundum, foramen ovale, and orbital fissures in order to identify perineural neoplastic spread.

Adenocarcinomas of the paranasal sinuses have a predilection for the ethmoid sinuses and appear more commonly in woodworkers. This tumor also tends to have low signal intensity on T2W MRI images but may have high signal intensity in a small percentage of cases. Sarcomas of the sinonasal cavities are very rare, with chondrosarcoma being the most common. Again, the histological diagnosis is probably better suggested by CT based on the characteristic whorls of calcification. However, for staging, MRI is competitive with CT, and, particularly if repeat examinations are going to be required, follow-up with MRI to avoid the radiation exposure of CT is recommended.
Melanoma is a tumor that is usually identified in the nasal cavity as opposed to the paranasal sinuses. It has been associated with melanosis in which there is field deposition of melanin along the mucosal surface of the sinonasal cavity. Therefore, multiplicity of lesions becomes a problem when dealing with melanomas. Neither CT nor MRI is particularly helpful in identifying the field “cancerization” of melanoma. When melanoma contains melanin there is paramagnetism which causes T1 and T2 shortening accounting for high signal intensity on T1W scans and low signal intensity on T2W scans (Atlas et al., 1990). However, an amelanotic melanoma may have bright signal intensity on T2W scans. The presence of hemorrhage associated with the melanoma, a common occurrence because of the coincidence of epistaxis, may further obfuscate the signal intensity pattern (Yousem et al., 1996c).

Lymphoma does occur in the paranasal sinuses and may have variable signal intensity as well. It is characterized by homogeneous signal intensity without necrosis and the association with cervical lymphadenopathy.

Metastatic disease to the paranasal sinuses is extremely rare. Of the primary causes of metastases to the sinuses, renal cell carcinoma is probably the most common. This tumor also has a propensity for hemorrhage and may also have a variable signal intensity depending upon the stage of hemorrhage.

C. Allergic Reactions

Allergic rhinitis is a common upper airway condition affecting about 30 million Americans with peak prevalence in the age group from 35–54 years (Baroody and Naclerio, 1991). Hyposmia or anosmia is common with allergic rhinitis, mainly caused by nasal obstruction by polyps or inflamed mucosa, which limit access of inspired air to the roof of the nasal vault (Cowart et al., 1993). The diagnostic work-up begins with a careful history, which attempts to identify offending allergens. Skin testing of specific antigens is often used to confirm the diagnosis. Medical imaging studies play a supplementary role in the evaluation of sinonasal airway status and differential diagnosis. CT and MRI are also important for detecting any complications such as sinusitis, mucoceles, and aggressive polyps in patients with allergic rhinitis. Rounded excrescences and enlargement of ostia are seen in the airway of patients with polyposis.

D. Congenital or Developmental Abnormalities

It is generally accepted that normal variations in the nasal anatomy may play a role in preventing the access of an odorant to the olfactory receptor area. The sense of smell is probably less than normal in many patients with craniofacial anomalies (Crysdale, 1981). Congenital developmental abnormalities include choanal atresia, hereditary nasal septal deviation, facial hypoplasia, cleft palate, nasal dermoids and epidermoids, cephaloceles, and gliomas, etc. Medical imaging techniques, especially high-resolution CT, play a key role to detect and evaluate the facial and bony changes (Barkovich et al., 1991; Klein et al., 1987). CT is most useful because surgical correction requires identification of and closure of the osseous abnormalities. MRI is most effective in defining soft tissue masses such as cephaloceles and nasal gliomas.

Congenital anosmia can be associated with a number of developmental and inflammatory conditions. Kallmann’s syndrome, also known as hypogonadotropic hypogonadism with anosmia, is a congenital X-linked disorder in which the olfactory bulbs and tracts are not formed. This is not associated with holoprosencephaly, and the usual deficits are related to hormonal abnormalities in the pituitary gland with the loss of sense of smell. Infertility often coexists. In 1993, an MR study of the olfactory system in Kallmann’s disease showed absence of the olfactory bulbs and tracts in 17 of 18 patients while confirming the presence of the olfactory bulbs and tracts in all 10 studied patients with idiopathic hypogonadotropic hypogonadism (Yousem et al., 1993, 1996a). Some patients have absence of the olfactory bulbs and tracts without Kallmann’s syndrome. It is unclear whether this represents congenital absence or whether an inflammatory condition early in infancy destroys the olfactory bulbs and tracts. Certain viruses have a propensity for injuring the olfactory system. A recent study has noted the incomplete formation of olfactory sulci in patients with congenital anosmia as well as a variable percentage of aplastic olfactory bulbs, tracts, and tubercles (Di Rienzo et al., 2002). Still others may have congenital absence of sense of smell on the basis of early head trauma where the ciliary nerves as they crossed the cribiform plate may be sheared and the olfactory system is affected. Infectious causes may also affect the sense of smell in early childhood, usually secondarily to viruses. In these cases one sees the olfactory bulbs and tracts; but they are not functional.

Holoprosencephaly is a congenital, multiple midline malformation disorder that has a known association with sensory deficits of vision and olfaction. Although variable amounts of aplasia and hypoplasia of the olfactory apparatus may be identified, the most common MR finding is complete absence of the olfactory bulbs, occurring in 92% of patients. A high association with absence of the olfactory nerves and tubercles is also seen. There does appear to be some, albeit poor, differentiation of the olfactory sulci and gyri recti, which were absent only in a little over half of the subjects (Barkovich and Quint, 1993).
E. Other Peripheral Causes

It is estimated that 30 million Americans have used cocaine and 5 million use it regularly (Gregler and Mark, 1986). Intra-nasal use of cocaine and heroin has reached epidemic proportions in the United States. Although hyposmia or anosmia has been suggested to occur often in cocaine abusers, few studies using quantitative measures of olfactory function have confirmed such reports. A sole study on this topic reported that of 11 cocaine abusers who underwent detailed olfactory testing, only one was found to be anosmic and another had mild olfactory discrimination dysfunction (Gordon et al., 1990). These authors note that most cocaine abusers do not develop permanent olfactory dysfunction. If, in fact, olfactory disturbance occurs as a result of heavy cocaine use, it could be due to associated conductive disorders, nasal airway obstruction, alteration in sinonasal aerodynamics, damage to the olfactory epithelium, damage to the central olfactory system, or osteolysis of the cribiform plate (Kuriloff, 1989).

Concerning the conductive disorders, several reports of osteolytic sinusitis and extensive osteocartilaginous necrosis of the nasal septum in cocaine abusers have been described (Newman, 1988; Schweitzer, 1986). Erosion of nasal septal cartilage is a known complication of cocaine abuse. Within the differential diagnosis for cartilaginous destruction, one should include Wegener's granulomatosis, syphilis, leprosy, lymphoma, rhinoscleroma (a klebsiella infection), and fungal invasion. CT, preferably in the coronal plane, can provide excellent views of septal perforation, osteolysis, and sinusitis.

To evaluate intracranial disorders associated with cocaine, MRI is the study of choice. Vasculitic infarcts, hypertensive hemorrhages, and white matter ischemic foci may be seen with MRI. Recently Tumeth and colleagues demonstrated multifocal cortical deficits with a special predilection for the frontal and temporal lobes on SPECT perfusion brain scans in chronic cocaine abusers (Tumeth et al., 1990). Similar findings have been reported by others (Holman et al., 1991; Kolow et al., 1988). These findings may suggest a central basis for some cases of cocaine-related decreased olfaction. Some studies also have revealed that cerebral atrophy develops in chronic cocaine abusers and that the severity correlates with the duration of abuse (Pascual-Leone et al., 1991).

Anosmia or hyposmia is a frequent sequela of high-level midface fractures in which the olfactory nerves may be severed at the level of the cribiform plate (Kassel, 1988; Mathog, 1992). Because ethmoid complex and cribiform plate fractures are difficult to detect on plain radiographs, thin-section coronal CT is the best measure to assess naso-ethmoid trauma (Daly et al., 1990; Kassel, 1988).

V. CENTRAL CAUSES OF Olfactory Diseases

There are numerous CNS disorders that are associated with olfactory dysfunction. The most common types fall in the categories of degenerative neuropsychiatric disorders, hereditary conditions, trauma, and central neoplasms. Of course, in some disorders the involvement of both peripheral and central neural processes may occur.

A. Alzheimer's Disease

It has been well documented that olfaction is significantly altered in Alzheimer's (AD). Nearly all studies of olfactory function in patients with AD have reported decreased smell relative to age-matched controls (see Chapter 23). These studies demonstrate marked impairment of smell function in early AD, whether measured by identification, discrimination, or threshold sensitivity (Doty, 1991; Doty et al., 1987; Serby et al., 1991).

Recent neuropathological studies have correlated well with these clinical findings. The anterior olfactory nuclei in AD patients contain senile plaques, neurofibrillary tangles, granulovascular degeneration, and cell loss (Averback, 1983; Esiri and Wilcock, 1984). The olfactory bulbs also show involvement (Esiri and Wilcock, 1984; Ohm and Braak, 1987), as does nasal sensory epithelium (Jafek et al., 1992). In addition, central olfactory structures, especially the amygdala and the entorhinal, pyriform, and temporal cortices, are frequently affected by Alzheimer's disease (Harrison, 1986; Pearson and Powell, 1989). Besides the above findings, devastating nerve cell loss and gliosis in the region of the hippocampal formation have been observed at autopsy in AD patients (Ball et al., 1985; Hyman et al., 1984).

Neuroimaging has played an important role in detecting some of the pathological changes of AD patients in vivo, and its uses are growing, both for clinical evaluation and as a research tool. Early CT studies in AD patients demonstrated generalized enlargement of the ventricular system and sulci (George et al, 1981; Naser et al., 1980). Several reports have noted that ventricular and sulcal enlargement correlate with the severity of AD (Albert et al., 1984; George et al., 1983). However, these findings are not specific and have relatively weak correlations. de Leon and colleagues (1989) have emphasized the rate of change in ventricular size with repeated CT scans as an important index in the diagnosis of AD. Recently, several investigators have recog-
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nized that CT and/or MRI delineation of atrophic changes in the temporal lobe and the hippocampus with enlargement of hippocampal-choroidal fissures strongly support the diagnosis of AD (de Leon et al., 1988; George et al., 1990; Kesslak et al., 1991; Kido et al., 1989).

McDonald and colleagues (1991) reviewed MRI scans in 22 patients with early-onset AD. The results showed that patients with AD were significantly more likely than age-matched controls to have MR evidence of periventricular hyperintensities on T2W scans. This study suggested that the increased frequency of periventricular hyperintensities may have a relationship to the disease process. Our own experience with MRI studies of AD patients is that most of the cases with AD have, in addition to ventriculomegaly and sulcal widening, significantly reduced volume of the temporal lobe and slight atrophy of olfactory bulbs. (Fig. 2).

Besides CT and MRI, SPECT and PET techniques are also useful for evaluating regional cerebral blood flow, regional oxygen, and glucose metabolism, which may provide evidence supportive of the diagnosis of AD (Jagust and Eberling, 1991). The above-mentioned structural atrophic changes by CT and MRI are also supported by functional imaging studies (McDonald et al., 1991; Ohnishi et al., 1991). The major findings of functioning imaging studies in patients with AD are abnormal regional cerebral blood flow pattern and flow reduction. The common sites of blood flow reduction are in the temporoparietal region and the frontal areas. In one report (Bonte et al, 1993), seven patients with possible diagnosis of AD studied by SPECT showed only frontal flow abnormalities. Is this an early imaging finding which may suggest a pathophysiologic basis to explain the decreasing smell sensation in AD? Of course, more studies are needed for further discovering the nature of AD. We believe that early and correct diagnosis of AD in vivo by neuroimaging techniques will be possible in the near future.

There is a dose-related association between apolipoprotein E-4 (APOE-4) allelic frequency and the development of AD (APOE-2 may confer protection). Recent studies have shown a decline in resting parietal, temporal, and prefrontal PET glucose metabolism in cognitively intact patients with APOE-4. It remains to be seen whether this, and/or an analogous fMRI study, may serve to be a predictor of development of AD.

Recently some investigators have used dynamic contrast susceptibility contrast imaging MR to try to duplicate the nuclear medicine flow studies. Indeed they have found that relative values of temporoparietal regional cerebral blood volume (as a percentage of cerebellar rCBV) were reduced by a factor of 20% bilaterally in the patients with Alzheimer disease compared to normals. Using left and right temporoparietal rCBV as index measures, specificity was 96% and sensitivity was 95% in moderately AD and 88% in mild AD (Harris, 1998).

B. Parkinson’s Disease

Odor detection and identification are significantly impaired in Parkinson’s disease (PD) patients (Doty et al., 1988, 1995; Montgomery et al., 2000) (see Chapter 23). It is unclear whether the olfactory deficits in PD and AD share the same cause. Not surprisingly, PD research into the cause of smell dysfunction has focused on dopaminergic changes. Brooks and colleagues (1991) have demonstrated by using PET that patients with PD show significantly reduced mean uptake of 18F-dopa in the caudate and putamen, especially in the posterior part of the putamen. Previous functional imaging studies have also indicated a reduction of striatal dopamine storage in PD.

Figure 2 A 60-year-old woman with Alzheimer’s disease. UPSIT scores revealed severe bilateral anosmia. (A) Normal olfactory bulbs are seen (arrows) on coronal MR. Dilation of the olfactory sulci (arrowheads) reflects generalized atrophy. (B) Coronal MR scan through the temporal lobes shows temporal horn enlargement and atrophic changes, slightly worse on the right side.
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and MR, recent reports have noted the presence of high signal intensity areas in the periaqueductal gray matter of the midbrain (40%), the paraventricular thalamic regions (46%), the mammillothalamic tract, and in tissue surrounding the third ventricle on T2W MR scans (T2WI). Reversible thalamic lesions in the dorsal medial nuclei have also been reported. These areas may or may not enhance (in some cases the enhancement may be dramatic, almost sarcoid-like) and may be associated with mammillary body atrophy. Mammillary body enhancement may be the sole manifestation of Wernicke’s encephalopathy. Myelin degeneration, mammillary body volume loss, intracellular edema, and microglial proliferation are seen pathologically (but may be present in alcoholics without Wernicke’s).

MRI findings in patients with KP may enable early diagnosis of the disease, which may have a positive effect on both treatment and prognosis (Gallucci et al., 1990).

E. Schizophrenia

Impaired olfactory function has been reported in schizophrenics, especially males (see Chapters 23 and 24). These olfactory deficits, which are not of the same magnitude as those seen in AD and PD, are perhaps not unexpected given the occurrence of olfactory hallucinations as symptoms in a number of patients with schizophrenia and the evidence linking both to temporal lobe dysfunction (Rausch et al., 1977; Roberts, 1988). Neuropathological studies in schizophrenic patients have reported neuronal loss in the entorhinal region and prefrontal cortex, gliosis in the basal limbic structures of the forebrain, and atrophy in temporolimbic structures (Benes et al., 1986; Falkai et al., 1988).

Neurophysiological function studies (including regional cerebral blood flow, brain electrical activity mapping, and regional metabolic activity in the brain) in patients with schizophrenia have demonstrated prefrontal cortex and temporal lobe dysfunction (Mesulam, 1990). Functional imaging, such as PET or SPECT, in the study of schizophrenia is limited and inconclusive. However, functional imaging has provided some evidence that certain schizophrenic patients have decreased blood flow and metabolism in the frontal lobes (hypofrontality) (Alavi and Hirsch, 1991).

Anatomical imaging findings have basically paralleled the neuropathological changes in the brains of patients with schizophrenia. The most consistent finding on both CT and MRI is an increase in the size of the cerebral ventricular system, especially in the frontal and temporal horns, and corresponding decreases in cerebral tissue, especially in the prefrontal cortex and in medial temporolimbic structures (Mesulam, 1990; Suddath et al., 1989; Young et al., 1991). Suddath and colleagues (1989) evaluated the volume of the temporal lobes in schizophrenias by a quantitative MRI study. The results showed that the volume of temporal lobe gray matter was 20% smaller in the patients than in the control subjects, and lateral ventricular volume was 67% larger in the schizophrenia group than in the control group. Schizophrenic patients tend to have smaller hippocampi that matched controls. Schizophrenias are also reported to have cavum septum pellucidum more frequently than controls. In a recent study, Turetsky et al. (2000) reported that patients with schizophrenia exhibited 23% smaller olfactory bulb volume bilaterally than comparison subjects by a quantitative MRI study.

F. Congenital Anosmia

Congenital anosmia, which traditionally has been defined as anosmia present from a patient’s earliest recollection, has been recognized for centuries. The most common form of congenital anosmia is Kallmann’s syndrome or olfactory dysplasia, which is characterized by hypogonadotropic hypogonadism and anosmia (Kallmann et al., 1944; Lieblich et al., 1982). The incidence of Kallmann’s syndrome is about 1:100,000 in men and 1:50,000 in women. There has been increasing interest in the pathology, pathophysiology, and genetics of this disorder. Pathological and surgical studies of patients with Kallmann’s syndrome have shown agenesis of the olfactory bulbs (DeMorsier and Gauthier, 1963; Males et al., 1973). Laboratory findings include decreased serum follicle-stimulating hormone and luteinizing hormone as well as decreased urinary gonadotropins (Lieblich et al., 1982).

In medical imaging studies, CT is a limited tool for the demonstration of sinonasal and intracranial abnormalities in patients with congenital anosmia (Klein et al., 1987; Moorman et al., 1984). Surface coil MRI is the optimal modality to reveal the intricate details of the olfactory bulbs, tracts, and rhinencephalon in vivo. Klingmuller and colleagues (1987) have clearly demonstrated the olfactory sulci in a normal control group by MRI, but not in the patients with olfactory dysplasia. More recently, the authors have studied two cases with Kallmann’s syndrome by MRI. Both showed no olfactory bulb at all and flattening of the gyrus recti (Yousem et al, 1993, 1996a); frontal and temporal lobe volumes were normal (Fig. 3).

In a mixed population of patients with congenital anosmia, we found olfactory bulb and tract absence (68–84%) and hypoplasia (16–32%) in all 25 cases studied. Eight individuals had Kallmann’s syndrome (hypogonadotropic hypogonadism with anosmia). Temporal and/or frontal lobe volume loss were noted in 5 individuals, mild in all but one individual. We concluded that congenital anosmia
Figure 3 (A) Coronal 500/20 scan from normal volunteer (64-year-old woman with normal smell function) demonstrates normal olfactory bulbs (arrows). (B) Coronal 500/17 scan of 27-year-old woman with congenital anosmia without Kallmann’s syndrome shows extremely atrophic olfactory bulbs (arrows). (C) Coronal 500/14 scan of 29-year-old male patient with Kallmann’s syndrome evidences absence of olfactory bulbs and tracts with flattened gyrus rectus (arrow) on the right side, but with normal-appearing gyrus rectus on the left side.

or hyposmia appears to be an olfactory bulb tract phenomenon rather than a central process (Yousem et al., 1996a).

G. Head Trauma

Craniofacial trauma can alter olfactory ability through one of several mechanisms: (1) damage to the nose, sinuses, or both with resultant mechanical obstruction to odorants, (2) shearing of olfactory filaments as they course through the cribriform plate, (3) contusion to the olfactory bulb, and (4) contusion or shearing injury of the cerebral cortex, particularly the frontal and temporal lobes (see Chapter 30). The incidence of anosmia or hyposmia after head trauma has been reported quite variably from 2 to 38%, (Deems et al., 1991; Doty et al., 1997; Hagan, 1967; Leigh, 1943; Levin et al., 1985; Schechter and Henkin, 1974; Summer, 1964; Zusho, 1982) and increases with the severity of injury (Levin et al., 1985; Summer, 1964). However, even a minor injury can sometimes result in anosmia or hyposmia (Schechter and Henkin, 1974; Summer 1964). Recent evidence has shown that the location of the hematoma or contusion of the brain after head trauma is one of the most important factors leading to olfactory dysfunction (Costanzo and Zasler, 1991; Doty et al., 1997; Levin et al., 1985; Yousem et al., 1996b). Specifically, diminished olfactory discrimination has been confirmed in patients with prefrontal lesions (Potter and Butters, 1980). Animal studies have shown that the prefrontal olfactory area plays a prominent role in the fine and specific discrimination of odors (Tanabe et al., 1975). Besides prefrontal lesions, temporal lobe structures are also involved in the odor processing of odor perception (Rausch and Serafetinides, 1975; Rausch et al., 1977). Indeed frontal or temporal lobe hematomas or contusions are now believed to be one of the most common causes of olfactory dysfunction after head injury (Costanzo and Zaster, 1991; Doty et al., 1997; Levin et al., 1985; Schellinger et al., 1993; Yousem et al., 1996b) (Fig. 4).

It has been established that plain skull radiography plays only a small role in the evaluation of head trauma (Masters et al., 1987). CT currently is the study of choice when diagnostic imaging is necessary after acute head trauma (Cohen, 1990; Kelly et al., 1988). CT can detect subarachnoid hemorrhage, fractures, and intraventricular blood, lesions for which MRI is less sensitive acutely. CT can be performed with close patient monitoring in a rapid fashion. However, MRI is superior to CT in the detection and characterization of subacute injuries, hemorrhage outside the subarachnoid space as in subdural hematomas, cortical contusion, and shearing injuries. MRI is exquisitely sensitive to diffuse axonal injuries leading to demyelination. MRI is also useful in the follow-up of brain contusion and/or hemorrhage, thereby eliminating the radiation exposure associated with CT (Cohen, 1990; Zimmerman et al., 1986).
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Figure 4 A 20-year-old woman with posttraumatic anosmia. (A) A small olfactory tract is seen on the right side (arrow), but none is seen on the left. Severe inferior frontal lobe encephalomalacia is soon on this coronal T1W MR scan. (B) Encephalomalacia is well seen on the T2W MR scan where hyperintense signal (S) has replaced the inferior frontal lobes (where smell processing occurs).

At our institution, 25 patients with posttraumatic smell dysfunction were evaluated by olfactory testing and MR. Quantitative and qualitative gradings for olfactory bulb, tract, subfrontal region, hippocampus, and temporal lobe damage correlated with olfactory test results. Twelve patients were anosmic, 8 had severe impairment, and 5 were mildly or impaired. Olfactory bulb and tract (88% of patients), subfrontal (60%), and temporal lobe (32%) injuries were found but did not correlate well with olfactory test scores (Doty et al., 1997b; Yousem et al., 1996b). Abnormalities on MR in patients with posttraumatic olfactory dysfunction occur at a very high rate (88%), predominantly in the olfactory bulbs, tracts, and inferior frontal lobes. Qualitative and quantitative assessments of damage show little correlation with olfactory tests probably due to multifocal injury, ciliary nerve damage, and the constraints of small sample size.

H. Brain Tumors

The incidence of chemosensory changes caused by intracranial tumors has rarely been investigated. In a study of 750 consecutive patients presenting with chemosensory disorders to the University of Pennsylvania Smell and Taste Center, only two cases (0.3%) were induced by brain tumors (Deems et al., 1991). In one study anosmia was reportedly present in 19 of the 26 cases of Foster-Kennedy syndrome (retrobulbar optic neuritis, central scotoma, optic atrophy on the side of the lesion and contralateral papilledema usually occurring in tumors of the frontal lobe of the brain which press downward) (Jarus and Feldon, 1982). Bakay (1984) emphasized that loss of smell perception is one of the first signs of olfactory meningiomas.

In general, tumors or other destructive lesions involving the olfactory bulb, tract, or prefrontal lobe may cause olfactory deficits. Temporal lobe tumors usually cause olfactory hallucinations. It is estimated that approximately 20% of the tumors of the temporal lobe produce some form of olfactory disturbance (Furstenberg et al., 1943). The presence of olfactory deficits correlates more with the location of tumors than the histology (Fig. 5).

I. Acquired Immunodeficiency Syndrome

Olfactory deficits of patients with human immunodeficiency virus (HIV) infection have been reported (Brody et al., 1991; Heald et al., 1998). These authors suggest that impaired olfaction might serve as a marker of early central nervous system HIV involvement. The principal histopathological abnormalities in the brain of acquired immunodeficiency syndrome (AIDS) patients are in the subcortical structures, predominantly in the central white matter, deep gray structures including the basal ganglia, the thalamus, and the brain stem (Petito et al., 1986; Price et al., 1988). Everall et al., (1991) have found that the neuronal numerical density in the frontal cortex is significantly lower in HIV patients than in controls—a loss of about 38% of neurons in the superior frontal gyrus in AIDS patients. This may account for the olfactory deficits in these patients.
Figure 5 Temporal lobe mass in a 62-year-old woman with olfactory hallucinations. (A) T2W MR scan reveals a relatively well-defined right temporal lobe mass with mild mass effect. (B) Contrast-enhanced T1W MR image shows peripheral enhancement of the tumor with a satellite nodule laterally. Sulci are effaced and the temporal horn is obliterated.

Neuroradiological study has found that patients with HIV infection show widened cortical sulci, enlarged ventricles, cerebral atrophy, and brain stem atrophy when compared with controls (Brun et al., 1986; Elovaara et al., 1990; Post et al., 1988). Opportunistic infections and CNS lymphoma may be superimpositional on these changes. The pathogenesis of the olfactory deficits of AIDS patients needs further investigating but most likely will relate to disease in the prefrontal lobe. In addition to CNS changes, sinusitis in HIV-infected patients is common and severe.

Therefore, the possibility of peripheral cause of olfactory deficits in AIDS patients also has to be taken into account in certain cases.

J. Multiple Sclerosis

Multiple sclerosis (MS), a markedly debilitating neurological disease, affects millions of Americans in the prime of their lives. Though the influence of MS on the sense of smell has long been controversial, recent MRI studies (Doty et al., 1997, 1999) have demonstrated that the olfactory function in patients with MS is closely correlated with the number of demyelinating plaques within central olfactory processing areas of the brain, as determined by MRI (Fig. 6, 7). A strong negative relationship (Spearman r = -0.94) was found between scores on the University of Pennsylvania Smell Identification Test (UPSIT) and the number of plaques within the inferior frontal and temporal lobe regions (Doty et al., 1997). A close association was present, longitudinally, between the remission and exacerbation of plaque numbers and UPSIT scores, with lower UPSIT scores occurring during periods of exacerbation (Doty et al., 1999).

K. Other Central Causes

There are also reports of olfactory dysfunction in hypochondriasis, amyotrophic lateral sclerosis, epilepsy, and migraine (Doty et al., 1991b; Mott and Leopold, 1991). Although the pathogenesis of olfactory dysfunction in these disorders is still unclear, it appears that a central mechanism is involved, rather than a peripheral one.

VI. OVERVIEW AND DISCUSSION

It is apparent from the studies reviewed in this chapter and the information presented elsewhere in this volume that olfactory dysfunction can be due to numerous causes. Once an olfactory disorder has been recognized, the most important step in the diagnostic process is to determine the site of the lesion, i.e., anatomical localization. Unfortunately, current clinical olfactory testing is unable to localize the site of morphological changes (Doty et al., 1984). Modern medical imaging techniques can be of great value in the anatomical classification and localization of the common causes of olfactory dysfunction (Li et al., 1994). The most common source of olfactory dysfunction is the peripheral pathway (Goodspeed et al., 1987; Mott and Leopold, 1991). In the evaluation of peripheral causes, the “sinus series” radiographs offer limited information. At present, high-resolution CT, especially coronal scans, is
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**Figure 6** A 55-year-old MS patient with no significant olfactory dysfunction, as measured by the UPSIT. Axial T2W MRI scan shows no obvious plaques in the inferior frontal and temporal lobe regions (A). Numerous plaques were identified in supraperiventricular regions (B).

the study of choice to look at the bony sinonasal structures and the ostiomeatal complex. CT can also provide important information as a road map, which may be needed for surgical treatment.

MRI possesses special ability in soft tissue discrimination and offers multiplanar capabilities. In the evaluation of the central causes of olfactory disturbances, MRI has a paramount role. Neuroimaging studies of patients with olfactory deficits related to neuropsychiatric problems have revealed interesting findings and possibly clues for understanding some of the links between olfactory deficits and pathophysiological changes of the brain. The neuroimaging findings of patients with AD, KP, or schizophrenia share some similarities. Thus, almost all of the abnormalities of the brain parenchyma revealed by neuroimaging studies in patients with AD, KP, or schizophrenia involve central brain areas that contain neurons of olfactory projections including areas of the prefrontal lobe, temporal lobe, hippocampus, and thalamus.

Recent studies have provided a clear physiological explanation for decreased olfactory function in patients with MS (Doty et al., 1991, 1998, 1999). Current studies from our laboratory suggest that MS, with its relatively discrete focal regions of demyelination lesion, may be of value in studying brain regions involved in sensory perception in addition to olfaction.

It is much more difficult to explain the olfactory dysfunction in PD patients, and presently imaging studies have been of little use in clarifying this matter. Loss of olfaction in these patients may be related to factors with dopamine

**Figure 7** Axial T2W MRI scans from a severely microsmic (UPSIT = 20) 50-year-old man with an 8-year history of MS. The place of section in (A) is 6 mm below that of (B). Note the prominent plaques (10 × 5 mm each) within the posterior part of the white matter of the gyrus rectus of the L and R subfrontal lobe regions (arrows 1 and 2, respectively), and the relatively high signal intensity plaques in the subtemporal lobe regions (arrows 3 and 4).
and dopamine receptors, although, as noted earlier, no return of function accompanies L-dopa treatment. In addition, pathological changes in the areas of putamen and caudate nuclei, which have fibers connected with limbic system and striatum, may contribute to the loss of the sense of smell. In this hypothesis, the olfactory dysfunction in PD patients might share a similar etiology to patients with HD.

In congenital disorders, such as Kallmann's syndrome, the cause of anosmia can be seen on MRI studies as the absence of olfactory bulbs (Yousum et al., 1993, 1996a). Other congenital abnormalities, such as choanal atresia and meningoencephaloceles, also can be detected by imaging studies (Klein et al., 1987; Moorman et al., 1984).

In the categories of head trauma and brain tumors, imaging studies have shown strong links between olfactory dysfunction and the location of the damaged brain. The histology of the tumor or traumatic injury is less critical than its location (Costanzo and Zasler, 1991; Jarrus and Feldon, 1982; Schellingen et al., 1983; Yousum et al., 1996b). Hyposmia or anosmia induced by occupational or accidental exposure to toxins, as well as that induced by intranasal use of drugs such as cocaine, has been traditionally thought to be due to damage to the peripheral pathways. However, one study has suggested that olfactory deficits caused by occupational exposure to toxins may have both peripheral toxic and CNS effects (Schwartz et al., 1989). Imaging studies have shown CNS complications in cocaine abusers (Holman et al., 1991; Kalkow et al., 1989). Imaging studies have shown strong links between olfactory dysfunction and the location of the damaged brain. The histology of the tumor or traumatic injury is less critical than its location (Costanzo and Zasler, 1991; Jarrus and Feldon, 1982; Schellingen et al., 1983; Yousum et al., 1996b).

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VII. SUMMARY

Medial imaging is an essential part of the evaluation of patients with olfactory disorders. In the assessment of the peripheral causes of olfactory deficits, medical imaging studies, especially CT and/or MRI, can reveal anatomical information and structural changes, suggest differential diagnosis, and provide the road map that may be needed for surgical intervention. On the other hand, in the evaluation of the central causes, MRI, fMRI, PET, or SPECT can provide information elucidating the links between olfactory dysfunction and the structural or functional changes in the living brain.

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