Handbook of Olfaction and Gustation

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Evaluation of Olfactory Deficits by 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 and (2) sensorineural disorders resulting from injury to the olfactory receptors (within the olfactory mucosa), the olfactory bulb or tract, or related parts of the central nervous system such as the prefrontal lobe, septal nuclei, amygdala, and temporal lobe (Doty and Snow, 1987). For medical imaging we categorize olfactory dysfunction into two major groups: (1) peripheral causes—sinonasal tract disorders, and (2) central causes—intracranial disorders. It is important to relate olfactory deficits to the appropriate anatomical and pathological changes. Unfortunately, clinical olfactory testing alone is often not capable of localizing the different causes of decreased sense of smell.

Modern medical imaging techniques offer a valuable means for evaluating and distinguishing disorders of olfaction. Although revolutionary changes in medical imaging techniques have occurred in the last few decades, very few articles have dealt with imaging studies related to chemosensory disorders (Goodspeed et al., 1987a; Kimmelman, 1991; Klingmuller et al., 1987; Schellinger et al., 1983). In an attempt to correct this paucity, this chapter will comprehensively review the pertinent medical literature on this topic and detail our own experience. We hope to bridge the chasm between imaging and clinical assessment of olfactory deficits.

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 because of recently developed imaging modalities and refined techniques (Carter and Runge, 1988; Healy, 1992; Jagust and Eberling, 1991; Jolles et al., 1989; Reiman and Mintun, 1990; Shapiro and Som, 1989; Vogl et al., 1990). 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 Som, 1989; Som et al., 1988). On the other hand, functional imaging (PET, SPECT) affords 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). The relevant imaging modalities that may be helpful in the evaluation of common causes of olfactory deficits are reviewed in this section.

A. Plain Radiographs

Plain film radiography, i.e., the “sinus series,” including the Caldwell view, the Waters view, the lateral view, and the base view, has long been a standard method of diagnosing nasal and paranasal sinus inflammatory disease. The variability in extent of sinus pneumatization, both in adults and in children, causes difficulty in plain film interpretation in certain cases. Even in the hands of an experienced radiologist, with the most careful and meticulous attention to detail, plain film examinations have substantial limitations. Misdiagnosis, overdiagnosis, or underdiagnosis of paranasal sinus diseases is not uncommon, especially in lesions located in the ethmoid sinus, sphenoid sinus, or high nasal vault (McAllister et al., 1989; Zinreich et al., 1987). In addition, problems of overlap and nonspecific findings are impossible to avoid. The most important deficit of the plain film is its inability to provide the road map of the ostiomeatal complex, which may be needed for endoscopic surgical intervention (Zinreich et al., 1987). We believe that plain radiographs should play only a minor role in the imaging evaluation of olfactory dysfunction.

B. Conventional Tomography

Conventional tomography is sometimes able to eliminate confusing superimposed detail. The main disadvantage of conventional tomography as compared with CT and/or MRI is the limitation of soft tissue resolution and differentiation. Multiplanar reconstructions are not possible and anatomical detail is lost. As more and more centers have gone to higher technological machinery, the tomographic unit has become almost anachronistic.

C. Computed Tomography

CT is well suited to the investigation of the sinonasal cavities. Because CT scanning is as sensitive to soft tissue disease as to bony changes, each scan can be photographed at an appropriate window width and level to optimally see insidious soft tissue differences in attenuation and fine bony detail. To study soft tissue, the window widths range from 150 to 400 Hounsfield units. Conversely, the bony detail is best observed at wide window settings—from 2000 to 4000 Hounsfield units. The basic CT scanning protocol should include all of the nasal cavity, paranasal sinuses, hard plate, anterior skull base, orbits, and nasopharynx. The brain should be included if central causes of olfactory dysfunction are suspected. The scans are commonly performed in both the axial and coronal planes for optimal assessment of the complex paranasal anatomy, but coronal scans are the most valuable for the anterior nasoethmoid (ostiomeatal) region. Alternatively, thin sections in one plane with multiplanar reconstructions may be adequate. For practical purposes, slice thicknesses of 3–5 mm are often employed. For the evaluation of the ostiomeatal complex (the maxillary sinus ostium, infundibulum, uncinate process, and middle meatus), 3 mm thick coronal sections are the routine at our institution. Intravenous contrast enhancement is usually reserved for the identification of vascular lesions, tumors, meningeal or parameningeal processes, and abscess cavities (Carter and Runge, 1988). In our experience, high-resolution CT is the most useful and cost-effective screening tool for the evaluation of sinonasal tract inflammatory disorders.

D. Magnetic Resonance Imaging

MRI’s multiplanar capability is especially advantageous in the evaluation of sinonasal tract neoplasms and brain disorders. MRI, however, is less sensitive for the detection of bony cortical
abnormalities and landmarks. Soft tissue discrimination, on the other hand, is more clearly illustrated by MRI than by CT. Most soft tissue disease processes can be accurately localized with a minor degree of tissue differentiation, i.e., infection versus tumor versus hemorrhage. The anatomical resolution of MRI in the brain is superior to CT. Because of their short scan time, one can use thin sections, larger matrices, and smaller fields of view, yet maintain high contrast to noise using T1 weighted scans or fast-spin echo T2 weighted images. T2 weighted scans can better delineate the contrast between normal and inflammatory or neoplastic tissue. Proton density images possess advantage of both T1 and T2 weighted scans (Shapiro and Som, 1989).

In the evaluation of skull base invasion by sinonasal tumors, MRI is superior to CT (Paling et al., 1987). Gadolinium-enhanced scans are particularly useful at the skull base to detect dural or leptomeningeal involvement. Gadolinium-DTPA, a paramagnetic contrast agent, has been widely utilized for enhancing the margin of sinonasal tumors and distinguishing solidly enhancing tumor from rim-enhancing inflammatory processes (Brasch, 1992; Vogl et al., 1990).

With regard to the olfactory system, CT and MRI play complementary roles in evaluating sinonasal tract neoplasms (Shapiro and Som, 1989; Som et al., 1990). However, MRI is the study of choice to evaluate the olfactory bulbs, olfactory tracts, and intracranial causes of olfactory dysfunction (Klingmuller et al., 1987; Suzuki et al., 1989; Yousem et al., 1993).

E. Nuclear Medicine

In general, radionuclide imaging plays no significant role in the diagnostic workup of patients with suspected sinonasal tract disease (peripheral causes of olfactory deficits), except in the case of cerebrospinal fluid (CSF) leaks. Functional imaging studies, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), are valuable in detecting alterations of regional brain function and biochemistry in vivo (Alavi and Hirsch, 1991; Fowler et al., 1988; Jagust and Eberling, 1991; Jolles et al., 1989; Reiman and Mintun, 1990). Recent studies have suggested that functional imaging is more sensitive than anatomical imaging in detecting abnormalities of the brain related to disorders such as Alzheimer’s disease and Parkinson’s disease—conditions associated with loss of olfactory function (Jajust and Eberling, 1991; Jolles et al., 1989).

F. Angiography

Since the introduction of CT and MRI, angiography, an invasive technique, has become less and less necessary. At present, its use in imaging of the head and neck is relatively limited to the visualization and embolization of aneurysms, arteriovenous malformations, sources of recurrent epistaxis, and highly vascular neoplasms.

III. BASIC ANATOMY AND PHYSIOLOGY OF THE OLFACTORY SYSTEM

Since the anatomy and physiology of the olfactory system are discussed elsewhere in this volume, we only briefly mention these topics here. The sensation of smell is induced by the stimulation of olfactory receptor cells by volatile chemicals. The olfactory receptor cells, i.e., the primary olfactory neurons, are encompassed in the neuroepithelium, which is located at the top of the nasal vault, the upper portion of the nasal septum, the superior surface of the superior nasal turbinate, and the region of the cribriform plate. Afferent information from the receptors is transmitted by the olfactory nerves, which course through the cribriform plate of the ethmoid bone to terminate in the glomeruli of the olfactory bulb (Doty et al., 1992a). In the olfactory bulb, the olfactory nerves make synaptic contact with dendrites of mitral and tufted cells. From there, the efferent neurons of the olfactory bulb give rise to fibers forming the olfactory tracts, which lie just under the gyrus rectus region in the olfactory sulcus of the frontal lobes. Axons from mitral and tufted cells project to central brain limbic system components, including the
piriform cortex and adjacent corticomedial amygdala (which together form the uncus), the ventral striatum, the parahippocampal area, and the anterior olfactory nuclei. From these areas there are widespread interconnections with many parts of the brain, including the mediodorsal thalamus, hypothalamus, orbitofrontal and dorsolateral frontal cortex, temporal cortex, and other areas of the limbic system (Doty et al., 1992a; Price, 1985, 1990).

IV. PERIPHERAL CAUSES OF OLFACTORY DISTURBANCE

Sinonasal tract disease is one of the common causes of olfactory disturbance (Goodspeed et al., 1987a,b). The etiology of the olfactory deficits among patients with nasal and paranasal sinus disease is most likely nasal airway obstruction. Recently, the influence of nasal obstruction on olfaction has been comprehensively reviewed (Doty and Frye, 1989). Any cause of bilateral obstruction can decrease smell sensations by limiting air flow to the olfactory receptors. In addition to the obstructive effect, lesions that are located in the upper nasal vault and/or cribriform plate region may also directly damage the olfactory epithelium and olfactory neurons. The common peripheral sinonasal tract causes of olfactory deficits include infections, tumors, allergic rhinosinusitis, congenital or developmental abnormalities, and others.

A. Sinonasal Infectious Disease

Paranasal sinusitis is a relatively common disorder affecting approximately 30% of the population at some time in their lives (Allphin et al., 1991). One of the common symptoms of acute and chronic paranasal sinusitis is decreased smell sensation, which is generally reversible. The prompt diagnosis and treatment of sinusitis are important for restoring olfactory function. Though the exact cause of chemosensory dysfunction secondary to sinusitis is elusive, alterations in nasal air flow and mucociliary clearance or obstruction from secretory products, polyps, or retention cysts may contribute to olfactory dysfunction (Loury and Kennedy, 1991).

In the diagnosis and evaluation of paranasal sinusitis, medical imaging plays an important role. At present, high-resolution CT is the preferred imaging technique, preceded by nasal endoscopic examination. Radiographic manifestations of sinusitis have been well documented. In general, air-fluid levels are usually indicative of acute sinusitis, whereas mucoperiosteal thickening can be seen in acute and chronic disease. CT is an excellent modality for the evaluation of bony abnormalities, such as osteitis or remodeling seen in some inflammatory lesions. CT will also identify the infundibulum, the maxillary sinus ostium, the middle meatus, the uncinate process, and the individual ethmoid air cells that make up the ostiomeatal complex. This will help the functional endoscopic sinus surgeon to plan effective surgery to restore normal mucociliary clearance. On the other hand, MRI is also highly sensitive for detecting mucosal thickening and other soft tissue abnormalities (Shapiro and Som, 1989). By and large, inflamed mucosa is usually high in signal intensity on T2 weighted MR images and low in intensity on T1 weighted scans. Secondary formation of polyposis, retention cysts, or mucoceles of sinonasal cavities can be clearly detected by either CT or MRI (Barat, 1990; Drutman et al., 1991; Shapiro and Som, 1989).

B. Tumors of the Nasal Cavity and Paranasal Sinuses

Neoplasms of the sinonasal tract are uncommon. Malignant tumors of the nasal cavity and paranasal sinuses account for only 0.2–0.8% of all human malignancies (Som, 1991). Early symptoms of sinonasal tract tumors, such as nasal discharge, unilateral nasal obstruction, and minor intermittent epistaxis may simulate low-grade chronic infection. Subsequently symptoms depend on the tumor’s location and pattern of growth. Neoplasms arising in the upper nasal cavity
and extending through the cribiform plate or into the ethmoid sinuses are often accompanied by frontal headache, visual disturbances, and decreased smell sensation. Almost all sinonasal tract tumors, and tumor-like conditions that grow to a large size may cause a decline in olfactory acuity by interfering with patency of the nasal airway or directly destroying the olfactory receptors. Two examples of intrinsic sinonasal tract tumors (the olfactory neuroblastoma and the inverted papilloma) that often cause hyposmia or anosmia may serve as prototypes for masses in this region.

1. Olfactory Neuroblastoma

Olfactory neuroblastoma, or esthesioneuroblastoma, is a rare nasal tumor originating from the olfactory neuroepithelium lining the roof of the nasal vault and in close proximity to the cribiform plate. Fewer than 300 reported cases can be found in the world literature. Olfactory neuroblastomas occur in all age groups, with a peak incidence in the 11–20 and 51–60 age groups. There is a slight preponderance of the tumor in women. The incidence of olfactory neuroblastoma has been estimated to range from 2% to 3% of all malignant intranasal neoplasms. The most common symptoms are unilateral nasal obstruction and recurrent epistaxis. Hyposmia or rhinorrhea is not unusual. Extension into the orbit, paranasal sinuses, or anterior cranial fossa may cause vision disturbances and headache (Elkon et al., 1979; Li et al., 1993; Newbill et al., 1985). In the detection and staging of olfactory neuroblastoma, CT and/or MRI plays an important role. Generally speaking, MRI is more accurate than CT in showing the tumor’s intracranial extent. MRI is also exquisitely useful in differentiating neoplasm from obstructed secretions because of the difference in the signal intensity (secretions are bright on T2, tumor intermediate) and gadolinium enhancement. Unfortunately, signal intensity characteristics of various sinonasal tract tumors overlap one another, so MRI cannot usually predict specific tumor histology. However, juvenile angiofibroma can usually be distinguished from other tumors on the basis of its high vascularity and marked enhancement.

2. Inverted Papilloma

The inverted papilloma is a relatively rare and locally aggressive sinonasal tumor. It constitutes 0.5–4% of primary nasal tumors and occurs predominantly in males in the fifth and sixth decades of life (Phillips et al., 1990). The most common presenting symptoms are nasal obstruction, epistaxis, and hyposmia. Subsequent sinusitis and tumor extension into the sinuses and orbits can cause purulent nasal discharge, pain, and diplopia (Som, 1991). Radiographic findings of inverted papilloma can vary from a small nasal polypoid nodule to an expansile large mass, which may remodel the nasal vault and extend into the sinuses, orbits, or even the anterior skull base. CT and MRI are useful in defining the location and extension of the tumor (Buchwald et al., 1990; Yousem et al., 1992) (Fig. 1, A and B). Calcification is not uncommon in this tumor.

Other sinonasal tract tumors, such as squamous cell carcinoma, adenocarcinoma, and melanoma, can also cause hyposmia or anosmia during their late stage. Squamous cell carcinoma accounts for 80% of paranasal sinus malignancies, is most commonly seen in the maxillary sinus, and usually demonstrates bone destruction at the time of presentation. Adenocarcinomas occur most frequently in the ethmoid sinus, and melanoma is usually seen intranasally.

C. Allergic Rhinitis

Allergic rhinitis is a common upper airway condition affecting about 30 million Americans with peak prevalence in the age group 35–54 years (Baroody and Naclerio, 1991). Hyposmia or anosmia is common with allergic rhinitis, mainly caused by nasal obstruction from polyps or inflamed mucosa, which limits access of inspired air to the roof of the nasal vault (Cowart et al., 1993). The diagnostic workup begins with a careful history, which attempts to identify offending allergies. Skin testing of specific antigens is often used to confirm the diagnosis. Medi-
Figure 1 Forty-year-old woman with 3-month history of decreasing smell sensation and left nasal obstruction. (A) Bone-targeted coronal CT shows an expanded opacified left nasal cavity with bowing of the lateral nasal wall (arrows) and opacification of the left maxillary and both sphenoid sinuses. (B) Axial contrast-enhanced CT scan shows erosion through the left lamina papyracea (arrow) with displacement of the medial rectus and globe laterally. The differentiation between tumor and obstructed secretions is not readily apparent with CT. Histological diagnosis: nasal cavity carcinoma arising within a dysplastic inverted papilloma.

cal 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, gliomas, and others. Medical imaging techniques, especially high-resolution CT, play a key role in detecting and evaluating the facial and bony changes (Barkovich et al., 1991; Klein et al., 1987). CT is most useful because surgical correction requires identification and closure of the osseous abnormalities. MRI is most effective in defining soft tissue masses such as cephaloceles and nasal gliomas.
It is estimated that 30 million Americans have used cocaine and five million use it regularly (Gregler and Mark, 1986). Intranasal use of cocaine and heroin has reached epidemic proportions in the United States. Although hyposmia and anosmia have been suggested to occur often in cocaine abusers, few studies using quantitative measures of olfactory function have confirmed such reports. A recent study 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 cribriform 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 published recently (Schweitzer, 1986; Newman et al., 1988). 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 (1990) demonstrated multifocal cortical deficits with a
special predilection for the frontal and temporal lobes on SPECT perfusion brain scans in chronic cocaine abusers. Similar findings have been reported by others (Holman et al., 1991; Kolkow et al., 1988). These findings may suggest a central basis for some cases of cocaine-related decreased olfaction. Some studies have also 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 cribriform plate (Kassel, 1988; Mathog, 1992). Because ethmoid complex and cribriform plate fractures are difficult to detect on plain radiographs, thin-section coronal CT is the best measure to assess nasoethmoid trauma (Daly et al., 1990; Kassel, 1988).

Olfactory deficits may also accompany Wegener’s granulomatosis, Paget’s disease, fibrous dysplasia, and leprosy. The mechanism of the olfactory deficits from these diseases is most likely related to conductive disorders of the sinonasal tract due to bony or soft tissue destruction of the airway.

V. CENTRAL CAUSES OF OLFACTORY DISEASES

Many central nervous system (CNS) disorders 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 disease (AD). Nearly all studies of olfactory function in patients with AD have reported decreased smell relative to age-matched controls. These studies demonstrate marked impairment of smell identification and an increased threshold for odor detection in early AD (Doty et al., 1987; Doty, 1991; Serby et al., 1991).

Recent neuropathological studies have correlated well with these clinical findings. The anterior olfactory nuclei in AD patients show evidence of 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, piriform, and temporal cortices, are frequently affected by AD (Harrison, 1986; Pearson and Powell, 1989). In addition to 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 well 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 recognized that CT and/or MRI delineation of atrophic changes in the temporal lobe and the hippocampus with enlargement of hippocampal-choroidal fissures strongly supports 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 MRI 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 (Figs. 2A and 2B).

In addition to 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 change shown 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 the temporoparietal region and the frontal areas. In a recent report (Bonte et al., 1993), seven patients with possible diagnosis of AD studied by SPECT technique showed only frontal flow abnormalities. Is this an early imaging finding that may suggest a pathophysiological basis to explain the decreased smell sensation in AD? Of course, more studies are needed to further elucidate 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.

B. Parkinson’s Disease

Odor detection and identification are significantly impaired in Parkinson’s disease (PD) patients (Doty et al., 1988; Ward et al., 1983). 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. Recently, 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. PET with 18F-dopa in PD patients has also demonstrated reduced basal ganglia activity (Alavi and Hirsch, 1991). However, the olfactory deficit is unrelated to severity of motor or cognitive symptoms and is not improved by L-dopa therapy (Doty et al., 1992b), so the underlying cause of olfactory dysfunction in PD still requires more study.

CT scanning has little role in establishing the diagnosis of PD, other than to exclude mass lesions in the brain. In general, CT shows no specific striatal abnormalities and occasionally only mild, nonspecific ventricular and sulcal enlargement. The major feature of PD on MRI appears to be a trend toward a decreased width of the pars compacta of the substantia nigra (Braffman et al., 1989). Moderate or marked cortical atrophy tends to occur more frequently in PD patients than in controls. MRI may occasionally show abnormal decreased T2W intensity in the putamen and to a lesser degree in the caudate nuclei and substantia nigra, suggestive of iron deposition (Drayer et al., 1986).

C. Huntington’s Disease

Patients with Huntington’s disease (HD) evidence olfactory dysfunction (Doty, 1991; Moberg et al., 1987). Neuropathological studies in HD have demonstrated premature neuronal cell death and reactive gliosis occurring most markedly in the head of the caudate nuclei bilaterally (Myers
Figure 2  Sixty-year-old woman with Alzheimer’s disease. Olfactory function was evaluated in this patient using the University of Pennsylvania Smell Identification Test (UPSIT). A severe bilateral loss of olfactory function was present. (A) Normal olfactory bulbs are seen (arrows) on coronal MR. Dilatation 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.
et al., 1991; Vonsattel et al., 1985). A loss of 70–80% of the striatal neurons may occur before functional impairment is obvious. Similar, but less extensive, changes also affect the putamen. Later, atrophy of the cerebral cortex occurs as well. All these progressive atrophic changes can be identified on CT and MRI scans, especially in the caudate nuclei where the volume of the caudate head decreases and the intercaudate distance increases (Simmons et al., 1986; Starkstein et al., 1985). PET scan studies of patients with HD have consistently demonstrated hypometabolism in the caudate nuclei, often before the development of atrophy on CT (Hayden et al., 1986). SPECT studies involving HD patients have also revealed decreased uptake in the caudate nuclei, including the caudates of one patient with early disease and no evidence of atrophy on MRI (Nagel et al., 1988; Reid et al., 1988). Thus, functional imaging with PET or SPECT may contribute to the early diagnosis of HD.

Theoretically, the input of caudate/putaminal fibers to the limbic system and striatum may be altered, leading to olfactory dysfunction, but the exact mechanism for hyposmia in HD patients remains to be worked out.

D. Korsakoff’s Psychosis

Patients with Korsakoff’s psychosis (KP) exhibit impaired odor detection, identification, and intensity estimation (Jones et al., 1975; Mair et al., 1986). Recently, an animal model study has shown that the behavior of rats recovering from pyrithiamine-induced thiamine deficiency shares several important features with the impairments of KP patients, including those observed for smell, hearing, learning, and memory (Mair et al., 1991). The mechanism of hyposmia and/or dysosmia in patients with KP is unclear and still under investigation. Olfactory perception may be selectively impaired in KP by the diencephalic lesions that are characteristic of this disease. Degeneration in the mediodorsal thalamic nucleus (the common neuropathological lesion in KP) and atrophy in the prefrontal areas may also cause the olfactory dysfunction (Mair et al., 1986).

A quantitative neuropathological study of the human cerebral cortex has shown that the number of cortical neurons in the superior frontal lobe of chronic alcoholic patients is significantly reduced (Happer et al., 1987). Traditional neuropsychological tests and functional imaging studies have also demonstrated disturbances of frontal-lobe function and metabolic deficits in patients with KP (Joyce and Robbins, 1991; Kopelman, 1991; Metter et al., 1989).

Brain CT scans have demonstrated that KP patients show more pronounced third and lateral ventricular dilatation and wider interhemispheric fissures than matched groups of normal controls and non-Korsakoff alcoholics (Jacobson and Lishman, 1990; Ron et al., 1982, Ron, 1983). Shrinkage appears to be especially pronounced in the frontal lobes and cerebellum (Jacobson and Lishman, 1990). A recent MRI study (Jernigan et al., 1991) has revealed that patients with KP show widespread reductions in gray matter volumes in addition to CSF increases, with the greatest reductions observed in diencephalic structures. The volume losses that best differentiate the KP patients from the alcoholic controls included losses in anterior portions of the diencephalon, mesial temporal lobe structures, and orbitofrontal cortices (areas involved in olfaction perception). Several other studies (Donnal et al., 1990; Gallagher et al., 1990; Squire et al., 1990; Victor, 1990) have also demonstrated that MRI is highly sensitive in detecting reversible diencephalic (medial thalamic) and mesencephalic (periaqueductal) lesions. 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 (Hurwitz et al., 1988; Kopala et al., 1989; Serby et al., 1990). These olfactory deficits, which are not of the same magnitude as those seen in AD and PD, are perhaps not unexpected, given the occur-
rence 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 findings (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 temporal lobes in schizophrenics 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 are also reported to have a cavum septum pellucidum more frequently than controls.

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 (De Morsier 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. 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); frontal and temporal lobe volumes were normal (Figs. 3 A, B, and C).

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 to the cerebral cortex, particularly the frontal and temporal lobes (Costanzo and Zasler, 1991; Mott and Leopold, 1991). The incidence of anosmia or
Figure 3  (A) Coronal 500/20 scan through a normal volunteer (64-year-old woman with normal smell function) demonstrates normal olfactory bulbs (arrows). (B) Coronal 500/17 scan of patient with congenital anosmia without Kallmann’s syndrome (27-year-old woman), showing extremely atrophic olfactory bulbs (arrows). (C) Coronal 500/14 scan of patient with Kallmann’s syndrome (29-year-old man), demonstrating absence of olfactory bulbs and tracts with flattened gyrus rectus (arrow) on the right side but with normally appearing gyrus rectus on the left side.
hyposmia after head trauma has been reported quite variably from 2% to 38% (Deems et al., 1991; Hagan, 1967; Leigh, 1943; Levin et al., 1985; Schechter and Henkin, 1974; Sumner, 1964; Zusho, 1982) and increases with the severity of injury (Levin et al., 1985; Sumner, 1964). However, even a minor injury can sometimes result in anosmia or hyposmia (Schechter and Henkin, 1974; Sumner, 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; Levin et al., 1985). 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 processing of odor perception (Rausch et al., 1977; Rausch and Serafetinides, 1975). 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 Zasler, 1991; Levin et al., 1985; Schellinger et al., 1993) (Figs. 4A and 4B).

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).
Figure 4  Twenty-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 seen 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).
H. Brain Tumors

The incidence of chemosensory changes caused by intracranial tumors has rarely been investigated. In a recent 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 emphasized that loss of smell perception is one of the first signs of olfactory meningiomas (Bakay, 1984).

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 with the histology (Figs. 5A and 5B).

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.
I. Acquired Immunodeficiency Syndrome

Olfactory deficits of patients with human immunodeficiency virus (HIV) infection have recently been reported (Brody et al., 1991). 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 and 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) found that the neuronal numerical density in the frontal cortex is significantly lower in the HIV group than in a control group—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.

Neuroradiological study has found that patients with HIV infection show widened cortical sulci, enlarged ventricle, 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 superimposed on these changes. The pathogenesis of the olfactory deficits of AIDS patients needs further investigation, but most likely will be found to 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 a peripheral cause of olfactory deficits in AIDS patients also has to be taken into account in certain cases.
J. Other Causes

There are also reports of olfactory dysfunction with major depression, hypochondriasis, and multiple sclerosis (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 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. The most common source of olfactory dysfunction is the peripheral pathway (Goodspeed et al., 1987a; 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 the study of choice to look at the bony sinonasal structures and ostiomeatal complex. CT can also provide important information as a road map that 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 the abnormalities of the brain parenchyma revealed by neuroimaging studies of patients with AD, KP, or schizophrenia involve central brain areas that contain networks of olfactory projections, including areas of the prefrontal lobe, temporal lobe, hippocampus, and thalamus.

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

In congenital disorders, such as Kallmann’s syndrome, the cause of anosmia can be seen in MRI studies as the absence of the olfactory bulbs (Yousem et al., 1993). Other congenital abnormalities, such as choanal atresia and meningoencephalocele can also be detected by imaging studies (Klein et al., 1876; 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; Jarus and Feldon, 1982; Schelling et al., 1983).

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 traditionally been 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.
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(Schwartz et al., 1989). Recent imaging studies have shown CNS complications in cocaine abusers (Holman et al., 1991; Kolkow et al., 1988; Pascual-Leone et al., 1991; Tumeth et al., 1990), and one report of anosmia as a sequela of hydrogen sulfide inhalation suggested the loss to be due to central brain damage (Tvedt et al., 1991).

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, 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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