

**TITLE: Olfactory Dysfunction and Disorders**

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## **Introduction**

Olfactory dysfunction can arise from a variety of causes and can profoundly influence a patient's quality of life. Approximately 2 million Americans experience some type of olfactory dysfunction. Studies have shown that olfactory dysfunction affects at least 1 % of the population under the age of 65 years, and well over 50% of the population older than 65 years. The sense of smell determines the flavor of foods and beverages and also serves as an early warning system for the detection of environmental hazards, such as spoiled food, leaking natural gas, smoke, or airborne pollutants. The losses or distortions of smell sensation can adversely influence food preference, food intake and appetite.

## **Anatomy and Physiology**

Three specialized neural systems are present within the nasal cavities in humans. They are 1) the main olfactory system (cranial nerve I), 2) trigeminal somatosensory system (cranial nerve V), 3) the nervus terminalis (cranial nerve 0). CN I mediates odor sensation. It is responsible for determining flavors. CN V mediates somatosensory sensations, including burning, cooling, irritation, and tickling. CN 0 is a ganglionated neural plexus. It spans much of the nasal mucosa before coursing through the cribriform plate to enter the forebrain medial to the olfactory tract. The exact function of the nervus terminalis is unknown in humans.

The olfactory neuroepithelium is a pseudostratified columnar epithelium. The specialized olfactory epithelial cells are the only group of neurons capable of regeneration. The olfactory epithelium is situated in the superior aspect of each nostril, including cribriform plate, superior turbinate, superior septum, and sections of the middle turbinate. It harbors sensory receptors of the main olfactory system and some CN V free nerve endings. The olfactory epithelium loses its general homogeneity postnatally, and as early as the first few weeks of life metaplastic islands of respiratory-like epithelium appear. The metaplasia increases in extent throughout life. It is presumed that this process is the result of insults from the environment, such as viruses, bacteria, and toxins.

There are 6 distinct cell types in the olfactory neuroepithelium: 1) bipolar sensory receptor neurons, 2) microvillar cells, 3) supporting cells, 4) globose basal cells, 5) horizontal basal cells, 6) cells lining the Bowman's glands. There are approximately 6,000,000 bipolar neurons in the adult olfactory neuroepithelium. They are thin dendritic cells with rods containing cilia at one end and long central processes at the other end forming olfactory fila. The olfactory receptors are located on the ciliated dendritic ends. The unmyelinated axons coalesce into 40 bundles, termed olfactory fila, which are ensheathed by Schwann-like cells. The fila transverse the cribriform plate to enter the anterior cranial fossa and constitute CN I. Microvillar cells are near the surface of the neuroepithelium, but the exact functions of these cells are unknown. Supporting cells are also at the surface of the epithelium. They join tightly with neurons and microvillar cells. They also project microvilli into the mucus. Their functions include insulating receptor cells from one another, regulating the composition of the mucus, deactivating odorants, and protecting the epithelium from foreign agents. The basal cells are located near the basement membrane, and are the progenitor cells from which the other cell types arise. The Bowman's glands are a major source of mucus within the region of the olfactory epithelium.

The odorant receptors are located on the cilia of the receptor cells. Each receptor cell expresses a single odorant receptor gene. There are approximately 1,000 classes of receptors at present. The olfactory receptors are linked to the stimulatory guanine nucleotide binding protein Golf. When stimulated, it can activate adenylate cyclase to produce the second messenger cAMP, and subsequent events lead to depolarization of the cell membrane and signal propagation. Although each receptor cell only expresses one type of receptor, each cell is electrophysiologically responsive to a wide but circumscribed range of stimuli. This implies that a single receptor accepts a range of molecular entities.

The olfactory bulb is located on top of the cribriform plate at the base of the frontal lobe in the anterior cranial fossa. It receives thousands of primary axons from olfactory receptor neurons. Within the olfactory bulb, these axons synapse with a much smaller number of second order neurons which form the olfactory tract and project to olfactory cortex. The olfactory cortex includes the frontal and temporal lobes, thalamus, and hypothalamus.

## **Classification**

Olfactory disorders can be classified as follows: 1) anosmia: inability to detect qualitative olfactory sensations (i.e., absence of smell function), 2) partial anosmia: ability to perceive some, but not all, odorants, 3) hyposmia or microsmia: decreased sensitivity to odorants, 4) hyperosmia: abnormally acute smell function, 5) dysosmia (cacosmia or parosmia): distorted or perverted smell perception or odorant stimulation, 6) phantosmia: dysosmic sensation perceived in the absence of an odor stimulus (a.k.a. olfactory hallucination), 7) olfactory agnosia: inability to recognize an odor sensation.

It is also useful to classify olfactory dysfunction into three general classes: 1) conductive or transport impairments from obstruction of nasal passages (e.g. chronic nasal inflammation, polyposis, etc.), 2) sensorineural impairments from damage to neuroepithelium (e.g. viral infection, airborne toxins, etc.), 3) central olfactory neural impairment from central nervous system damage (e.g. tumors, masses impacting on olfactory tract, neurodegenerative disorders,

etc.). These categories are not mutually exclusive. For example: viruses can cause damage to the olfactory neuroepithelium and they may also be transported into the central nervous system via the olfactory nerve causing damage to the central elements of the olfactory system.

## **Evaluation and Diagnosis of Olfactory Disorders**

The etiology of most cases of olfactory dysfunction can be ascertained from carefully questioning the patient about the nature, timing, onset, duration, and pattern of their symptoms. It is important to determine the degree of olfactory ability prior to the loss. And any historical determination of antecedent events, such as head trauma, upper respiratory infection, or toxic exposure, should be sought. Fluctuations in function and transient improvement with topical vasoconstriction usually indicate obstructive, rather than neural, causes. Medical conditions frequently associated with olfactory dysfunction should be identified, such as epilepsy, multiple sclerosis, Parkinson's disease, and Alzheimer's disease. Also any history of sinonasal disease and allergic symptoms, including any previous surgical therapy for sinonasal disease should be investigated. Medications being used prior to or at the time of the symptom onset should be determined, because some can profoundly influence olfaction (e.g., antifungal agents, angiotensin-converting enzyme inhibitors). Smoking history should be obtained. Studies have shown that smoking can cause olfactory dysfunction and cessation of smoking can result in improvement in olfactory function over time. Occupational history is also important since certain industrial agents are associated with olfactory dysfunction. In addition, while patients present with the complaint of taste loss, quantitative olfactory testing usually reveals an olfactory disorder.

The physical exam should focus on the neurologic system and intranasal anatomy. With nasal endoscopy, the nose should be examined for nasal masses, polyps, exudates, and mucous membrane inflammation. The presence of polyps, adhesions of the turbinates to the septum, and marked septal deviation can decrease airflow to the olfactory epithelium. The neurologic exam should include cerebral function, cranial nerves and cerebellar function.

Laboratory tests are suggested by history and physical exam only. Radiographic studies should be reserved for specific indications. A CT scan is ideal for investigation of nasal and sinus disease. It provides detailed information on mucosal disease, structural abnormalities and the presence of sinusitis or a neoplastic process. MRI is superior to CT for intracranial pathology. It is the study of choice to evaluate the olfactory bulbs and tracts, as well as other intracranial causes of olfactory dysfunction.

There is a wide range of olfactory tests available to evaluate olfactory function. The most widely used quantitative clinical test is the University of Pennsylvania Smell Identification Test (UPSIT), also known as the Smell Identification Test, which was developed by Dr. Richard Doty. The UPSIT test consists of four booklets containing 10 microencapsulated odors in a "scratch-and-sniff" format. There are four response alternatives accompanying each odor. The patient is asked to identify (or guess) each smell. The test can be self-administered in the waiting-room or in the patient's home, and can be scored in less than a minute by non-medical personnel. Scores are compared to varying patient groups and compared against sex- and age-related norms. The patient's score is then classified into one of these categories: normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia and probable malingering.

The reliability of this test is very high. Electrophysiologic tests are also available for assessing olfactory function. However, they are mostly used in experimental setting and confined to university centers.

## **Etiologies of Olfactory Dysfunction**

Olfactory dysfunction originates from a multitude of causes. Nearly 2/3 of cases of chronic anosmia and hyposmia that present to a clinic are likely due to prior upper respiratory tract infection, head trauma, and nasal and paranasal sinus disease. And most can be expected to reflect significant damage to the olfactory neuroepithelium.

### **Post-Upper Respiratory Tract Infection**

The most frequent cause of smell loss in the adult is an upper respiratory tract infection (URI). Patients usually complain of smell loss following a viral-like URI. The URI is often described to be more severe than usual. The smell loss is most commonly partial. Occasionally patients may present with dysosmia or phantosmia, but these symptoms usually subside over time. The physical examination is usually unremarkable in these patients.

Exactly what predisposes someone to viral- or bacterial- induced smell loss or the mechanisms underlying it remain unclear. Direct insult to the olfactory neuroepithelium is presumably the primary basis of the problem. Viruses can cause edema and hyperemia of nasal membranes, necrosis of cilia, and cellular destruction. And they can produce varying degrees of destruction. Biopsy studies of olfactory epithelia from patients with post-URI anosmia showed greatly reduced numbers of olfactory receptors. Those receptors that are present usually have dendrites that do not reach the epithelial surface. Occasional dendrites that are present at the free surface usually lack the sensory cilia. The replacement of sensory epithelium with respiratory epithelium is also a common finding. In patients with hyposmia following a URI, biopsy studies show greatly reduced number of olfactory receptors while the rest of the epithelial structures appear normal. The direct insult can be followed by resolution of infection and regeneration. Anosmia results when there is lack of regeneration secondary to severe destruction of the epithelium. If there is patchy destruction, patients may have hyposmia. If the regeneration of receptor neurons and their central attachments are “misguided” to reach abnormal locations in the brain, patients may experience dysosmia. In addition to direct insults, many viruses can invade the CNS via the olfactory neuroepithelium to cause subsequent dysfunction.

No effective treatment has been found for post-URI hyposmia. Even though spontaneous recovery in some patients is theoretically possible, meaningful recovery is rare when marked loss has been present for a period of time.

### **Head Injury**

The first published report of post-traumatic anosmia appeared in the London Hospital Report in 1864. Early studies of posttraumatic olfactory loss suggest a 4-7% incidence of anosmia following head injury. More recent studies have shown a higher incidence of anosmia, reaching 60 % in severe head injury. This might be due to 1) increased awareness of olfactory dysfunction in head trauma, 2) the use of standardized tests for the measurement of olfactory

function, or 3) a selection bias introduced when studying patients who present to smell and taste centers for evaluation and treatment of their dysfunction.

Several studies have shown that the likelihood of anosmia is associated with the severity of the injury. Heywood et al. (1990) matched Glasgow coma scale (GCS) with the patients' olfactory test scores and found a correlation between the severity of the injury and the amount of olfactory dysfunction. In Mild injury (GCS 13-15), 13 % of patients were totally anosmic and 27% showed olfactory impairment. In moderate injury (GCS 9-12), 11% of patients were anosmic and 67% with olfactory impairment. In severe injury (GCS 3-8), 25% of patients were found to be anosmic and 67% had some degree of impairment. Parosmia has also been reported in 25-33% patients with head trauma.

Posttraumatic olfactory dysfunction may be caused by several mechanisms: 1) sinonasal tract alteration, 2) shearing injury of olfactory nerve filament, or 3) brain contusion and hemorrhage within the olfactory-related brain regions.

Although olfactory dysfunction caused by sinonasal tract alteration is not common, it is important to recognize it. Following head trauma, patients may have mucosal hematoma, edema, or avulsion within the olfactory cleft with direct injury to the olfactory neuroepithelium. Also scarring with synechia formation, nasal skeleton fracture or posttraumatic rhinosinusitis may subsequently alter the airflow that prevents odorants from reaching the olfactory epithelium. This conductive olfactory dysfunction is potentially treatable. Often, reduction of mucosal edema, repair of nasal fractures with relief of airway obstruction, or the treatment of sinusitis can improve olfaction.

The axons of olfactory receptor cells are delicate and pass through small foramina of the cribriform plate at the base of the skull and synapse directly in the olfactory bulb. Any tearing or shearing of the axons during the trauma can result in olfactory dysfunction. It may occur with fractures of the naso-orbito-ethmoid region, involving the cribriform plate, or with rapid translational shifts in the brain secondary to coup or contracoup forces generated by blunt head trauma.

Head trauma often results in traumatic brain injury in the form of cortical contusion or intraparenchymal hemorrhage. Contusion of the olfactory bulbs or cortical lesions at the olfactory-related brain regions (e.g. amygdale, temporal lobe region, frontal lobe region) can lead to post-traumatic anosmia.

In evaluation of the patient with head injury and olfactory dysfunction, the patient should be asked about pre-traumatic olfactory function, present olfactory function, and the severity and nature of the loss. The time course of the olfactory disturbance is important. Most post-traumatic olfactory losses are due to shear injury to the olfactory nerve fibers. Such injuries typically result in immediate smell loss. The gradual, progressive losses are more commonly associated with an inflammatory process. The patient should also be asked about clear rhinorrhea or "salty-tasting" postnasal drip to rule out cerebrospinal fluid (CSF) leak. On physical exam, nasal endoscopy is recommended to inspect the olfactory cleft for mucosal edema, hematoma, ecchymosis, laceration, or CSF leak. Radiographic imaging is valuable in the diagnosis of post-traumatic smell loss. High-resolution CT with axial and coronal cut can show

cribriform plate fractures. Intracranial soft tissue injury is best evaluated by MRI.

Many post-traumatic olfactory disturbances are irreversible. Doty et al. (1997) followed 66 patients with olfactory dysfunction related to head trauma over periods ranging from 1 month to 13 years. 36.6% showed improvement. 18% worsened and 45% had no change. Only 3 patients (5% of the study sample) regained normal olfactory function.

### **Nasal and Sinus Disease**

Olfactory impairment that accompanies nasal or sinus disease has been traditionally viewed as being solely conductive. Although marked airflow blockage undoubtedly alters olfactory sensitivity in some patients, empirical data suggest that surgical (e.g., excision of polyps) or medical (e.g., administration of topical or systemic steroids) treatment rarely returns function to normal, implying that blockage alone cannot completely explain the olfactory loss. In general, olfactory dysfunction is related to the severity of rhinosinusitis. The defining factor may be the severity of histopathological changes within the olfactory mucosa.

Doty and Mishra (2001) have reviewed multiple studies that investigate the olfactory function in rhinitis and rhinosinusitis. In aggregate, the studies reviewed suggest that the degree of olfactory loss is usually associated with the severity of nasal sinus disease, with the greatest loss occurring in patients with rhinosinusitis and polyposis. Using quantitative tests (e.g., UPSIT), olfactory function has been shown to improve in some patients following systemic corticosteroids, as well as topical administration of corticosteroid sprays. However, only rarely has corticosteroid treatment restore patients' olfactory function to normal. Most patients still have olfactory function at the range of mild hyposmia. This implies that some chronic permanent loss of olfactory function is present. And no study has been able to document in rhinitis patients an association between olfactory test scores and intranasal airway access factors save total or near-total blockage, whether measured by rhinoscopy, rhinomanometry, or acoustic rhinometry. Therefore, the hypothesis is that in addition to conductive loss, chronic inflammation may be toxic to olfactory neurons. Histological evidence shows that the severity of histopathological changes in the olfactory mucosa of patients with chronic rhinosinusitis is positively related to the magnitude of the olfactory loss. Replacement of neuroepithelium with respiratory epithelium is again noted. The olfactory epithelium is also noted to be atrophic and thin, comprising mainly support cells and basal cells.

Surgical treatments for sinonasal disease may have an impact on olfaction. Again, Doty and Mishra reviewed a number of studies investigating the effect of different forms of nasal surgery on olfaction. Studies have shown that septoplasty and rhinoplasty do not have long-term deleterious influences on smell function. Most common operations impacting olfactory function are performed in patients with chronic rhinosinusitis and /or polyposis. The procedures being studied most include middle turbinate medialization, polypectomy, uncinectomy, anterior ethmoidectomy, posterior ethmoidectomy, and sphenoidectomy. Most studies showed improvement of olfactory function postoperatively by UPSIT score or self-rating method. However, the degree of improvement is incomplete.

## **Other Causes of Olfactory Dysfunction**

The inhalation of a number of environmental and industrial chemicals can lead to olfactory dysfunction. The degree of olfactory damage seems to be related to the timing and length of the exposure, concentration of the agent, and the toxicity of the agent. Chronic exposure to low levels of benzene, butyl acetate, formaldehyde, and paint solvent has been commonly reported with associated olfactory dysfunction. Many dusts produced in industry have also been associated with olfactory dysfunction, including grain, silicone, cotton, paper, cement, lead, coal, chromium, and nickel.

Olfactory dysfunction can also result from a variety of intranasal and intracranial tumors. Intranasal tumors include inverting papilloma, hemangioma, and esthesioneuroblastoma. Intracranial tumors include meningioma in the olfactory groove or cribriform plate, pituitary tumor with suprasellar extension, and frontal lobe tumors. Around 20% of the tumors of the temporal lobe or lesions of the uncinate convolution are said to produce some form of olfactory disturbance, most typically the hallucination of a bad smell.

Congenital anosmia has also been reported. Most cases are assumed to be hereditary. The phenotype ranges from being unable to detect only one or a few compounds to total anosmia. In the vast majority of cases of anosmia, appropriate MRI evaluation of the cribriform and gyrus rectus regions reveal agenesis or dysgenesis of the olfactory bulbs and tracts.

A number of endocrine disorders have been associated with olfactory dysfunction. The mechanisms responsible for the smell loss are poorly understood. The disorders shown to have olfactory dysfunction include Addison's disease, Turner's syndrome, Cushing's syndrome, hypothyroidism, pseudohypoparathyroidism, and Kallmann's syndrome.

A number of psychiatric disorders are reportedly associated with altered smell function, including schizophrenia and chronic hallucinatory psychoses, seasonal affective disorder, and severe stage anorexia nervosa.

## **Treatment of Olfactory Disorders**

In cases of conductive loss, treatment is directed at relieving the physical obstruction. Obstruction may arise from several causes, including allergic rhinitis, polyps, chronic sinusitis, or rhinitis. Effective treatments for olfactory loss secondary to allergic rhinitis include allergy management, topical cromolyn, topical and systemic corticosteroids, and surgical procedures to reduce inflammation or obstruction. A brief course of systemic steroid therapy can be used in distinguishing between conductive and sensorineural olfactory loss. Patients with nasal polyps or chronic sinusitis typically present with a longstanding history of inflammation and congestion. Surgery is indicated to treat the obstructed breathing and to improve smell function. Surgical procedures that reduce nasal obstruction have been demonstrated to improve olfactory function. Surgical patients may require ancillary treatment. In patients who remained anosmic after surgery for nasal and sinus polyps, studies have shown that oral steroids were effective in restoring smell function to normal in most patients.

Olfactory dysfunction secondary to sensorineural causes is difficult to manage. And the

prognosis is generally poor. There are advocates for zinc and vitamin therapies, but there is no compelling evidence that these therapies work except in cases where zinc or vitamin deficiency exist.

## **Bibilography**

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