

TITLE: Can You Smell That? Anatomy and Physiology of Smell
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Introduction

Olfaction is an often over-looked but vital sense to our everyday living. As Otolaryngologists we are often at the forefront for diagnosis and treatment of patients with olfactory disorders. The sense of smell is the most ancient of our distal senses and is found in nearly all air-, water-, and land-dwelling creatures. Olfaction determines the flavor of foods and beverages. Also, olfaction plays a significant role in nutrition, safety, and maintenance of a person's quality of life. There are 2.7 million adults (1.4%) in the U.S. alone with olfactory dysfunction.

There are multiple professions for which olfaction is depended on for making a living. These include cooks, firefighters, plumbers, wine merchants, perfumers, cosmetic retailers, and chemical plant workers. The sense of smell is often downplayed but may be the first sign of other disorders which will be discussed in detail later.

Definitions

In order to better understand olfaction and olfactory disturbances, it is best to define the various disorders. Total anosmia refers to the inability to smell all odorants on both sides of the nose. Partial anosmia refers to the inability to smell certain odorants, while specific anosmia refers to the lack of the ability to smell one or few odorants. Hyperosmia is described as an abnormally acute smell function which is often interpreted as a hypersensitivity to odors. Dysosmia refers to a distorted or perverted smell perception. Parosmias or cacosmias are changes in the quality of an olfactory cue. Phantosmia, which can be a very debilitating disorder, is a sense of odor, often foul, in the absence of an olfactory stimulus. Olfactory agnosia is the inability to recognize odor sensations despite olfactory processing, language, and intellectual function being intact. Olfactory agnosia is often seen in certain stroke and post encephalitic patients. Presbyosmia, which some believe is not a true disorder, is smell loss due to aging.

Nasal Anatomy and Olfaction

Odor reception is the function of 4 cranial nerves. The olfactory nerve serves the greatest role in olfaction and will be emphasized in this talk. Also, the trigeminal nerve (CN V),

glossopharyngeal nerve (CN IX), and vagus nerve (CN X) play roles in olfactory input. Olfactory nerve stimulation requires odorant molecules to reach the olfactory mucosa at the top of the nasal cavity. In order for this to occur, a form of nasal airflow must exist. There are two basic types of nasal airflow in relationship to olfaction. Orthonasal flow is the airflow toward the olfactory epithelium on inhalation or sniff. Retronasal flow occurs during eating. This flow is often what contributes greatly to the flavor of food. The physiologic airflow of the nasal passages is directed most toward the middle meatus. Only approximately 15% of the total airflow of the nose passes through the olfactory region, and only 35% of total airflow passes through the inferior meatus. This should come as no surprise that obstructive nasal disease, even minor, can cause major changes in olfactory sensing.

When presented with odors, it is our natural instinct to sniff. However, there is no clear understanding why we sniff. Studies on the physiology of sniff have found no clear evidence that sniffing causes effects in the rapid change of flow velocity on the in vivo airflow pattern. Scherer and colleagues found percentages and velocity of airflow to the olfactory region to be similar for various steady-state rates in the normal physiologic range. There are some theories that sniffing may allow the trigeminal nerve to alert olfactory neurons that an odorants will soon arrive. Finally, it appears that a person's natural sniff seems to optimal for their own nasal anatomy. One study analyzed patients' sniff and various other sniff patterns but concluded that the natural sniff of the patient was optimal.

As olfactory molecules enter the nasal cavity, they must pass through the tall but narrow nasal passages. Olfactory epithelium is wet with variable thickness and is aerodynamically "rough" in quality. This allows for turbulent flow to occur which can lengthen the time air passes through the epithelium. Schneider and Wolf observed that olfactory ability is at its best when the epithelium is moderately congested, wet, and red. These are all condition associated with a viral URI. Also, studies have shown that olfaction seems to improve when the nasal chambers are somewhat narrowed. The nasal cycle, however, does not have any effect on olfactory ability. Olfactory epithelium is found at the anterior skull base along the cribriform plate. Olfactory neuroepithelium also exists along the superior turbinate and superior medial septum.

Absorption

An important step in the detection of odorants is the absorption of molecules from the air into the mucus lining the epithelium. This helps in increasing the travel time through the nasal passageways. The absorption of odorants may have a profound influence on the spectrum of chemicals reaching the olfactory cleft. Highly absorbable chemicals may have minimal or no odor as they never reach the olfactory cleft.

Olfactory mucus is produced by Bowman's glands and goblet cells of the adjacent respiratory epithelium. As mentioned, partitioning odorant molecules between the air phase and mucus phase is important in the odorants reaching the olfactory epithelium. Odorant molecules must be absorbable enough in the mucus but not too absorbable as to not interact with the receptors. Many medications can play a role in the properties of the overlying mucus. These include adrenergic, cholinergic, and peptidergic agents. Just as important as absorbing molecules, clearing odorant appears to be another important role in the olfactory mucus-epithelial system. There is controversy about the role the olfactory mucus plays in deactivating, removing, or desorbing odorants from the olfactory area.

Olfactory sensory neurons are protected in a 1-mm-wide crevice of the posterosuperior nose which covers roughly 1 cm² on each side. The neuroepithelium is a pseudostratified columnar epithelium. The neurons are exposed to the outside world through their dendrites and cilia. These axons synapse at the base on the brain in the olfactory bulb. In the olfactory epithelium, there are at least six morphologically and biochemically distinct cell types. Uniquely, the olfactory neuroepithelium is a bipolar receptor cell that projects from the nasal cavity into the brain without an intervening synapse. This can be a major route of viral and xenobiotic invasion into the central nervous system. There have been case reports and recent events in the news concerning deaths and cases of Naegleria infections caused by sinus rinse use due to infiltration through the cribriform plate.

The major cell in the olfactory neuroepithelium is the olfactory receptor cell. Each receptor cell expresses a single odorant receptor gene. There are over one thousand different types of receptor cells present within the olfactory epithelium. The olfactory receptor genes account for approximately 1% of all expressed genes in the human genome. This makes it the largest known vertebrate gene family. It appears that receptors are not randomly distributed along the mucosa but confined to one of several non-overlapping striplike zones. Each cell appears to be responsive to a wide, but circumscribed, range of stimuli. Mouse models have shown that their olfactory epithelium is roughly divided into four zones. Studies have shown groups of different olfactory receptor subtypes are confined within the designated zone. It also appears that most receptors are specific for certain odorants. Loss of specific odor receptor genes creates an inability to perceive particular odorants in mice.

The stimulatory guanine nucleotide-binding protein G_{olf} links olfactory receptor proteins. The olfactory receptor cell is derived from the ectoderm and is a first-order neuron. It has the ability to regenerate after damage. Glial-type cells ensheath the olfactory neurons and support axonal growth of both olfactory and nonolfactory neurons. These cells have served as special interest in the research of spinal cord injury and demyelinating diseases. The cilia of the olfactory receptor cells differ from respiratory epithelium. The cilia are generally longer and lack dynein arms. Lacking dynein arms makes these cilia immotile. Overall, the surface area of the cilia exceeds 22 cm² in humans. In sharp contrast, the surface area of cilia in a German Shepard dog exceeds 100 cm².

Besides the olfactory receptor cell, there are 5 other cells identifiable. The supporting or sustentacular cell contains microvilli and insulates the bipolar receptor cells. It also helps to regulate composition of olfactory mucus. Microvillar cells are poorly understood cells located at the epithelial surface. A fourth cell type lines Bowman's glands and ducts. Horizontal or dark and globose or light basal cells are located near the basement membrane. These cells function to create the other cell types of the olfactory epithelium.

Olfactory Transduction

Once the odorant molecule has been absorbed properly in the mucus, olfactory binding proteins act to bind and solubilize the hydrophobic odorant molecules into the hydrophilic olfactory mucus. The ability of the odorant binding proteins to solubilize the odorant particles increases the concentration of the odorants into the surrounding environment by as much as 1,000 to 10,000 times more than their concentration in the ambient air. There is speculation that the binding proteins also act to remove odorant molecules from the regions of the receptor cells. Once an odorant molecule links to the G protein receptor molecule, an enzyme cascade activates

cAMP which then opens Ca,Na ion channels which depolarize the cell and start an action potential. cAMP and IP₃ appear to be the primary signaling pathways mediating olfactory transduction. Deficiencies of cAMP and stimulatory G_{olf} have been found in patients with Type 1a Pseudohypoparathyroidism. These patients often complain of olfactory losses.

Vomeronasal Organ

In the human septum there is an identifiable pit or groove at the anteroinferior part of the nasal septum. This area contains chemosensitive cells. There is debate about whether this correlates with a functioning chemosensitive organ in humans. In most animals, there is an identifiable nerve connecting these cells to the central nervous system. In humans, however, there is no identifiable connection from the vomeronasal organ (Jacobson's organ) in humans to the CNS. Physiological studies have shown that activation of the area produces negative action potentials without a subjective response from the individual tested. Experts are unsure of the exact role the vomeronasal organ plays but it may function as a neuroendocrine system. It should be remembered that this area should be left undisturbed during nasal surgery unless necessary.

Olfactory Bulb

The olfactory neuroepithelium synapse together in bilateral structures at the frontal cortex base known as the olfactory bulbs. These bulbs act as the first relay station in the olfactory pathway. First order neurons synapse with post-synaptic nerves which form dense aggregates called glomeruli. Studies have shown that a given region of the bulb receives its most dense input from a particular region of the mucosa. Inputs to a particular region of the bulb are composed of many receptor cells distributed throughout a certain zone of the mucosa. With intricate connections, excitatory and inhibitory influences narrow the neural stimulus from the olfactory mucosa.

Aging appears to have a profound effect on the olfactory bulb. Younger persons have thousands of the 50- to 200- μ m glomeruli arranged in single or double layers. It appears that these glomeruli decrease gradually in number with age. Often, these glomeruli area nearly absent in persons older than 80 years of age.

Olfactory Connections

The central processing of the sense of smell is complex with connections to many different structures. The olfactory system is connected with the olfactory tubercle, prepiriform cortex, amygdaloid nuclei, and the nucleus of the terminal stria. The vast amount of connections ties olfaction into many functions including: food intake, temperature regulation, sleeping cycle, vision, memory, hearing, and taste. Smell appears to have intimate connections with our other senses. It helps to shape our memory and is often one of the strongest triggers for our memories.

Olfactory Cognition

As previously stated, our sense of smell is very important in our everyday life. However, it appears that our everyday lives have an equally important role in our cognition of smell. We appear to understand odors largely based on experience. Each person develops his or her own hedonic code within a culture restraint. Smell has a very strong association with memory. Studies have shown that odor memory can last at least 1 year while visual memory may last only a few months. Interestingly, odor memory is best facilitated by bilateral nasal stimulation. Some studies have suggested that patients with one-sided nasal obstruction may form poorer odor

memories. Even at birth, odor cognition plays an important role. Macfarlane examined 30 women and their newborn babies. Women washed one of their breasts prior to feeding and placed their newborns in a prone position over the midline chest. 22 out of the 30 newborns selected the unwashed or odorous breast.

Pheromones

There is debate whether humans secrete or respond to pheromones. Pheromones are chemicals released by one member of a species and received by another member that results in a specific action or developmental process. There are multiple behavioral and anatomic studies that support the possibility of human communication through odorants. Russell and associates placed underarm secretions and alcohol on 5 experimental subjects and alcohol on 6 control subjects. They found that over a period of 5 months, there was a statistically significant greater tendency for menstrual synchrony.

Evaluation of Olfaction

Patients will often present to the clinic with complaints of lack of taste, but often these patients have a definable lack of olfactory sensation. An evaluation of 750 patients with chemosensory dysfunction demonstrated that most patients presented with both smell and taste loss. However, less than 5% had identifiable whole-mouth gustatory deficit. Taste is defined as true gustation while flavor is the olfactory-derived sensation from food. Whole-mouth taste function is much more resistant to injury than olfactory function due to its redundancy of innervation. Patients with total loss of olfaction are left with only sweet, sour, salty, bitter and umami (MSG-like) sensation. It is important that the clinician be aware of the complaints of patients with relation to taste and flavor and differentiates an olfactory deficit versus a gustatory deficit.

The evaluation of olfaction begins with a thorough clinical history. It is important to define the nature and onset of the chemosensory problem. Discovering associated events such as viral or bacterial infections, head trauma, exposure to toxic fumes, systemic diseases, or signs of dementia is very important in the work-up. Also, defining the scope of olfactory loss and distinguishing between anosmia and hyposmia is important. One should discuss with the patient whether there is total loss of odorants or a loss of a few odorants. The timetable of the loss is very important in the prognosis of the olfactory loss. The possibility of spontaneous recovery is related to the duration of the problem. After approximately 6 months, spontaneous recovery is often minimal. The clinician should examine the patient's taste. Anosmic patients will still be able to differentiate the saltiness, sourness, or sweetness of foods.

Clues into the cause of anosmia can be found in a thorough past medical and surgical history. Reviewing the patient's past endocrinologic state may reveal a history of delayed puberty that may point to Kallmann syndrome. A history of allergies or a history of nasal or sinus infection may point toward the cause of anosmia. One should ask about a history of radiation therapy and a current list of medications. Previous sinus or nasal surgeries should be inquired. Although it is rare, olfactory deficits can occur after nasal surgery.

Social history can offer clues into causes of anosmia. It is important to examine the patient's smoking history. Tobacco use can cause partial or total anosmia. It has been found that olfactory ability decreases as a function of cumulative smoking dose. One should counsel patients on smoking cessation. Cessation can result in improvement in olfactory function over

time. While the underlying cause of the olfactory loss may not be directly attributed to tobacco use, cessation of smoking can improve the ability to a degree.

Physical Examination

The physical examination should include a full otolaryngologic examination with anterior rhinoscopy and nasal endoscopy. Studies have shown, however, that nasal endoscopy is not overly sensitive. Often positive findings on endoscopy do not correlate with symptoms. During nasal endoscopy, one should examine the nasal mucosa for color, surface texture, swelling, inflammation, exudates, ulceration, epithelia metaplasia, erosion or atrophy. Noting polypoid disease may further lead to clues. Even minor or minimal polypoid disease at the olfactory cleft can account for olfactory dysfunction. Performing a cranial nerve examination can elicit potential central or peripheral neuropathies. It is also important to perform an optic disc examination determine whether there is increased intracranial pressure. Foster Kennedy syndrome is secondary to tumors of the olfactory groove or sphenoidal ridge. The syndrome involves ipsilateral anosmia or hyposmia, ipsilateral optic atrophy, and central papilledema. Physical examination is an important part in differentiating the causes of olfactory disturbances.

Olfactory Testing

Olfactory testing continues to develop. Currently olfactory testing is mostly subjective. Objective testing of olfaction has limited applications currently. However, olfactory testing is essential for many factors. It is often essential in validating a patient's complaint. It can characterize the specific nature of the problem. Testing can monitor changes in function over time. Importantly, objective testing can also detect malingering. Often, patients complaining of anosmia or hyposmia have normal function relative to age and gender. Also, some populations have demonstrable smell loss and do not know it. 90% of patients with idiopathic Parkinson's Disease have smell loss, yet less than 15% are aware of their problem.

Developing olfactory testing has improved our diagnostic ability. Asking a patient to sniff odors is like testing vision by shining a light in each eye and asking whether the patient can see the light. However, there is no current testing that can distinguish central and peripheral deficits. Unilateral testing is often warranted and can be easily accomplished by sealing the contralateral naris using Microfoam tape. Having the patient sniff naturally and exhale through the mouth stops olfactory stimulation secondary to retronasal flow.

Anosmia has many indications in medical/legal matters. Anosmia is common in head injuries and is often the only residual neurologic impairment. Claims of accidental and iatrogenic smell disturbance often result in substantial financial awards. The Veterans Administration awards a 10% whole-body disability for total anosmia. Also, many occupations rely heavily upon the sense of smell and should justly be taken into account in disability issues.

There are three main types of olfactory testing available. Psychophysical testing is the most common and least expensive. The most well-known olfactory test is the UPSIT (University of Pennsylvania Smell Identification Test or simply the Smell Identification Test). The test is made of 4 booklets of 10 odorants apiece. It can easily be administered in 10 to 15 minutes by most patients. The stimuli embedded into 10- to 50- μ m diameter microencapsulated crystals. The test is made of multiple choice questions with four response alternatives. The test is force-choice. This requires the participant to choose an answer even if none seems appropriate. Repeated testing has shown that chance performance is 10 out of 40. With this, lower scores can

often represent avoidance. There are norms available based on the cumulative data from administration to 4,000 people. Individuals are ranked relative to age and gender. The test can classify an individual's function into 6 categories: normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia, and probable malingering. The test has been proven very reliable with a test-retest Pearson $r=0.94$. In medical/legal considerations, the UPSIT is sensitive to malingering. The theoretical probability of a true anosmic to score UPSIT 5 or less is 0.05%. The theoretical probability of true anosmic scoring a 0 on the UPSIT is 0.00001. The UPSIT has become a mainstay in olfactory testing and should be considered in patients with olfactory disturbances.

Electrophysiologic testing is available. It offers objective testing but its application is largely experimental. Two procedures are currently available. Odor Event-Related Potentials (OERPs) and Electro-olfactogram (EOG) are the two electrophysiologic testing. Odor Event-Related Potentials (OERPs) involves discerning synchronized brain EEG activity recorded on the scalp from overall EEG activity following presentations of odorants. The stimuli are presented in a precise manner using equipment that produces stimuli embedded in a warm, humidified air stream. The problem is that test reliability is poor, and necessary trials cannot be performed to establish normative data. The data cannot make any inference in regarding the location of a lesion or deficit. OERPs can be usefully in detecting malingering. Electro-olfactograms measure electrodes placed on the surface of the olfactory epithelium. However, few patients are amenable to recordings as the electrodes must be placed under endoscopic guidance without local anesthesia. This can be quite unpleasant and cause sneezing or mucous discharge. In many subjects, it cannot be reliably recorded. Also, the presence of a robust EOG does not always represent olfactory functioning. Anosmic patients with Kallmann syndrome and hyposmic patients with schizophrenia have large EOG responses. These tests have some limited application at this time.

Due to a strong association between Alzheimer's and Parkinson's disease and olfactory dysfunction, neuropsychologic testing can be very helpful. In certain situations, patients complaining of anosmia warrant a brief neuropsychologic testing to determine the presence of dementia. The Mini-Mental Status Examination is a quick screening tool for dementia and can be administered in a few minutes. More specific testing should be left to a qualified Neurologist.

Neuroimaging

In cases where olfactory dysfunction has no known cause, imaging is warranted. Often in idiopathic cases, high-resolution CT is the most useful and cost-effective screening tool. MRI is useful in evaluating the olfactory bulbs, olfactory tract, and intracranial structures. MRI can detect decrements of anosmia associated with patients with schizophrenia.

Olfactory Biopsy

If tissue is needed in diagnosis or treatment, a small amount of superior septal tissue can be removed. This is often best accomplished by an experienced rhinologist as there is an increased risk of CSF leak. It is recommended to take multiple biopsies as to get sufficient olfactory neuroepithelium. Especially in older persons where much of the olfactory neuroepithelium is replaced with respiratory epithelium, it is very important to take more biopsies.

Disorders of Olfaction

As discussed earlier, anosmia and olfactory disturbance affects over 2 million Americans. There are more than 200 conditions associated with changes in chemosensory ability and olfactory deficiency. While there are so many categories, breaking them down into broader categories will make it easier to form a differential diagnosis during the work-up.

Obstructive Nasal and Sinus Disease

Obstructive nasal disease is the most common form of olfactory dysfunction and anosmia making up 20-33% of all olfactory loss. The anosmia is generally produced by nasal polyps, mucosal swelling and/or nostril occlusion which generally resolves when the obstruction is released. The opening to the olfactory cleft is medial and anterior to the lower part of the middle turbinate. Scarring from surgery between the middle turbinate and nasal septum can effectively close off the olfactory cleft to airflow and cause anosmia. Any anatomical changes to this area can result in anosmia. One of the most practical ways to diagnosis obstructive causes is a 1- or 2-week course of steroids. The anosmia will generally resolve after the steroid therapy. It is rare that an external nasal deformity can cause anosmia from obstruction. Chronic rhinosinusitis causes edema and polyps which then obstruct the olfactory cleft. Kern studies the affects of rhinosinusitis on olfactory mucosa. He found inflammatory changes in olfactory epithelium. This appeared to be an inflammation-driven, primary neuron dysfunction. This observation may explain why chronic rhinosinusitis can contribute to olfactory dysfunction without signs of obstruction and why some patients do not improve with steroids. Kern found evidence of active apoptosis of olfactory receptor neurons. Correcting obstructive causes and treating with anti-inflammatory medications can improve or cure obstructive forms of anosmia.

Upper Respiratory Infection

Upper respiratory infections cause roughly 10-15% of all olfactory dysfunction. Patients often complain of olfactory loss during a URI. This is most often secondary to obstruction and resolves within 1 to 3 days. However, there is a small percentage of patients who suffer total loss after a URI. This occurs more commonly in patients in their fourth, fifth, or sixth decade of life. There is also a larger (70-80%) disparity toward women. Often in these patients, biopsy results reveal decreased numbers of olfactory receptors. Total olfactory loss after an upper respiratory infection is generally poor.

Head Trauma

The incidence of olfactory loss in adult patients with head trauma is 5 to 10%. In general, the severity of the trauma is associated directly with the loss. Frontal blows are the most frequent cause of olfactory loss; however, occipital blows carry a 5 times higher risk of total anosmia. Onset of anosmia is generally immediate and the rate of recovery is less than 10%. The quality of olfactory ability that is generally recovered is poor. Unfortunately, the exact injury from head trauma is not totally understood. Most believe that it is secondary to the shearing of the olfactory nerves on the cribriform plate or contusions to the olfactory bulbs.

Aging

Aging contributes greatly to olfactory loss and most will suffer with olfactory loss as one age. Olfactory identification sharply decreases in the sixth and seventh decade of life. Olfactory loss plays an understated role in the elderly patient. It causes a decrease in magnitude matching of smells, changes in the perception of pleasantness, decrease nutritional status due to loss of

flavor, and a decrease in the ability to discriminate flavors in everyday foods. This olfactory loss can have a profound effect on the quality of many older individuals.

Dementia-related Diseases

The two main dementia-related diseases associated with anosmia are Parkinson's Disease and Alzheimer's Disease. Alzheimer's Disease is characterized by the presence of neurofibrillary tangles and neuritis plaques found in the central olfactory pathways. Interestingly, there are similar pathologic changes and testing abnormalities in patients with Down's syndrome which may suggest a possible genetic link related to olfactory losses. Also, it is interesting to note that Alzheimer's affects the olfactory system disproportionately to the other areas of the brain. Pearson et al examined cadaveric brains and showed marked involvement of the olfactory system contrasting with minimal abnormality in other areas of the brain. The authors concluded there may be an environmental agent that could cause Alzheimer's Disease.

Parkinson's Disease encompasses a number of nonmotor defects including depression and cognitive loss. The olfactory losses are independent of the cognitive and motor symptoms. The duration of the disease is strongly correlated with the neuronal losses in the olfactory bulb. In any patient diagnosed with Alzheimer's Disease or Parkinson's Disease who does not exhibit olfactory loss, one must be suspicious for alternative diseases.

Congenital Dysfunction

Most patients with congenital olfactory loss are unaware of their loss until early adolescence when others point out the losses. The most well-known of these congenital disorders is Kallmann Syndrome. Kallmann syndrome is hypogonadotropic hypogonadism. Most commonly, it is a defect in the X chromosome KAL1 gene which encodes anosmin-1. Patients have agenesis of the olfactory bulbs and stalks. They also have incomplete development of the hypothalamus. Some authors believe that that existence of Kallmann syndrome shows a strong association between sexual development and olfaction.

Toxic Exposure

Many laborers can be exposed to toxins in the work place which can put their olfactory ability at risk. There are many toxins that have been shown to cause olfactory loss. Most of these toxins are aerosolized. It is important to consider the concentration and duration of the exposure. Some toxins can cause loss immediately and others will not present until much later. Also, some over-the-counter medications can lead to toxic damage. One of the most well-known is the over-the-counter allergy spray, Zicam. Lim et al studies the effects of Zicam, also known as zinc gluconate, and compared these effects to other common nasal sprays. They showed near absent responses on EOG on Zicam-treated mice. Most interestingly, they found nasal mucosa of Zicam-treated mice to be irreversibly destroyed.

Neoplasms

Both intranasal and intracranial tumors can affect the sense of smell. Intranasal tumors can include inverted papillomas, adenomas, squamous cell carcinomas, and esthesioneuroblastomas. Intracranial tumors can include meningiomas, pituitary tumors, and gliomas. Approximately 25% of temporal lobe tumors can have olfactory disturbances.

HIV

There is a correlation among patients with HIV and olfactory disturbance that is poorly understood. The loss of olfactory ability is often variable. Also, the olfactory losses are independent of most HIV markers including CD4 count. Also, the losses do not correlate with body weight, body composition, management, or diet.

Psychiatric Disease

Olfactory complaints are common in patients with depression, schizophrenia, and hallucinations. Studies have shown that olfactory identification deficits are only found in schizophrenia. Patients with intrinsic olfactory hallucinations believe a smell emanates from their own body. Extrinsic olfactory hallucinations cause the patient to believe the odor emanates from a source other than the patient's own body. In olfactory reference syndrome, patients exhibit an obsessive concern over minor or absent odors. These patients often bathe frequently and wear excessive perfumes or colognes. "Marcel Proust" syndrome describes psychiatric disorder where certain smells trigger such a strong memory as to disrupt daily routines. This can be very debilitating for these patients and psychotherapy is often helpful.

Medications

There are many medications that can cause anosmia and the list continues to grow. It is beneficial to look over the list of common medications that can cause anosmia and be aware of which ones one uses. Often, avoiding certain medications in more susceptible patients can help avoid further disturbance.

Surgery

Surgical procedures can cause loss of smell. There are reports of olfactory loss after rhinoplasty. Champion et al reviewed 100 consecutive rhinoplasty patients. He found that 20% of patients complained of olfactory loss 6-18 months after surgery. Fortunately over 95% of the losses were temporary. With the advancement of endoscopic skull base and sinus surgery, there is now more accurate surgery and less olfactory damage. Patients with total laryngectomies have decreased olfactory ability due to shunting of air away from the nasal cavity. Patients can perform certain exercises to induce airflow into the olfactory clef. *Studies have shown olfactory receptors in these patients to function many years after the laryngectomy. Cranial and skull base surgeries can lead to total and permanent loss of olfactory ability.

Treatment and Management

In determining the treatment options for patients, it is important to differentiate the conductive and receptive losses. As discussed, conductive losses of smell are responsive to treatments of nasal disease. There are many treatments available for the opening of the nasal passageways including, intranasal steroids, antibiotics, allergy therapy, addressing ethmoid sinusitis via ethmoidectomy or treating intranasal tumors.

In receptive loss treatment, options are very limited and without much benefit. Some advocate the use of Vitamin A. Vitamin A is necessary in the repair of epithelium. Studies have shown that white rats become anosmic on a Vitamin A deficient diet. Also, mammalian olfactory epithelium contains a considerable amount of Vitamin A. Duncan and Briggs studied Vitamin A supplementation on patients with anosmia and found successful restoration of at least

partial olfactory ability in 50 out of the 56 patients. However, many other authors have been unable to reproduce the same benefits from Vitamin A supplementation.

Zinc has also been implicated in the treatment of receptive olfactory loss. Zinc-deficient adult mice have been found to be anosmic. Zinc deficiency is rare and difficult to substantiate. There are occasional reports of improvement in anosmia with the treatment of zinc. Also, some authors advocate for the use of Aminophylline as cAMP has a strong role in the transduction of the olfactory signal. Again, few studies have shown marked improvement with Aminophylline.

Management

One of the most important steps in the management of olfactory loss is reassurance. Explaining the prognosis can be helpful and explaining that other patients suffer with the same losses can be comforting. The physician should discuss with the patient improving the seasoning of the diet for the remaining sensory modalities. Emphasizing taste, color, texture, viscosity, and the feel of the foods can improve the quality of life. With anosmia, smoke and fire detectors are mandatory. Patients with olfactory disturbance should elicit the confidential advice of others in matters of odor. A patient with anosmia should also be counseled on switching appliances from natural gas to electric or non-explosive heating.

Finally, patients with complaints of phantosmia can be challenging to treat. Phantosmia is the perception of odor in the absence of a true odor. This is, most often, unpleasant. An effective therapy has been instilling four nasal saline drops in the affected nostril with the head positioned forward and down. Some have tried applications of topical cocaine hydrochloride to the olfactory mucosa. There is a lack of good results with this treatment and a risk of total anosmia. In patients refractory to conservative treatment, surgical options are available including neurosurgical resection of the olfactory bulbs through a craniotomy. Endoscopically, olfactory epithelium can be removed from the underside of the cribriform plate. This approach requires the repair of CSF leak. Good outcomes have been demonstrated with surgical treatment of phantosmia but have inherent risks.

Conclusions

The sense of smell remains of the most primitive but important senses in our daily lives. It plays an integral role in our general well-being and quality of life. There is a strong correlation of our sense of smell with many of our other senses, our memories, and our quality of life in general. The Otolaryngologist needs to be aware of these disorders which cause anosmia especially as it can be a presenting symptom of many diseases. Unfortunately, current diagnostic tools and treatment options remain limited. Further study and advancement are needed to help understand and correct disorders that affect over 2 million Americans.

DISCUSSTION January 30, 2012

Dr. Harold Pine

Has anybody used the Zycam to treat these fantasmias? Seems like it would be a great treatment for someone who has this horrible smell. It would be like squirting Gentamicin in the middle ear for someone who was a vestibular cripple. And then another question: you briefly mentioned that each of the little cells is designed for its own particular odorant and you mentioned that there seems to be some cultural or difference among different populations. I remember very distinctly that I was on a trek somewhere in New Zealand when the guide pulled me off to the side of the road and said "Here, smell this flower." And it was something like anise which is like a licorice flavor and he said very specifically, "We have certain populations of people that come here that can't smell this particular smell " which I thought was really weird. There was a certain kind of Asian population that was coming through and they couldn't smell it.

Finally, is there something we can do or someone that wants to go into one of these jobs where the sense of smell is really important. Is it trainable? They sell these wine appreciation kits with the different individual odorants that apparently if you practice enough you can get better at identifying certain smells. I used to take high doses of vitamins A, C, E and selenium back in college during the anti-oxidant craze and I wonder if that has something to do because I felt like God had turned up my sense of smell ten-fold and I remember the day when my sense of smell became awesome and it's continued like that and I tell people on rounds that I'm really good at smelling a couple things, like, you know, women's perfume, and pus.

Dr. Bruce Liepzig:

How useful is the University of Pennsylvania smell identification test?

Dr. Patton:

What I've shown here that if you do have anosmia, your chances are still to be ten out of forty so if you have somebody with true anosmia with this smell test I don't think it's enough if you want to have an actual distinct diagnosis of total anosmia because somebody with a partial anosmia can still score kind of low. The important thing about that test is that if you score less than ten the chance probability is that you have total anosmia. It's probably very useful in malingering and in setting them up whether you have sense of smell or taste problems.

Dr. Pine:

Just one more comment from a medicolegal standpoint, Most of you know that I was involved in a medicolegal case in which it came out after the fact was what I had done to her had ruined her sense of smell. That was her chief complaint and the prosecution's argument that we had caused her anosmia. What's so interesting about it was that we had gone to the patient and given her one of these smell tests suggesting that we hadn't and then months and months later there was very little that there was very little motivation on the part of our team to get her objectively tested so that there's still among the general population and among lawyers that a loss of the sense of smell is a very subjective complaint so just by the fact that she was moaning about it that carried weight even though objectively I suspect that she had very little real loss in her sense of smell.

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