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Pain Update

Anosmia

A review in the context of coronavirus disease 2019 and orofacial pain

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Olfaction is the sense of smell. It is one of the chemical senses, involving the detection of chemical stimuli and conversion of these stimuli into electrical energy for perception via the central nervous system.[1] Apart from playing a role in the determination of the flavor of food and beverages, olfaction has a role in acting as an early warning system to detect hazards. Reduction of olfactory function has been shown to be associated with loss of appetite, consumption of bad food, and, in many people, problems with cooking.[2] It has been hypothesized that olfaction aids in possible avoidance of food poisoning.[3] Olfaction also plays a significant role in the process of enjoyment of food. Most information regarding the flavor of food is thought to come from olfaction.[4] Lack of proper olfaction also has been associated with weight loss and weight gain.[5,6] The sense of smell is reported in the literature as connected to emotions, either positive or negative.[7] Quality of life is reduced significantly in patients with olfactory disorders.[8] Olfactory disorders have been reported as prominent features that can be possible early signs of neurodegenerative (ND) diseases.[9] Loss of this sensation has been attributed to be one of the first manifesting symptoms in COVID-19.[10] In our article, we highlight the basic principles underlying the physiology and pathophysiology of olfaction and its possible relationship with disease entities. We also look at the significance of olfaction as it relates to dentistry and orofacial pain.

PHYSIOLOGY OF OLFACTION

The chemosensation of olfaction is mediated via the cranial nerves CN I (olfactory) and CN V (trigeminal).[11] CN I is responsible for olfaction, whereas CN V mediates general sensory innervation including chemosensation. The olfactory epithelium present in the superior part of the nostrils contains olfactory cells, which are the receptor cells for olfaction.[12] An action potential is generated when the odorant molecule binds to the olfactory receptor.[13] The action potential is carried via the axons of these primary afferent neurons to the olfactory bulb, where the synapsing with second-order neurons occurs.[14] Anatomically, the olfactory bulb is positioned over the cribriform plate of the ethmoid bone. These second-order neurons form the olfactory tract carrying signals to the higher centers in the brain.[15] These centers include the primary and secondary olfactory cortices.[16] Figure 1 shows the gross structures involved in olfaction and olfactory pathways.

DISORDERS OF OLFACTION

Olfaction disorders may be classified as congenital or acquired. Being born with an olfactory disorder is rare.[8] Quantitatively, olfactory disorders can be divided into anosmia, hyposmia, and hyperosmia. Anosmia is the inability to perceive odors. It includes total anosmia, which is an inability to perceive all odors, and partial anosmia, which is an inability to perceive some but not all odors. Reduced ability to smell is termed hyposmia. Enhanced ability to smell is termed hyperosmia, which is relatively rare.[17]

Disorders of olfaction can be categorized qualitatively as paraosmia and phantosmia.[18] Distorted smell perception in the presence of odorant is dysosmia or paraosmia.[19] In particular, when this perception is fetid, it is referred to as cacosmia.[16] Phantosmia refers to the perception of an odorant

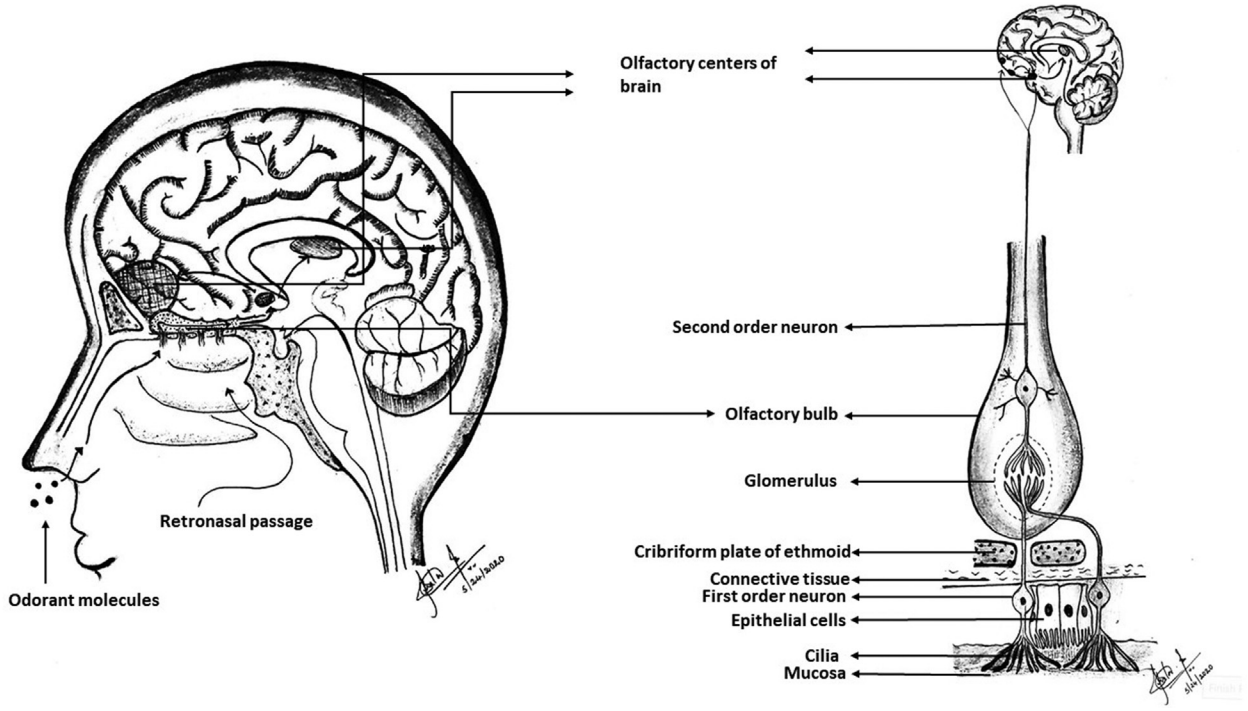

Figure 1. Structures involved in olfaction and olfactory pathways. Drawing courtesy of Dr. Sita M. Baddireddy.

in the absence of one. It is a form of olfactory hallucination.[20] Figure 2 shows the classification of olfactory disorders.

In a 2019 article, the author attempted to classify the degrees of anosmia and hyposmia as mild, moderate, severe (for hyposmia), and total among populations of patients who experienced hazardous events because of a smell disorder.[21] It has been reported that the risk for hazardous events increased proportionately with an increase in the degree of olfactory impairment.[22] On the basis of quantitative olfactory tests, the overall prevalence of olfactory dysfunctions has been reported variedly as approximately 20% through 25% in earlier studies.[23,24] A 2017 study placed the overall prevalence at an average of 20% and prevalence in older people at an average of 40%.[25]

ETIOLOGY OF OLFACTORY DISORDERS

On the basis of etiology, olfactory disorders can be categorized as local or systemic. Olfactory disturbances most commonly occur owing to local nasal diseases. These can prevent odorants from reaching the nasal epithelium owing to conductive and inflammatory issues. These issues include polyposis, seasonal rhinitis, allergic rhinitis, sinusitis, and trauma or malignancy of the nose, paranasal sinuses, and nasopharynx.[26-31] Numerous systemic factors are known to be associated with disorders of olfaction. Many bacterial, viral, and fungal infections have been known to be associated with smell disorders.[32-34] Trauma involving the head has been associated with olfactory dysfunctions.[35,36] Abnormalities of olfaction are involved in several neurologic conditions. Olfactory dysfunctions, including aura, have been documented with epilepsy.[37-39] Literature has shown the presence of olfactory dysfunctions with migraine episodes.[40] The association of osmophobia with migraine is well documented in the literature. Some odors have been reported to be triggers for migraines.[41,42] To a lesser extent, migraine also can be associated with phantosmia and cacosmia.[43]

Olfactory disorders are seen in patients with multiple sclerosis.[44] As the disease progresses, olfactory function impairment increases.[45] ND diseases including Parkinson and Alzheimer have been associated with olfactory dysfunctions. Studies have suggested that olfactory disorders could be an early indicator of these ND diseases.[46,47]

Several endocrinologic disease entities have been documented to have an association with olfaction disorders. Diabetes, Addison disease, Cushing syndrome, and hypothyroidism are some of the endocrine diseases associated with smell dysfunctions.[48-51] Chronic renal disorders and their relation to dysfunctions of olfaction, including hyposmia and anosmia, have been documented in

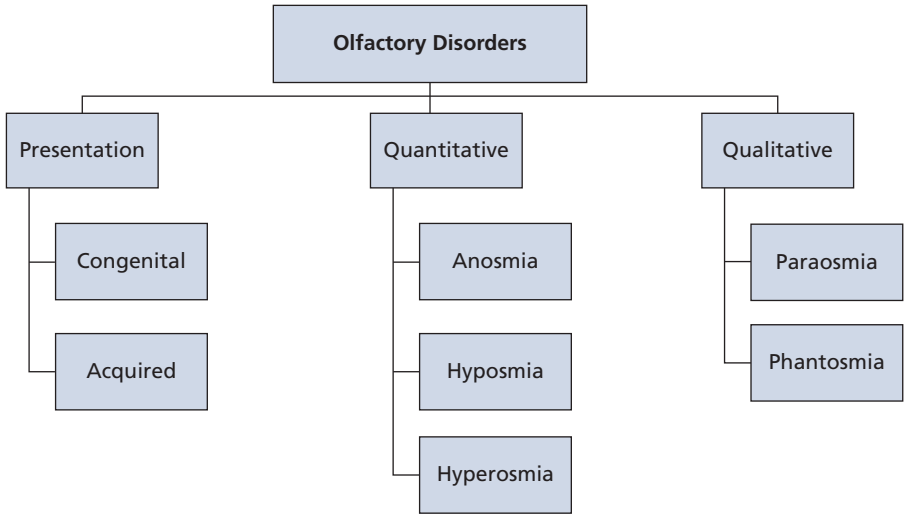

Figure 2. Disorders of olfaction.

Box. Etiology of olfactory disorders.

Local

- Polyposis
- Seasonal rhinitis
- Allergic rhinitis
- Sinusitis
- Trauma
- Malignancy

Systemic

- Infections: viral, bacterial, fungal
- Endocrine: diabetes, Addison disease, Cushing syndrome, hypothyroidism
- Trauma
- Neurologic: epilepsy, migraine, multiple sclerosis, neurodegenerative diseases
- Drugs
- Renal disease
- Kidney disease

the literature.[52,53] Olfactory functions are altered in liver diseases as well.[54] Certain drugs such as antibiotics and antidepressants have been known to cause olfactory dysfunction.[55-59] The box shows the etiology of olfactory disorders.

RELEVANCE IN DENTISTRY AND OROFACIAL PAIN

The sensory innervation to oral, perioral, and nasal structures comes predominantly from the trigeminal nerve.[60] The trigeminal and olfactory systems are distinct yet interrelated entities in the nasal cavity.[61] Most chemosensory stimulants on entering the nasal cavity produce olfactory and trigeminal sensations.[62] The stimulation of the trigeminal nerve by such stimulants can produce different sensations like burning, prickling, and stinging.[62] There is ample evidence that the trigeminal nerve works concurrently with the olfactory nerve to bring about the perception of smell.[63] Variations in trigeminal nerve sensitivity also have been reported to coexist in patients with olfactory disorders.[64]

Relation to taste

Taste, smell, and touch contribute to providing the flavor of food and beverages.[65] Olfaction plays a major role in the perception of flavors. A neurologic connection between smell and taste sensations

is well documented in the literature.[66] Olfaction via particular retronasal passages is involved in the perception of taste and flavor.[2,67] In the process of mastication, volatile molecules from the food travel to the nasal cavity through the posterior part of the oral cavity. This is responsible for the phenomenon of retronasal olfaction.[68] Dysgeusia is an altered perception of taste in response to a tastant stimulus. Phantogeusia is unpleasant taste due to a gustatory hallucination (in the absence of any stimulus).[69] Olfactory dysfunctions have been known to affect gustatory function.[70] Often, patients who have taste disorders have olfactory disorders rather than gustatory dysfunction.[71,72] Patients may not be completely aware of the presence or severity of anosmia or hyposmia.[73] Patients tend to consult the dentist if they perceive a disordered taste sensation. Dental practitioners must be aware of this fact.

Protective nature of olfaction

Compared with other mammals and other animals, humans have lost a good percentage of our strength of olfactory senses through evolution.[74] It is conceivable that humans use olfaction to detect the relative quality of the food that is about to be consumed. We use the sense of smell as a sense of protection to check if the food is suitable for ingestion. Literature suggests approximately 50% of the patients with olfactory dysfunctions may eat rotten food and approximately 30% may eat burnt food, possibly causing food poisoning.[3] This points to a possible protective nature of olfaction as related to sustenance of life. Olfaction alone might not serve this protective function fully, but it may do so in conjunction with other senses such as gustation. Anosmia or hyposmia has been known to induce potentially deleterious habits of consumption, such as excessive eating of sweet and high-fat food.

Burning mouth syndrome

Burning mouth syndrome (BMS) is a pain condition classically described as coexisting with taste alterations. Taste disturbances are present in approximately 70% of patients with BMS.[75] Literature suggests patients with BMS can exhibit varied taste disturbances such as dysgeusia and ageusia, which can occur as alteration on taste perception, persistently altered taste, or both.[76,77] However, there are reports of concomitant alterations in olfaction as well. Studies have shown the olfactory threshold to be higher in patients with BMS than control patients.[78,79] Patients with BMS are proposed to have reduced capability of identifying odors compared with control patients.[80] Odors have been shown to induce changes in perception of taste.[81] The interaction between trigeminal, olfactory, and gustatory systems also has been proposed in the literature with regard to the pathophysiology of BMS.[79] It has been well documented in the literature that olfactory dysfunctions coexist with abnormalities in thresholds for pain, tactile sensation, temperature perception, and gustation.[79] The brain center responsible for convergence of impulses from the olfactory and gustatory pathways is the orbitofrontal cortex.[82,83] Pain syndromes such as BMS and dysfunctions of olfaction are similar because both these entities are affected or modulated via the same or similar centers in the brain.

Sjögren syndrome

Complex interactions exist between the immune and olfactory systems. Changes in the immune system can affect olfaction.[84] Sjögren syndrome (SS) is an autoimmune disease affecting multiple organ systems, including salivary and lacrimal glands. Impaired smell and taste are common symptoms reported by patients with SS.[80,85] In patients with SS, there is a reduction in olfactory acuity. By and large, this is related to generalized hyposmia in these patients. There is no definitive inability to recognize or detect any specific odor in these patients.[86] Mechanisms involved in olfactory changes of SS include decreased mucin (an odorant carrier), recurrent rhinosinusitis, septal ulcerations, crustings, and immunologic mechanisms.[80,84]

INFECTIONS

Pathogens like bacteria and viruses are known to cause olfactory disturbances.[87,88] The most common causes are local nasal infections and upper respiratory diseases. Patients with chronic sinusitis have symptoms of pain and persistent smell loss even after medical or surgical treatment.[28] Viral infections are hypothesized to cause damage to the olfactory epithelium.[89,90] Olfactory dysfunctions like anosmia and hyposmia are common during severe upper respiratory infections and persist long after the other symptoms have resolved.[91] Detection of the virus in patients with postviral infections could indicate the role of the virus in olfactory dysfunction.[92]

The mechanism underlying olfactory dysfunction in infections is controversial. It could be the result of a conductive problem (preventing air from reaching the olfactory neuroepithelium), or it could be the result of nasal inflammation (inhibiting function).[16] There is some evidence that postviral anosmia may be mediated centrally, with decreased metabolism of certain regions of the brain in which olfactory information is perceived.[93] This postviral anosmia is also poorly responsive to treatment, although antiinflammatory medications or steroids are beneficial in some cases.[91]

COVID-19 AND ANOSMIA

The COVID-19 pandemic has prompted researchers to look into the association of this new disease to anosmia. COVID-19 is caused by a new strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[94] In addition to the common clinical features such as dry cough, fever, sore throat, shortness of breath, and headache, there are several reports of anosmia and hyposmia associated with this condition.[95-98] Much like as in viral infections discussed above, a study from 2020 showed the presence of olfactory dysfunctions in patients with COVID-19.[97] The earliest reports of anosmia occurring in patients with COVID-19 came in February 2020.[99,100] Since these reports, there have been others describing new-onset anosmia that occurs concomitantly with COVID-19. It is the belief of the scientific community that olfactory dysfunction is potentially an early symptom of COVID-19.[101] The Centers for Disease Control and Prevention has added "new loss of taste or smell" to the symptom list (the symptoms starting within 2-14 days of COVID-19 exposure).[102] The prevalence of olfactory dysfunction is reported to be an average of 50% in patients with COVID-19.[103]

Anosmia is being considered as a marker for COVID-19 by reputed international medical entities such as the British Association for Otorhinolaryngology.[104] In addition, there is a suggestion that patients with new-onset anosmia, even if they are asymptomatic for COVID-19, quarantine themselves in anticipation of the possible onset of COVID-19. This might help in reducing the further community spread of the disease.[105] It has been hypothesized that the 2 possible routes of entry of the COVID-19 virus into the central nervous system are through the circulation or across the cribriform plate of the ethmoid bone (the site of olfactory nerve entry).[106]

Two medications used in orofacial pain management, ibuprofen (for inflammatory pain) and renin-angiotensin system blockers (angiotensin-converting enzyme inhibitors for prophylactic treatment of migraine), have come into the literature with researchers putting forward the hypothesis that they facilitate or worsen the effects of COVID-19 infection.[107] However, other researchers have questioned this and disputed that these drugs play any such role.[108] Redeployment or reassignment of practicing pain physicians in the backdrop of the pandemic has put further significant constraints on access to care for patients with chronic pain. Remotely supported e-health pain management services are being deployed substantially in the United States and Europe in an attempt to address this problem.[109] With the COVID-19 pandemic, health care systems are stretched thin, access to care for patients with chronic pain has been hampered, and clinicians in pain and orofacial pain management find it increasingly difficult to coordinate optimum pain management for their patients.[110] Most articles published since the start of the pandemic refer to the latest guidelines such as consensus recommendations from expert pain management physician panels.[111]

Clinical pearls

Dental and orofacial pain practitioners must be aware of anosmia and hyposmia, associated entities such as BMS, and gustatory alterations when screening patients. The importance of this knowledge lies in the fact that subtle taste alterations and olfactory disorders may not be evident or noticed by the patient. A careful and complete history may enable astute dental clinicians to detect early signs of COVID-19. Traditionally, a new onset of anosmia or hyposmia would evoke suggestion of a possible onset of a ND disease or similar systemic entity or local causes. In the context of the global COVID-19 pandemic, clinicians should consider new-onset anosmia or hyposmia as a red flag for the infection. Dentists could be the first-line defense against COVID-19 by means of promptly screening routine patients for possible recent-onset anosmia or hyposmia.

CONCLUSIONS

Although the exact mechanisms involved in the pathophysiology of anosmia are not clear, it is becoming increasingly evident in the literature that it could have an association with several local

and systemic disease entities. Olfactory disorders range in etiology from a simple local infection to a brain lesion to a serious autoimmune or ND disorder. Anosmia or hyposmia can be a significant cause of change in the quality of life, especially if it is long lasting. There have been several case reports of patients describing anosmia and hyposmia as affecting their lives in an unusually negative manner. Developments in the global COVID-19 pandemic have brought this anomaly to the forefront of the scientific community. Even in an otherwise asymptomatic person, new-onset anosmia or hyposmia could be an indication of an underlying cause that could be life-altering for that patient. Dental professionals could be instrumental in screening for anosmia via asking simple questions, thereby facilitating a prompt referral to an appropriate medical professional as needed. ■

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