ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Olfactory dysfunction: a narrative review from diagnosis to treatment

Distúrbios do olfato, uma revisão narrativa do diagnóstico ao tratamento

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ABSTRACT

Olfactory dysfunction significantly impacts quality of life, and allergists and clinical immunologists must be informed about it for diagnostic and interventional purposes. The causes are varied: allergic rhinitis, chronic rhinosinusitis with or without polyps, upper airway infections, exposure to chemicals, neurological diseases, drugs, trauma, and aging itself. Olfactory function can be evaluated and measured by several tests that use different methodologies to evaluate and identify odors, olfactory threshold, and olfactory discrimination. These tests are fundamental for objectively characterizing patient complaints and evaluating olfactory function before and after therapeutic interventions. Olfactory disorders are treated according to their etiology, so determining their cause is a major factor in treatment efficacy. The main options include topical corticosteroids, which have a significant impact on patients with sinus disease, olfactory training, other therapies (such as omega 3 and intranasal vitamin A), in addition to therapies that require further research.

Keywords: Rhinitis, olfactory dysfunction, anosmia, sinusitis, COVID-19.

RESUMO

Os distúrbios do olfato (DO) impactam de forma significativa na qualidade de vida dos indivíduos, e o conhecimento teórico a respeito do assunto deve ser de domínio dos alergologistas e imunologistas clínicos, possibilitando, assim, o seu diagnóstico e implementação de intervenções. Suas causas podem ser variadas, entre elas estão: rinite alérgica, rinossinusite crônica com ou sem pólipos, infecções de vias aéreas superiores, exposição a substâncias químicas, doenças neurológicas, drogas, traumas e o próprio envelhecimento. O olfato pode ser avaliado e mensurado através de testes com metodologias diferentes, cujo objetivo é avaliar parâmetros como a identificação de odores, limiar e discriminação olfativa. Esses testes são de fundamental importância para caracterizar objetivamente a queixa do paciente, como também avaliar o olfato antes e após determinada aplicação terapêutica. O tratamento das desordens olfativas é baseado em sua etiologia, portanto determinar a sua causa é indispensável para uma melhor eficácia no manejo. Entre as principais opções estão os corticoides tópicos, com impacto significativo nos pacientes com doença sinusal associada, treinamento olfatório e outras intervenções como ômega 3, vitamina A intranasal, e terapias que ainda requerem mais estudos.

Descritores: Rinite, transtornos do olfato, sinusite, anosmia, COVID-19.

Introduction

Olfactory and taste disorders were frequently reported during the SARS-CoV-2 pandemic. Approximately 30% of infected individuals had some level of olfactory deficit[1,2]. Thus, a symptom heretofore little studied became the focus of clinical studies and part of the daily routine in doctors' offices.

Olfaction plays an important social role by providing information about the environment. Decreased or

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Submitted Sept 27 2022, accepted Mar 07 2023.

Arq Asma Alerg Imunol. 2023;7(2):154-62.

http://dx.doi.org/10.5935/2526-5393.20230021-en

absent olfaction interferes significantly in personal and social functions, consequently decreasing quality of life due to reduced sense of taste, loss of pleasure from eating, weight loss, increased risk of eating spoiled food, difficulty recognizing toxic chemical substances, and interference with interpersonal relationships[3,4].

Allergic rhinitis is among the most common nasosinusal conditions seen by allergy specialists and clinical immunologists, affecting approximately 10 to 25% of the world's population. Although the most common symptoms, such as nasal obstruction, rhinorrhea, sneezing, and itching are well recognized and addressed in clinical practice, olfactory disorders (OD) and taste disorders can also be present in these patients, with an estimated prevalence of 23% to 31%[5,6]. Thus, this review was conducted to describe the pathophysiology of olfaction, its causes, diagnostic tools, and olfactory disorder treatments.

Methods

For this narrative literature review, LILACS, MEDLINE, and SciELO were searched between May and August 2022 for studies including the following descriptors: rhinitis, sinusitis, COVID-19, olfactory disorders, sinusitis and anosmia. Full-text articles in Portuguese, English, or Spanish published in the last 20 years (2002 to 2022) were eligible for inclusion. The titles and abstracts were reviewed and analyzed, with preference given to systematic reviews, meta-analyses, and randomized controlled trials. After title and abstract reading, 45 studies were selected for full text reading and analysis, of which 35 were included: 2 were included despite predating the publication range (1982 and 1997) and 1 relevant book chapter was also included.

Pathophysiology

Adequate olfactory function depends on several factors, such as appropriate stimulus to receptors in the nasal mucosa, the reception, transmission, and processing of information by the olfactory bulb, the olfactory cortex, and components of the limbic system[7].

The olfactory mucosa is located in the upper nasal cavity, covering part of the septum, cribriform plate, and superior turbinate; it measures approximately 2 cm² and is usually covered by mucus. Pseudostratified columnar epithelium consists of 4 main cell types,[4,7,8] as described below.

– *Olfactory sensory neurons:* bipolar cells that connect the epithelial surface with the olfactory bulb.

– *Support cells:* provide support for sensory neurons and for the detoxification and phagocytosis of substances to which the olfactory epithelium is exposed.

– *Basal layer cells:* small cells responsible for maintaining the balance between apoptosis and neogenesis, differentiating to replace injured olfactory sensory neurons or support cells.

– *Microvillar cells:* function still unknown.

Odors produce a stimulus, whose path passes through the paleocortex, the oldest part of the brain, triggering emotions and producing memories. Olfactory perception is influenced by emotion, and unpleasant odors, which can provoke a sense of alert or danger, are perceived more quickly than pleasant ones, even increasing the heart rate.[4]

Olfactory disorders

Olfactory disorders can be classified as quantitative or qualitative. Quantitative disorders include hyposmia (reduced olfactory function) and anosmia (no olfactory function). Qualitative disorders are subdivided into parosmia (distorted perception of an odorant) and phantosmia (perception of an odor that is not present) (Table 1).[4]

Causes of olfactory dysfunction

Exposure to chemical substances, pollution, neurological diseases, drugs, trauma, aging, and nutritional disorders can lead to OD (Table 2). However, two-thirds of ODs are caused by upper respiratory tract infections or paranasal sinus diseases.

Rhinitis

Little is currently known about olfactory alterations in rhinitis, especially allergic rhinitis. It is assumed to be a mixed mechanism involving inflammatory and physical changes.[9] Among inflammatory alterations, Guilemany et al. identified 2 important

Table 1
Classification of olfactory disorders

Olfactory disorders	
Quantitative	**Qualitative**
Hyposmia	Parosmia
Anosmia	Phantosmia

markers: peripheral eosinophilia and eosinophilic cationic protein in the nasal mucosa. They also found a correlation between olfaction and persistent allergen exposure: in perineal allergic rhinitis involving continuous exposure to mites, there could also be persistent hyposmia, while in seasonal allergic rhinitis, hyposmia occurs only during natural exposure to pollens.

This remarkable observation could be because the late phase of allergic reactions is characterized by eosinophilic granulocytes and humoral and cellular alterations in the nasal mucosa, which was more frequent in patients with perennial allergic rhinitis than seasonal rhinitis. It has been inferred that chronic inflammation reduces the flow of information through the olfactory receptors, thus reducing olfactory detection. Hence, allergen type and inflammation duration trigger different mechanisms.[1] In addition to clarifying this mechanism, Passali et al. found that OD was more severe in patients with allergic rhinitis than in those with non-allergic rhinitis.[9,10]

Another study analyzed the epithelium of the nasal mucosa in mice with allergic rhinitis sensitized and chronically exposed to fungi. Significant thinning was observed in the olfactory epithelium, in addition to apoptotic markers and numerous eosinophilic infiltrates. It is speculated that apoptosis is mediated by tumor necrosis factor and interferon, like the pathophysiology of asthma. In this model, increased tumor necrosis factor was directly associated with apoptosis of olfactory neurons.[11]

Table 2
Causes of olfactory disorders

Chemical agents
Pollution
Neurological diseases
Drugs
Nutritional disorders
Upper respiratory tract infections
Nasosinusal diseases
Trauma
Tumors
Aging
Kallmann syndrome

It is also believed that the physical mechanism plays an important role in OD, since nasal obstruction also impedes the transport of odor particles to the olfactory epithelium.[9] Nasal obstruction is mainly due to hypertrophy of the mucosa of the lower, middle and/or upper turbinates, or through the formation of polyps as a result of a degenerative process caused by poorly controlled allergic rhinitis.[12]

Chronic rhinosinusitis

The prevalence of chronic rhinosinusitis (inflammation of the mucosa and paranasal sinuses > 12 weeks) is 10% among adults in Europe and the USA and 5.5% in Brazil. The symptoms include facial pain, nasal secretion, congestion, and hyposmia or anosmia. Olfactory changes occur in 30.0% to 78.2% of patients, varying according to age, sex, and the presence of polyps.[13]

The disease has 2 main phenotypes: chronic rhinosinusitis with and without nasal polyposis (CRSwNP and CRSwoNP, respectively).[13] The pathophysiology of chronic rhinosinusitis goes far beyond impaired ventilation and sinus cavity drainage. Current conceptualization involves immunology of the nasosinusal mucosa, including deviation of inflammatory signatures (type 1, 2 and/or 3), in which each determines the endotype of chronic rhinosinusitis, the severity of the disease, prognosis, and treatment response.[13]

Soler et al. investigated inflammatory proteins in the mucus of the olfactory slit in patients with CRSwNP and CRSwoNP. The olfactory changes in these patients were documented using the Sniffin' Sticks test (Burgardt, Wedel, Germany). No difference was observed between the CRSwNP and CRSwoNP groups in terms of risk factors that interfere with olfaction: age, sex, asthma, allergic rhinitis, diabetes mellitus, depression, and smoking. However, an inverse relationship was observed between olfaction and chemokines CCL2 and CCL3, cytokines IL5, IL6, IL13, IL10, IL9 and IL23, and total IgE. However, high levels of VEGF-A and CXCL5 have been associated with better olfactory performance. All of these proteins were higher in the CRSwNP group except VEGF-A,[14] which would explain why patients with CRSwNP have lower olfactory performance.

In addition to histological analysis, this study also assessed the degree of olfactory fossa opacification in computed tomography, finding that the greater the opacification, the greater the presence of proteins harmful to olfaction.[14] In addition, CRSwNP can mechanically obstruct the olfactory epithelium through polyp formation, leading to greater impairment than CRSwoNP. Aspirin-exacerbated respiratory disease stood out in the CRSwNP group, with olfactory impairment occurring in up to 72% of the patients.[14]

Upper airway infections

Upper airway infections, which are responsible for 18% to 45% of olfactory dysfunction cases, can have a gradual onset and are more frequent in women aged 40 to 50 years. Other significant causes include respiratory infections with rhinovirus, adenovirus, and coronavirus. Symptoms usually improve spontaneously within 3 months of infection.[15]

OD cases increased during the COVID-19 pandemic, highlighting the importance of this cause. It is speculated that in 2020, 35% to 85% of patients with COVID-19 also had OD and, of these, 10% to 17% did not spontaneously improve. Unlike OD due to other viruses, these patients had sudden changes in taste perception.[15] The mechanism of action is still uncertain, involving physical aspects, mucosal edema, and mucus, which prevent particle-bound compounds from reaching the olfactory slit. In addition, the inflammatory aspect of SARS-CoV-2 infection, the release of mediators such as tumor necrosis factor-alpha, IL1-alpha and IL1-beta, in addition to neurotropism and the involvement of support cells in the olfactory epithelium, may also explain the rapid clinical course and worse prognosis of OD in SARS-CoV-2 than other respiratory viruses.[15,16]

Trauma

Trauma, which may cause 8% to 20% of OD cases, is usually head trauma. Loss of olfaction often occurs immediately, although some patients may take months to notice. Hyposmia occurs more in frontal lesions, while anosmia is 5 times more prevalent in occipital lesions. In such cases, odor discrimination may be more impaired than odor identification.[2]

Toxins/inhaled drugs

Drugs such as amphetamines, antibiotics, and antihypertensives can affect olfaction reversibly or

irreversibly. Heavy metals or toxic gases such as nicotine, carbon monoxide, and solvents can lead to OD in 2% to 6% of exposed individuals. Since the work environment can be the source of exposure (occupational disease), the use of personal protective equipment should be reinforced and OD should monitored through olfactory tests.[2]

Syndromes

Syndromes lead to a small number of OD cases (≤ 4%). Kallmann syndrome is the best known of these, presenting clinical signs such as hypogonadotropic hypogonadism, infertility, and hyposmia/anosmia.[2]

Aging

The olfactory threshold progressively reduces with aging, which can directly affect nutrition in older adults by reducing pleasure from eating. It can negatively affect cognition and can be the initial symptom in dementia syndromes such as Alzheimer's disease and Parkinson's disease.[17]

Tumors and neoplasms

Tumors, such as olfactory groove meningioma, esthesioneuroblastoma, and hamartoma, may be related to olfactory dysfunction and require assessment through imaging tests, especially brain magnetic resonance imaging.[2]

Olfactory assessment methods

Olfaction can be assessed through several tests, each with different characteristics and standardized for a target population. Some of these include Sniffin' Sticks, which are widely used in Europe, and the University of Pennsylvania Smell Identification Test and the Connecticut Chemosensory Clinical Research Center olfaction test, which are widely used in the USA.

These tests evaluate olfactory identification, threshold, and discrimination through different methods. They are of fundamental importance for objectively characterizing patient complaints and are useful for assessing olfaction before and after therapeutic interventions.

University of Pennsylvania Smell Identification Test

This test, which only assesses olfactory identification, is easy to apply and can be performed by the patient at home. It contains 40 scratch-and-sniff items that patients identify from a list of responses. Total scores classify patients as normosmic, hyposmic, or anosmic. This test has been validated for use in Brazil.[18]

Connecticut Chemosensory Clinical Research Center odor identification test

This test assesses not only odor identification, but the olfactory threshold, adding further information to the final evaluation, which is derived from the sum and average scores of each test.

In the identification test, the examiner opens an unlabeled bottle that the patient smells and identifies from a list of possible responses. N-butanol is presented at different concentrations compared to a bottle of distilled water. The patient decides which bottle has an odor and, after consecutive responses, the patient's olfactory threshold is determined. This test has also been validated for use in Brazil.[19]

Sniffin' Sticks test

Sniffin' Sticks is a more complete test that takes longer to apply. It assesses odor threshold, discrimination, and identification. In its 3 steps, which can be applied separately, the patient smells pen-like odor-dispensing devices (sticks).[20]

To assess odor threshold, the patient must choose between 3 sticks, one of which contains n-butanol diluent and the other 2 are odorless. The 16 sets of odorants contain increasing diluent concentrations, and the test is reapplied at each successful response to avoid random identification. The threshold is determined by the mean concentration of the last 4 successful responses. Odor discrimination is tested by distinguishing between 3 sticks: 2 of which have the same odor. Sixteen sets are presented, and the score is the sum of the successful responses. In the identification stage, a series of 16 sticks are presented to the patient, who must identify the corresponding odor from a list of 4 responses. This stage is still being validated for use in Brazil.

Treatments

Since olfactory disorders are treated according to their etiology, determining the cause of the dysfunction is essential for more effective treatment.[21]

Glucocorticoids

Topical corticosteroids are widely used for olfactory disorders, regardless of etiology. They have a significant impact on patients with chronic rhinosinusitis, whereas in other etiologies they require further study. Nevertheless, due to the low risk of side effects, they can be used as monotherapy or in association with other treatments.[21] For SARS-CoV-2-related OD, if they were previously taken for allergic rhinitis or chronic rhinosinusitis, their continued use is recommended.[22]

Although topical corticosteroids seem to assist in recovery after SARS-CoV-2-related OD, their effectiveness must be carefully evaluated, given that one-third of these patients partially or completely recover spontaneously. Since there is no well-established scientific evidence about the benefit of topical corticosteroids for post-infection anosmia, no recommendations have been made regarding their routine use.[22]

It should be pointed out that nasal corticosteroid spray only partially reaches the olfactory cleft, so some studies have used techniques involving a long applicator or nasal wash with a high volume of saline solution associated with diluted corticosteroids (fluticasone or budesonide).[23]

High-volume nasal budesonide has been used for OD in chronic rhinosinusitis, with proven safety in short term treatment (4-8 weeks). Regarding side effects and possible changes in the hypothalamic-pituitary-adrenal axis, Smith et al. evaluated the safety of long-term high-volume nasal corticosteroid use in adults with chronic rhinosinusitis who had previously undergone endoscopic sinus surgery. High-volume irrigation with 1 mg nasal budesonide was performed at least twice a day for an average of 38.2 months (patients who had recently used systemic corticosteroids were excluded). The authors failed to find evidence that the hypothalamic-pituitary-adrenal axis had been suppressed by > 2-year courses of daily high-volume nasal budesonide irrigation.[24]

The benefits of systemic corticosteroids in OD include reducing inflammatory mediators and influencing expression of the olfactory gene. Systemic corticosteroids should be used with caution due to their side effects and the lack of evidence.[24] Some studies have shown benefits for short-term use after COVID-19. Disease duration, age, sex, and parosmia were unrelated to corticosteroid treatment response.[22]

Sodium citrate

A study found that intranasal sodium citrate led to better odor identification scores in patients with post-infection hyposmia than placebo, but there was no significant change in patients with hyposmia of other etiologies, such as trauma, nasosinusal, or idiopathic disease. Since calcium has an inhibitory role in olfactory signal transduction, it is believed that improvement is due to the action of sodium citrate in reducing the intracellular calcium influx, leading to reduced free calcium in the nasal mucus layer.[25]

Another randomized, double-blind study assessed the therapeutic and side effects of sodium citrate. The effects were transitory, peaking 30 to 60 minutes after application, with mild adverse effects: oropharyngeal pain, nasal paresthesia, mild rhinorrhea, and itching.[26] However, these findings were limited and had a low evidence level when replicated in a larger study. Nevertheless, it was effective for phantosmia.[27]

Alpha-lipoic acid

It is believed that due to the release of growth factor and antioxidant effects, alpha-lipoic acid can be used to treat post-upper respiratory tract infection OD, leading to olfactory receptor regeneration. In one study, 23 patients with olfactory loss for a mean of 14 months who received oral alpha-lipoic acid (600 mg/day) for 4.5 months showed improved olfactory function, with young people having better olfactory recovery than those > 60 years of age. Although the main reported side effect was gastric intolerance, further research is still needed.[28]

Vitamin A

Vitamin A can help treat post-infectious olfactory loss due to its role in the regeneration of olfactory neuronal receptors; its topical use has been linked to good results and has been increasingly studied.

A retrospective study of 170 patients assessed the efficacy of vitamin A in patients with post-infection and post-traumatic olfactory disorders: 46 patients were treated with 12 weeks of olfactory training, while the remaining 124 received olfactory training and topical vitamin A 10,000 IU/day for 8 weeks. The Sniffin' Sticks test was performed after 10 months. Olfaction improved in 37% of the vitamin A group and 23% of the control group. In addition to showing that vitamin A plus olfactory training had greater benefits than training alone, it was concluded that topical Vitamin A is a viable treatment option for post-infection OD, although further research is needed.[29]

Omega-3

In a prospective, non-blinded study of 58 patients with post-infection OD, omega 3 supplements plus olfactory training proved more beneficial than olfactory training alone. Age, sex, and symptom duration had no influence on any of the groups.[30]

Another randomized, prospective study evaluated omega-3 supplementation in patients with olfactory disorders after endoscopic resection of a skull base tumor. The patients in this study were divided into a group that underwent nasal lavage with saline solution plus omega-3 supplementation and a control group that underwent nasal lavage with saline solution only. The omega-3 supplementation group had fewer persistent olfactory disorders than the control group, which may be due to its effects on olfactory neuron healing and regeneration.[31] Due to its low potential for side effects, it might be useful as a therapy for some types of OD, although further research is required.

Olfactory training

The pathophysiological mechanism involved in olfactory training is still unclear. It is believed that repeated exposure to pungent odors can promote the regenerative capacity of olfactory neurons and improve their function.[22,32] The effectiveness of this treatment was clearly established in a recent meta-analysis, even for OD etiologies with worse prognosis, such as traumatic brain injury.[33]

Patients should undergo training twice a day for an average of 12 weeks, smelling 4 pungent odors (phenyl ethyl alcohol [rose], eucalyptol [eucalyptus], citronellal [lemon], and eugenol [clove]). Training must occur in a quiet place, with the patient concentrating on the odor for 20-30 seconds. Increasing the treatment duration up to 56 weeks and changing the odors can increase the treatment's effectiveness.[22,33] After 12 weeks of training in patients with post-infectious anosmia, a study found neural reorganization in functional magnetic resonance imaging.[32]

Surgical treatment

Since one cause of OD could be that odor molecules are prevented from reaching the olfactory cleft, certain anatomical alterations, such as deviated septum, turbinate hypertrophy, and concha bullosa might have a great impact on olfaction and should be surgically evaluated and corrected.[2]

Immunobiologicals

Patients with chronic rhinosinusitis with nasal polyposis have responded well to biological drugs, such as dupilumab, omalizumab, and mepolizumab, despite their limited applicability due to high cost and indication criteria. Their use is still restricted, with formal indication limited to chronic rhinosinusitis-related OD.[34-36]

Conclusions

ODs have a great socioeconomic impact. Their etiologies and treatment are the focus of increasing research due to significantly increased prevalence with the SARS-CoV-2 pandemic. It is important for specialists to understand the involved anatomy and the phenotypes and endotypes of OD related to nasosinusal diseases, as well as the impact of the cytokines related to each immunological profile. Efforts to expand diagnostic testing to objectively assess olfaction are equally important, since it is the only way to correctly monitor and diagnose OD.

Alternative therapies, such as olfactory training, should also be further investigated, since they could stimulate olfactory neuron regeneration, improve olfactory function, and are consistently recommended. Studies are still needed to validate other promising therapeutic options, such as omega 3, alpha-lipoic acid, intranasal citrate, and intranasal vitamin A.

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No conflicts of interest declared concerning the publication of this article.

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