



The optimal evaluation and management of patients with a gradual onset of olfactory loss

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Purpose of review

The aim of this review is to provide an overview of the causes of olfactory dysfunction, their evaluation and management, with a main focus on the gradual/progressive loss of smell.

Recent findings

As the sense of smell gives us essential information about our environment, its loss can cause nutritional and social problems while threatening an individual's safety. Recent surveys have shown quite a substantial prevalence of hyposmia (one out of four people) and anosmia (one out of 200 people) in a variety of populations.

Summary

Nasal inflammatory diseases such as allergic rhinitis and predominantly chronic rhinosinusitis account for the major and common causes of gradual/progressive loss of smell. However, they are also among the most successfully treated forms of olfactory dysfunction. The management of gradual/progressive smell deficit must always address its etiological causes. In most cases, a detailed medical history and nasal examination, smell testing, and imaging will help to establish an appropriate diagnosis. In addition to anti-inflammatory therapy, mainly nasal and systemic corticosteroids, recent investigations on smell training suggest that the controlled exposure to selected odors may increase olfactory performance.

Video abstract

See the Video Supplementary Digital Content 1 (<http://links.lww.com/COOH/A8>).

Keywords

allergic rhinitis, anosmia, chronic rhinosinusitis, hyposmia, loss of smell, olfactory training

INTRODUCTION

Smell is a sense of crucial significance that provides us critical information about nourishment, sensual attraction, emotions, and even warnings of potential hazards such as fire or spoiled food [1,2,3^{*}]. In the late 1980s, the National Geographic Smell Survey (NGSS) studied a large US sample population (1.2 million) for which the minimum age of inclusion was 10 years. Participants could not smell three or more of the six odorants ($\geq 50\%$) using a smell test specially designed for the survey [4]. In a Swedish study, the reported prevalence of olfactory impairment was 19.1% [5] whereas in a French survey this was 5.6% increasing up to 16% in the elderly [6]. In Catalonia (Spain), the Olfaction in Catalonia (OLFACAT) survey [3^{*}] reported an overall prevalence of olfactory dysfunction in the general population as high as 19.4%, including a total loss of smell of 0.3%. However, only 6.9% of participants subjectively considered their smell as being poor or very poor. Women usually perform better on

olfactory outcomes than men do. In addition, aging, poor smell self-perception, and low educational level also constitute risk factors for smell impairment [3^{*},4]. Based on the NGSS, Barber [7] found that African participants had significantly higher percentages of detection than Americans suggesting some differences according to ethnicity.

The main objective of this review article is to provide an overview of the main causes of

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KEY POINTS

- The sense of smell subsides with age in both sexes, impairing good nutrition, and often producing considerable disability with poor QoL.
- Smell loss related to allergic rhinitis, acute, and chronic rhinosinusitis, either with or without nasal polyps, are the most common causes of gradual/progressive olfactory dysfunction.
- Validated olfactory tests are useful tools to objectify the olfactory loss and to quantify its degree of severity.
- Management of olfactory dysfunction is mainly based on diagnosing and treating the cause, upper airway inflammatory diseases being among the most successfully treated forms of smell loss.
- Patient's education, prevention, and olfactory training are also strongly recommended in all causes of olfactory dysfunction.

gradual/progressive loss of smell usually seen in ear, nose, and throat (ENT) outpatient clinics including current diagnostic tools, potential therapies, and patient's follow up.

ANATOMY AND PHYSIOLOGY OF OLFACTION

Odorants reach the olfactory mucosa directly through the nostrils (ortho-olfaction) and backward flow through the nasopharynx (retro-olfaction). The retronasal pathway is crucial for smell perception by allowing food odorants to reach the olfactory receptors during eating, drinking, and chewing [8].

The first cranial nerve provides the organoleptic characteristics of odorants whereas the fifth cranial nerve provides the sensitive/somatosensory perception of odorants, playing also a role in nasal reflexes when a harmful odorant is inhaled [1,2].

There are approximately 1000 different odor receptor genes in the mammalian genome, representing about 3% of the human genome. In humans, 40% of these genes code for olfactory receptors (about 350) and the remaining 60% are nonfunctional pseudogenes [9,10]. Most odorants induce activation of more than one olfactory receptor. Although many reviews empirically state that humans are able to identify about 10 000 odors, the number of potential combinations of stimulated olfactory receptors is almost limitless.

The olfactory neuroepithelium (10 cm² of surface area) is located at the upper part of the nasal cavities on the under surface of cribriform plate, medial surface of upper, and middle turbinates,

and upper nasal septum [11,12]. It contains three main cell types: the olfactory receptor cells, the supporting cells, and the basal cells. The olfactory receptor cells are bipolar neurons that project a single dendrite to the surface of the olfactory neuroepithelium, expressing unique types of olfactory receptors in humans, and a single axon, which forms the olfactory nerve, to the olfactory bulbs. Smell information is processed in the olfactory bulbs and delivered through olfactory pathways to the limbic system, memory nuclei, and the primary olfactory cortex [13].

IMPORTANCE OF DEFINITIONS

There is no clear and general agreement when it comes to defining the organoleptic characteristics of the senses of smell, taste, or flavor. This is because definitions may rely on either the symptom or a subjective/objective smell test. *Normosmia* refers to the ability to smell all available odorants whereas *hyposmia* and *anosmia* are terms reserved for partial or total, respectively, inability to smell. *Dysosmia* describes a distortion of the sense of smell, which may be linked to the presence (*parosmia*, or *cacosmia* when it is unpleasant), or absence (*phantosmia*, *troposmia*) of an odorant [1]. Hyposmia may also be defined in terms of the 10th percentile's global score of a specific olfactory test in comparison with the performance of healthy individuals under 40 years old [14]. However, the terms anosmia and hyposmia, representing more objective measures and having a greater consensus, will be mainly used in this review.

Four taste receptors corresponding to equivalent taste qualities have been identified: salted, sweet, bitter, and acid. More recently, a fifth taste quality/receptor recognized taste was termed *umami*, acting in response to sodium glutamate, which is commonly used to enhance food flavor [15]. The term flavor is given to the combination of taste, temperature, texture, sensitivity, and retronasal smell organoleptic sensations when eating, drinking, or chewing [2,8].

CAUSE OF OLFACTORY LOSS

Different causes of olfactory loss can be classified depending on its onset (Table 1). Three main causes, sinonasal inflammatory disease, postviral olfactory loss, and trauma brain injury (TBI), account for 60–70% of all smell disorders [16].

Sudden onset and/or congenital causes

Concerning the sudden onset and/or congenital causes, the most representative causes of olfactory

Table 1. Main etiologic causes of olfactory loss according to symptom onset

Sudden onset and congenital	Gradual/progressive onset
Postviral	CRSwNP and CRSsNP
TBI	Allergic rhinitis
Congenital disorders (i.e., Kallmann syndrome, Turner Syndrome)	Nonallergic rhinitis
Iatrogenic (i.e., skull base surgery, ESS)	Tumors
Posttracheostomy	Toxic and chemical products (i.e., smoking)
	Aging
	Neurodegenerative (i.e., Alzheimer's disease, Parkinson's disease, multiple sclerosis)
	Mechanical (i.e., adenoid hypertrophy, septal deviation, nasal foreign body)
	Endocrine or metabolic disorders (i.e., diabetes mellitus, hypothyroidism)

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; ESS, endoscopic sinus surgery; TBI, trauma brain injury.

dysfunction are postviral, TBI, congenital, and iatrogenic.

Postviral anosmia

This usually occurs after a common cold with a prevalence of 11–40%. In daily clinical practice, smell diagnostic tests are often unavailable and patients do not usually seek specialized medical consultation while waiting for spontaneous smell recovery [17]. It has been described as being more prevalent among women 40–80 years old. Biopsies reveal direct damage of the olfactory receptor cells, although key mechanisms are still misunderstood [18].

Trauma brain injury

Anosmia related to TBI ranges from 10 to 66.8%. The supposed mechanisms implicated are the lesion of the first cranial nerve filaments or the intracranial contusion to the olfactory cortex, mainly when frontal or occipital blunt impact occurs [19].

Congenital causes

Congenital anosmia is a condition linked to chromosomal disorders such as Kallmann, Turner [20], or Klinefelter syndromes. Kallmann syndrome is the best known and its major features include hypogonadotropic hypogonadism and smell impairment affecting 1:8000 males and 1:40000 females [21].

Iatrogenic causes

Sinonasal surgery mainly accounts for most iatrogenic causes of olfactory dysfunction. Transnasal endoscopic approaches for skull base surgery often require mucosal flaps that may cause loss of smell postoperatively [22–24]. A by-pass of the

physiologic nasal breathing (e.g., tracheostomized) may also be related to the loss of smell [25].

Gradual and/or progressive onset causes

Concerning the gradual and/or progressive onset causes, the most representative causes of olfactory dysfunction are: aging, sinonasal inflammatory diseases (allergic rhinitis, acute/chronic rhinosinusitis), benign or malignant tumors, toxic substances, and neurodegenerative diseases.

Aging

The loss of smell with age seems to have a multifactorial origin. It may occur as a part of the neurosensorial degeneration corresponding to natural aging process and/or to age-related diseases. The histologic metaplasia from olfactory neuroepithelium to respiratory epithelium, resulting in an impairment of smell detection, seems to increase later in life [26].

Sinonasal inflammatory diseases

Allergic rhinitis and mainly chronic rhinosinusitis (CRS) with (CRSwNP) or without (CRSsNP) nasal polyps are the most common conditions related to gradual/progressive loss of smell seen in daily clinical practice [27].

Chronic rhinosinusitis

According to EPOS 2012 [28^{***}], the reduction or loss of the senses of smell is one of the major symptoms required for the definition of CRS, predominantly in CRSwNP. Olfactory dysfunction affects up to 65% of patients with CRS and nasal polyps [29–31] because of two major mechanisms: nasal obstruction, in

which the mucosal edema or polyps size restrict nasal airflow to the olfactory cleft, and nasal inflammation, due to a direct inflammatory infiltration and damage of the neuroepithelium [32,33,34[¶]].

Allergic rhinitis

Allergic rhinitis is an inflammatory disease of the nasal mucosa approximately affecting 500 million people all over the world and about 20% of the general population in Europe and the United States [35,36]. In the most prevalent areas, allergic sensitization may reach up to 50% of the population. Approximately, a third of allergic rhinitis patients report a certain degree of smell loss [37], which is linked to disease severity [33]. The pathogenesis of olfactory dysfunction in allergic rhinitis is probably similar to CRS, that is, a mixture of nasal obstruction and inflammation [33,38]. A deterioration of the sense of smell may also be associated with other types of rhinitis such as atrophic rhinitis, nonallergic rhinitis with eosinophilia syndrome [35], or aspirin-exacerbated respiratory disease [39].

United airways

A number of diseases of the lower airways such as bronchiectasis, COPD, and asthma are associated with upper airway diseases such as rhinitis and rhinosinusitis, suggesting the concept of 'united airways'. Because of this association, patients with bronchiectasis [40], COPD [41], and asthma [42] usually report a major impact on the sense of smell and this symptom may be used as a risk factor for upper and lower airway disease association.

Tumors

Olfactory dysfunction can result from a variety of intranasal and intracranial tumors. The olfactory bulbs and tracts are very sensitive to pressure from neoplasms from the dura of the cribriform plate and surrounding regions. Although it is more typical to find it associated with other neurological symptoms, sometimes the olfactory dysfunction may present as the sole symptom [43].

Toxic substances

Exposure to toxic substances such as cocaine, cigarette smoke, several chemical products, and even through chemotherapy is related to the loss of olfactory capabilities. Toxic concentration and length of exposure may directly correlate with the potential damage of the olfactory system, with smell loss usually being permanent. In the case of smoking, the changes have been reported as reversible [44] and there are even ongoing arguments as to

whether smoking is a potential mild protective factor for smell recognition [3[¶]].

Neurodegenerative diseases

Decreased sense of smell is often the first sign of Alzheimer's disease and Parkinson's disease [45]. Most Parkinson's disease patients (74.5%) present with significant olfactory loss at the earlier stages of the disease [46].

DIAGNOSIS

A complete history of the smell function (Fig. 1) detailing the onset and clinical course of the disorder is often paramount in establishing the causes, and in many cases multiple causes have to be considered [39,47]. Along with the loss of smell, almost two thirds of patients complain of taste alteration.

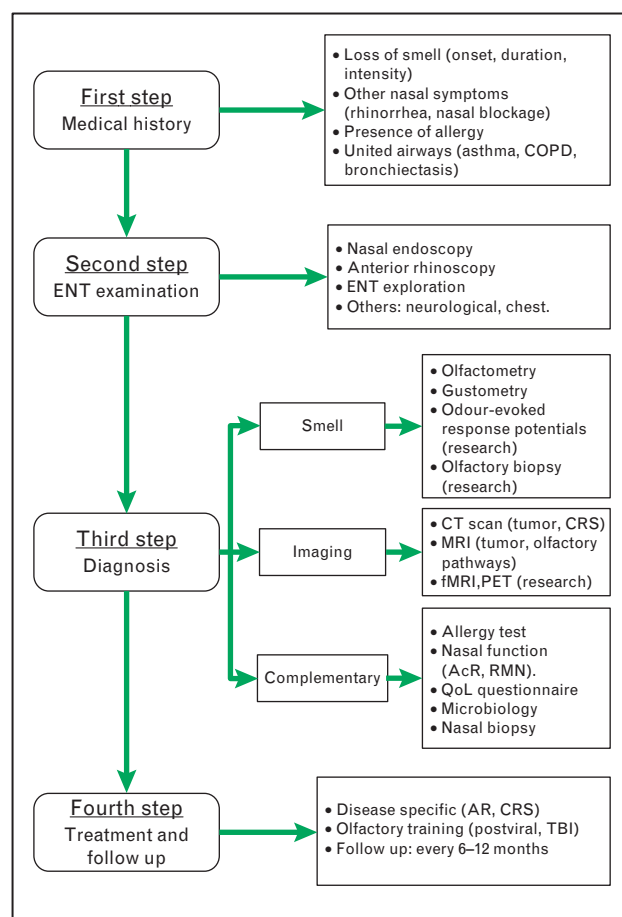


FIGURE 1. Four-step management of patients with hyposmia or anosmia. AcR, acoustic rhinometry; AR, allergic rhinitis; COPD, chronic obstructive pulmonary disease; CRS chronic rhinosinusitis; CT, computed tomography; ENT, ear, nose, and throat; fMRI, functional MRI; PET, positron emission tomography; QoL, quality of life; RNM, rhinomanometry; TBI, trauma brain injury.

However, when performing a meticulous clinical history, patients are usually able to taste with the sense of smell being what is really impaired, thus affecting flavor (a combination of smelling and tasting) [45].

Medical history

This should include demographics, major illnesses, ongoing medication, hormonal alterations, degree of loss of smell, and other sinonasal symptoms (rhinorrhea, nasal blockage, itching, facial pain/pressure), as well as personal and family health records of systemic diseases such as diabetes mellitus or hypothyroidism [1].

Ear, nose, and throat examination

Physical exploration must include anterior rhinoscopy and/or nasal endoscopy in addition to ENT examination (mouth, nose, ears, eyes). Assessment of chest and neurological symptoms should be performed if deemed necessary [48].

Smell test/subjective olfactometry

Most of the available smell tests are subjective because they depend on active patient collaboration. An optimal smell test should be rapid to perform, validated and adapted to the studied population, and offer reliability in terms of scoring smell loss. The existing inventory of smell tests (Table 2) [14,49–52] consists of standardized supraliminar

odor concentrations to be identified by patients, or different concentrations to determine the olfactory threshold of olfaction [53]. The most widespread test used is the University of Pennsylvania Smell Identification Test that can be performed at outpatient clinics or at home [49]. The Connecticut Chemosensory Clinical Research Center additionally allows the assessment of olfactory threshold using several n-butanol dilutions [50]. The Swiss Smell Diskette Test is an excellent means for smell screening [51]. The German Sniffin’ Sticks [14] is a versatile test offering a variety of sets for different purposes. The Barcelona Smell Test 24 (BAST-24) [52] is a Spanish validated test that includes sensory and sensitive odorants as well as chemical gustometry. In a trial assessing the olfaction changes before and after endoscopic sinus surgery (ESS) for CRSwNP, the authors found a correlation between inflammation severity and olfactory test outcomes [54].

The odor-evoked response potentials have provided important insights into the understanding of the olfactory system. Its use in humans has however been limited so far to research studies. This is partly because the distribution of olfactory receptor neurons across the human nasal cavity is not well understood [55].

Imaging

Imaging is a very useful tool for diagnosing the causes of olfactory loss in the case of specific

Table 2. Characteristics of the most used smell tests/subjective olfactometries						
Smell test/olfactometry	Country of validation	Supraliminar	Threshold	Duration (min)	Scoring	Test retest
UPSIT (Doty <i>et al.</i>) [49]	USA	40 encapsulated odors scratch-and-sniff technique Olfactory/trigeminal	No	15	Reference values according to age and gender	$r=0.981$
CCCRC (Cain <i>et al.</i>) [50]	USA	10 odors in jars Sniffing technique Olfactory/trigeminal	Yes ^a	35	(0–7 scale) < 2, anosmia 2–5, hyposmia 6–7, normosmia	N/A
Smell diskettes test (Briner and Simmen) [51]	Switzerland	8 odors in diskettes Sniffing technique Olfactory/trigeminal	No	5	(0–8 scale) 0–6, hyposmia 7–8, normosmia	$r=0.990$
Sniffin’ Sticks (Hummel <i>et al.</i>) [14]	Germany	16 odors in pens Sniffing technique Olfactory/trigeminal	Yes ^a	25	Considered normal when forced choice identification > 75%	$r=0.730$
BAST-24 (Cardesín <i>et al.</i>) [52]	Spain	24 odors in semisolid state sniffing technique Olfactory/trigeminal	No	20	Reference values according to: age, gender, and smoking habit	N/A

BAST-24, Barcelona Smell Test 24 odors; CCCRC, Connecticut Chemosensory Clinical Research Center test; N/A, not available. UPSIT, University of Pennsylvania Smell Identification Test.
^aThreshold assessment using increasing dilutions of n-butanol.

indications. Computed tomography scan is the gold standard to study paranasal sinus diseases, the skull base, and the olfactory cleft [56]. It provides excellent bone and soft-tissue details, with this being indispensable for surgical planning. MRI focuses on evaluating the olfactory bulbs, tracts, and grooves, as well as other intracranial causes of olfactory dysfunction (e.g., tumors, neurodegenerative diseases). Decker *et al.* [57] found that in idiopathic olfactory loss in 1122 cases, MRI demonstrated an intracranial neoplasm in 4.9%, thereby justifying the cost of MRI screening for patients with idiopathic loss of smell.

Olfactory functional MRI (fMRI) measures brain activity in response to olfactory stimuli. Although its use is still limited to research studies, a low activation of olfactory brain structures has been found in the elderly and in TBI patients [58]. Kim *et al.* [59] evaluated the usefulness of positron emission tomography in postviral olfactory loss in a small number ($N=9$) of patients by finding a significant hypometabolism in their olfactory cortex.

Complementary tests

Laboratory tests may be of help in seeking allergies (total and specific IgE), diabetes mellitus, thyroid diseases, nutritional deficiencies, or malignancies. The study of nasal patency by acoustic rhinometry (AcR) and/or rhinomanometry is advisable in specific situations. Questionnaires such as the Sino-nasal Outcome Test 22 may help to evaluate the impact of the loss of smell in a patient's quality of life (QoL) [60]. Nasal sampling for microbiology and/or biopsies for histopathology are often recommended in the case of concomitant nasal disorders. Although pathological changes of olfactory mucosa (e.g., CRSwNP) including patches of olfactory bipolar cells disrupted by respiratory metaplasia or inflammatory eosinophilic infiltration have been found [54], olfactory mucosa biopsies should nowadays be still considered for research without a clear application in routine clinical practice.

TREATMENT

As in many conditions, medical care not only comprises a specific treatment, it also consists of prevention and thinking of new alternatives for the problem.

Prevention and education

Clearly, the prevention of nasal viral infections with impact on smell (e.g., common cold, flu), smoking and toxic exposure are highly recommended. In

patients at risk (i.e., over 65 years old or with asthma), annual influenza vaccination is recommended. For individuals in which sense of smell is already impaired, treatment compliance (when available), enhancing food odor and taste, and implementation of safety measures such as gas alarm systems and spoiled food avoidance may be of great help. Education is also an important component of prevention and control of allergic rhinitis, CRSwNP, and CRSsNP.

Disease-specific treatment

Smell loss related to upper airway inflammatory diseases is probably the most treatable form of olfactory dysfunction, this effect being nevertheless partial. The complete treatment evidence for CRS is widely described in the EPOS consensus [28²²]. As in CRS, Allergic Rhinitis and its Impact on Asthma guidelines explain in detail the management for allergic rhinitis [35]. Antihistamines and intranasal corticosteroids (INS) constitute the most effective drugs to improve the loss of smell in allergic cases [38,61,62].

INS, alone or combined with oral corticosteroids, constitutes the first-line therapy for CRS [61–64]. In a randomized trial in severe CRSwNP patients, Alobid *et al.* [34²¹] have recently found that after corticosteroid treatment, the sense of smell improves in correlation with nasal congestion but not nasal inflammation. When medical treatment fails, ESS is recommended but the impact of surgical and medical treatments on smell are similar [65]. In a prospective trial in ARS and CRS patients undergoing ESS, a direct positive relationship between smell recovery and QoL improvement has been also found [66].

Olfactory training

Some studies have revealed that the olfactory function has the ability to recover with repeated short-term exposure to odors. This improvement has been observed in patients with either postviral anosmia, idiopathic olfactory loss, or TBI anosmia [14].

Future therapies

The recognition of neural stem cells in the olfactory epithelium makes it a promising model system for the identification of mechanisms regulating cellular self-renewal and differentiation, which can be a future treatment for tissue regeneration after olfactory system injury [67,68]. Recent trials using monoclonal antibodies such as mepalimumab [69], omalizumab [70], or even dupilumab [71] to treat

CRSwNP and/or asthma may, in future approaches, offer better therapy for the loss of smell stemming from upper airway inflammatory disease.

CONCLUSION

Smell dysfunction is a challenging condition of significant prevalence that has a major impact on an individual's safety and QoL. It must be systematically assessed with a complete medical history and nasal exploration, including smell testing, to find out the original cause, and then offer to the patient its best available treatment.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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