

The sense of smell in chronic rhinosinusitis



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Smell dysfunction has a significant impact on quality of life (QOL), potentially leading to food poisoning, a reduction in appetite and eventually malnutrition, immunity reduction, and worsening of medical illness.¹

OLFCAT (OLFAction in CATalonia), the largest population-based European epidemiological smell survey, reported an overall prevalence of olfactory dysfunction of 19.4% (82 million European Union citizens).² Decreased olfactory function is very common in the older population. A cross-sectional survey reported that smell dysfunction affects 13.5% (20.5 million) of the US population 40 years or older, with loss of smell being an independent risk factor for increased mortality. Poor olfactory self-perception, postviral infections, head trauma, pregnancy, male sex, alcohol consumption, and chronic rhinosinusitis (CRS), mainly with comorbid asthma, have been described as risk factors for olfactory disorders.²

Causes of acquired smell loss include respiratory viruses (common cold, flu), traumatic brain injury, upper airway inflammation (rhinitis, rhinosinusitis), neurodegenerative diseases, intracranial/sinonasal tumors, drugs, exposition to toxic substances, irradiation, or iatrogenic among others. CRS is a very prevalent disease affecting 10% to 14% of the US and European population and has great impact on patients' QOL, being the most frequent cause of gradual olfactory dysfunction.^{1,3,4}

PATHOPHYSIOLOGY

Odorants reaching the olfactory epithelium, which covers the cribriform plate and the upper part (8–10 cm²) of the nasal septum

and the middle/upper turbinates, dissolve in the mucus layer and bind/activate olfactory receptors. Up to 30 million receptor neurons, which express up to 350 different olfactory receptors, can be found in the olfactory epithelium. A complex combinatorial coding, by which each odorant ligand may be recognized by an olfactory receptor combination, enables humans to detect billions of different odors. Olfactory information, processed and integrated in the olfactory bulb, is then projected onto the primary olfactory centers such as the limbic system (emotions) and the hypothalamus (memory) and finally projected to the olfactory cortex where humans acquire consciousness of smelling (Fig 1, A–D).²

Smell loss in CRS is caused by a multifactorial combination of mechanical obstruction of odorant transmission in the olfactory cleft due to mucosal type 2 inflammation (edema or nasal polyps),⁵ leading to shedding and/or degeneration of the olfactory epithelium and causing the reduction or loss of the sense of smell (Fig 1, A, E, F, and G).

DIAGNOSIS CRITERIA

CRS has 2 main phenotypes, with (CRSwNP) and without (CRSSNP) nasal polyps. Smell loss is one of the main symptoms of CRS, constituting 1 of the 4 symptoms to clinically diagnose CRS in both the American and the European rhinosinusitis guidelines.^{3,4} In addition, nasal endoscopy may show the presence of nasal polyps or mucopurulent discharge from the middle meatus, whereas imaging such as computed tomography scan or magnetic resonance imaging may show the presence of mucosal changes within the ostiomeatal complex and/or sinuses.^{3,4}

Smell assessment may be easily performed in daily clinical practice with subjective tools such as visual analogue scale (0–10 cm), smell tests, and QOL questionnaires. Olfactory psychophysical tests may include smell detection, memory/recognition, and forced-choice identification, as well as smell discrimination and olfactory thresholds (Table I). These smell tests are usually limited to the region/country where they have been developed and validated because odor identification tasks are culturally dependent.¹

In the United States, the most commonly used smell identification test is the University of Pennsylvania Smell Identification Test. In Europe, the Sniffin' sticks test, which includes supraliminal identification, discrimination, and threshold tests, has been validated in several countries. Barcelona Smell Test – 24 has been extensively used in Spanish-speaking populations. It also contains a chemical gustometry that is important to differentiate between pure taste and flavor (smell plus taste) disorders (Table I).

Objective tests such as olfactory functional magnetic resonance imaging or olfactory event-related potentials are expensive and usually limited to experimental and research use in specialized centers.

In patients with CRS, loss of smell has been found to be a clinical marker of disease severity, being more marked in patients

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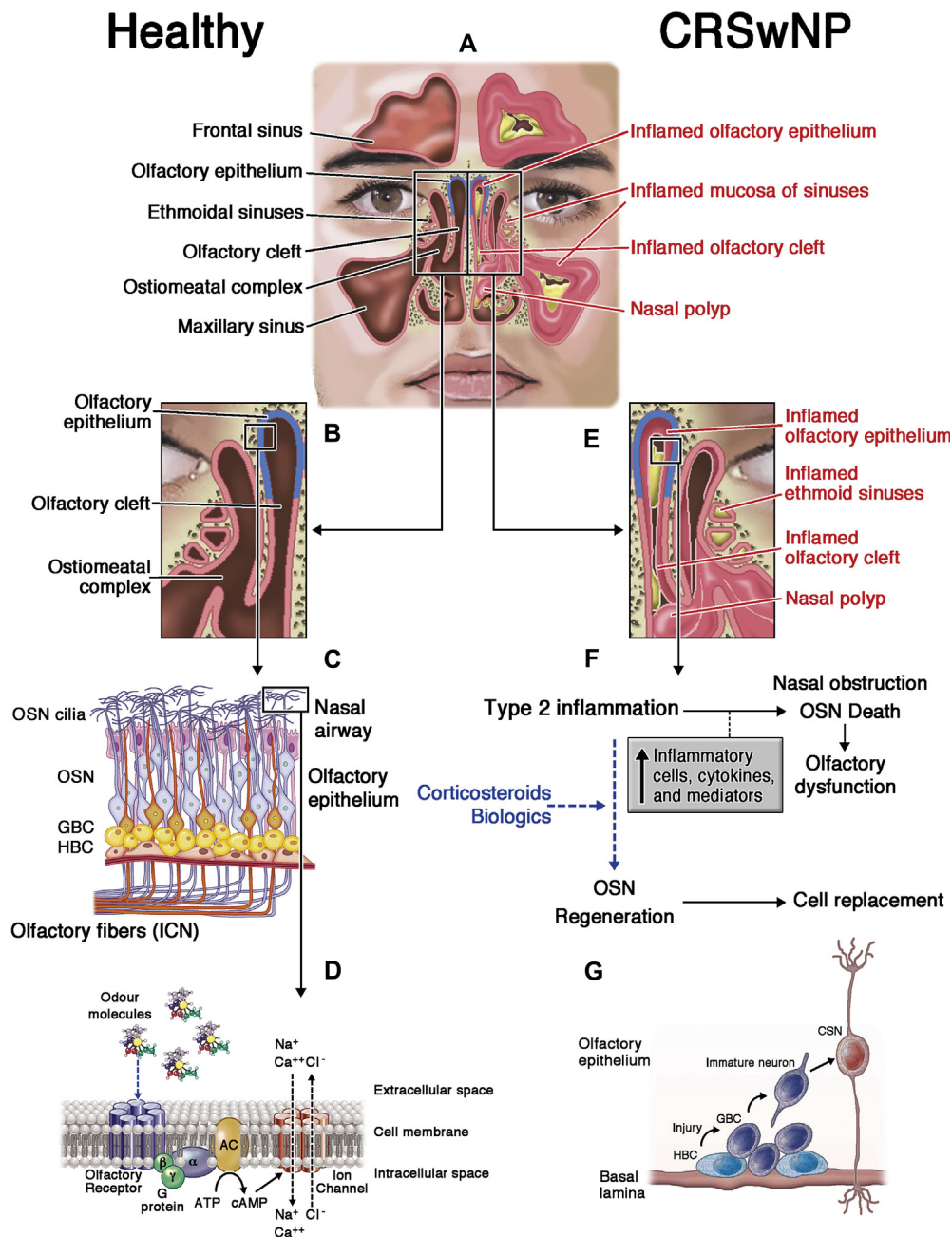


FIG 1. The peripheral olfactory system in health and disease. **Healthy status:** **A** and **B**, The olfactory epithelium is located in the olfactory cleft, in the upper part of the nasal cavity. **C**, This olfactory epithelium contains the cell bodies of mature and immature olfactory sensory neurons (OSNs) generated from horizontal (HBC) and globose (GBC) basal stem cells (BSCs). OSN axons exit the olfactory epithelium in fascicles of olfactory fibers projecting the first cranial nerve (ICN) through the cribriform plate to olfactory bulbs. **C** and **D**, Odor transduction occurs in the cilia from OSN dendritic knobs where olfactory receptors (7-transmembrane domain G-protein-coupled receptors) recognize odor molecules through the activation of the adenylyl cyclase (AC) pathway and membrane ion channels. **Inflammatory status in CRSwNP:** **A-E**, CRS inflammation, with or without nasal polyps, affects the mucosa of bilateral paranasal sinuses and nasal cavities, including the olfactory cleft and epithelium. **F** and **G**, Type 2 inflammation (mainly eosinophilic) of the olfactory cleft mucosa leads to olfactory epithelium shedding and OSN degeneration through potential causes of the loss of smell. Anti-inflammatory therapy (corticosteroids, biologics, and others) potentially reduces olfactory cleft inflammation and induces BSC proliferation and OSN regeneration (dashed arrows), causing the partial or total recovery of the sense of smell. α - β - γ , G-protein subunits; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; Ca^{++} , calcium ion; Cl^- , chloride ion; Na^+ , sodium ion.

TABLE I. Subjective and objective tests to assess the sense of smell commonly used in patients with/without CRS

Subjective smell scales				
Visual analogue scale (VAS)	A straight horizontal line of 10-cm length measuring severity of smell loss (0 corresponds to normal smell and 10 to total smell loss)			
Likert scale	Responses are scored along a range of 4-7 items to rate smell loss (ie, mild, moderate, severe from 0 to 3 or 0 to 6)			
Psychophysical smell tests				
Smell test	Author, year (country)	Supraliminal	Threshold	Population and scoring
University of Pennsylvania Smell Identification Test (UPSIT)	Doty, 1984 (USA)	A total of 40 encapsulated odors. Scratch-and-sniff. 4 AFC	—	Adults Reference values according to age and sex 0-40 points score: ≤18 anosmia 19-34 hyposmia/microsmia >34 normosmia
Connecticut Olfactory Test (CCCRC)	Cain, 1983 (USA)	A total of 10 odors, in jars. Forced choice among 20 descriptors. Separate nostrils	N-Butanol. 2 AFC. 4-correct-in-a-row	Adults 0-7-point scale: <2 anosmia 2-5 hyposmia 6-7 normosmia
Smell Diskettes	Briner, 1999 (Switzerland)	A total of 8 diskettes that must be opened to release the odor. 3 AFC	—	Adults and children 0-8-point scale: 0-6 hyposmia 7-8 normosmia
Sniffin’ sticks	Kobal, 1996 (Germany)	Identification: 16 odors in felt-tip pens. 4 AFC Discrimination: 16 odors in 3 AFC. Identify the pen having the different smell	N-Butanol in 3 AFC. Single staircase method	Adults: Normosmia if >75% forced-choice identification. Updated normative values according to age and sex in Stevens et al, ⁵ 2019
Barcelona Smell Test (BAST-24)	Cardesín, 2006 (Spain)	A total of 24 odors (semisolid gel) in glass jars. Evaluates detection, identification, and 4 AFC identification	—	Adults: Reference values according to age, sex, and smoking habit
Universal Sniff Test (U-Sniff)	Schriever, 2018 (multinational)	A total of 12 odors in felt-tip pens. 4 AFC. Descriptors presented in writing and in pictures	—	Children: 0-12-point scale. Normative data reported for each country
Objective smell tests				
Olfactory event-related potentials	Collection of the electrical activity by means of external electrodes while presenting the patient with odors			
Olfactory electrogram	Recording the electrical activity of the nasal olfactory epithelium by applying intranasal electrodes Mainly for research. Not suitable for clinical application because electrodes are difficult to place and hard to tolerate			
Olfactory functional magnetic resonance imaging	Identifies the brain cortical areas that are activated in the presence of an olfactory stimulus It is expensive and used only in research			

AFC, Alternative forced-choice paradigm.

with CRSwNP with lower airway comorbidities such as bronchiectasis, asthma, and aspirin- and nonsteroidal anti-inflammatory drug-exacerbated respiratory disease.⁶ Moreover, smell loss, measured with smell tests, significantly correlates with other CRS outcomes such as computed tomography scan, nasal endoscopy, or QOL.

THERAPEUTIC OPTIONS

According to existing guidelines,^{3,4} intranasal corticosteroids and short course of systemic corticosteroids (CSs) are recommended in patients with olfactory dysfunction secondary to CRS.⁷ The highest efficacy of CSs in the loss of smell is obtained by systemic administration followed by nasal drops and, finally, intranasal spray. The CS-induced improvement in

sense of smell in CRS might be related to the reduction of inflammation/obstruction of olfactory cleft and/or increased regeneration of the olfactory epithelium (Fig 1, F and G). Other therapies such as antileukotrienes, corticosteroid sinus implants, or aspirin desensitization have also been shown to improve smell loss in patients with CRS. Because recent studies have demonstrated a poor middle- to long-term efficacy of endoscopic sinus surgery in smell loss, the role of CRS surgery in improving the sense of smell, apart from the effect of first surgeries,⁸ remains under debate and should not be used as the unique indication criteria for CRS surgery.

Like other type 2 diseases such as asthma, urticaria, atopic dermatitis, or eosinophilic esophagitis, biological therapies are currently being investigated for the treatment of CRSwNP. At present, only dupilumab, the mAb against IL-4Rα receptor that

activates the signaling of both IL-4 and IL-13 pathways, has been recently approved in both the United States (Food and Drug Administration) and the European Union (European Medicines Agency) to treat patients with CRSwNP not responding to CS treatment. In addition to a significant efficacy in CRSwNP (severity, nasal polyp size, nasal function, nasal symptoms, sinus occupation, QOL, and T2 inflammatory markers) and asthma (lung function and control) outcomes and up to 1 year of treatment, dupilumab has shown an outstanding and fast (2 weeks) improvement in loss of smell, the most difficult-to-treat symptom in patients with severe CRSwNP with or without asthma or aspirin/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease.⁹ All these findings have promoted “loss of smell” as one of the main criteria for indication of and response to biological treatment.¹⁰

Olfactory training is recommended in patients with olfactory loss of postviral and posttraumatic origin, but no data are available to recommend its use in patients with CRS. Finally, the management of patients with moderate to severe olfactory loss should include counseling regarding safety items, such as placing of smoke/gas detectors, disposing of spoiled food, personal hygiene, as well as being aware of potential environmental hazards.¹

CONCLUSIONS

Smell loss is a very prevalent and difficult-to-treat symptom in CRS, being usually identified by patients as the symptom affecting their QOL the most. Smell loss represents a clinical marker of disease severity in both rhinitis and rhinosinusitis and is associated with type 2 inflammation of the sinonasal mucosa and the presence of respiratory comorbidities such as asthma and

bronchiectasis. Therapeutic options include intranasal and systemic corticosteroids, surgery, and, more recently, biological therapy in CRSwNP.

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