

Olfaction in Chronic Rhinosinusitis

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Abstract Olfactory dysfunction is a frequent complaint in chronic rhinosinusitis patients and has a significant impact on quality of life. Therefore, it is essential that clinicians are aware of the importance of olfactory dysfunction in chronic rhinosinusitis (CRS) patients and know how to deal with it. Notably, the evaluation of olfactory function (i.e., using psychophysical testing) and imagery of olfactory bulb play an important role in the evaluation of patients and give essential information about the “baseline” olfactory function. Because the high impact of olfactory function on quality of life and medical and/or surgical treatment should be proposed to patients. However, it remains difficult to predict the outcome of treatment as well as long-term efficacy. The first section of this review is dedicated to the assessment of olfactory function. Secondly, we will discuss the etiopathology of olfactory dysfunction in CRS with and without nasal polyps. Finally, we

will review literature findings about the efficacy of different treatments on olfactory function.

Keywords Chronic rhinosinusitis · Smell · Olfaction · Nasal polyps

Introduction

Chemosensory perception is a global perception of olfactory, gustatory, intranasal trigeminal chemical stimuli involving different cranial nerves and allowing the perception of both the inside world (food ingestion, flavor through the retronasal route) and the outside world (odors sniffed in with air through the orthonasal route).

All involved cranial nerves must be functional to deliver a global “picture” of the chemosensory stimulus to the subject. Many disorders can impede this normal chemosensory perception. On particular, several conditions may affect olfactory function; and olfactory dysfunction is relatively frequent, affecting up to 20 % of the general population [1, 2]. Olfactory disorders can be classified into sinonasal and non-sinonasal-related olfactory disorders.

The degree of olfactory dysfunction associated with sinonasal disorder varies as a function of the etiology, with quantitative olfactory loss that is more important in chronic rhinosinusitis with nasal polyps, followed by chronic rhinosinusitis without polyps, non-allergic rhinitis, atrophic rhinitis, and allergic rhinitis.

Non-sinonasal origin of olfactory dysfunction are diverse and encompass different diseases such as post-infectious olfactory loss; post-traumatic olfactory loss; congenital anosmia; toxic/drug-induced causes; neurologic causes (Alzheimer’s disease, Parkinson’s disease); metabolic or endocrine; and finally, idiopathic origin when there is no

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obvious cause after a meticulous work-up. This last entity account for ± 20 % of the causes in large cohort of patients presenting themselves to smell and taste centers [3].

Olfactory disorders may also be categorized as either quantitative or qualitative. Quantitative olfactory disorder refers to a modification of the perception of intensity of odorants. Quantitative olfactory disorders are hyposmia (decreased ability to smell), hyperosmia (enhanced ability to smell), and anosmia (lack of ability to smell). Qualitative olfactory disorders refer to the modification of the quality of odorants. They are parosmia (sensation that a given odor is different from the typical odor for this substance), phantosmia (perception of an odor in absence of the odour source), and olfactory agnosia (inability to recognize odorants). Studies have revealed that qualitative olfactory disorders are affecting the quality of life even more as compared to quantitative ones [4, 5]. In sinonasal-related olfactory dysfunction, olfactory symptoms are mainly quantitative.

Clinical management of patients complaining of an olfactory dysfunction requires a deep anamnesis (predisposing factors, medical history, toxic environment, and current medications); and a complete clinical examination, including otorhinolaryngological and neurological examinations. Although the clinician may already have some diagnosis at this stage, it is widely admitted that a complete work-up is required, notably; it is essential to assess the olfactory function, using psychophysical testing for both ortho- and retronasal functions. It is also mandatory to note that there is a frequent confusion between olfaction and taste. Indeed, people often use the term “taste” to refer to the flavor, which is mainly determined by retronasal olfaction. In that way, it has been demonstrated that although the majority of patients complain of taste loss, it usually reflect loss of smell function [6]. Therefore, a complete psychophysical testing is helpful to assess the quantitative dysfunction. Besides these psychophysical testing, imagery of the olfactory pathway and electrophysiological recording are also helpful.

Assessment of Olfactory Function

Several methods have been developed and validated to quantify olfactory function: psychophysical testing, electrophysiological testing, and structural and functional imaging. *Psychophysical testing* of olfactory function is usually based on the presentation of different odors with a precise concentration. The subject/patient is asked to answer to a requested task. A lot of different tests culturally and socially adapted are available worldwide.

Orthonasal Tests

In the USA, the most frequently used is the University of Pennsylvania Smell Identification Test (UPSIT) [7, 8]. The UPSIT uses 40 items. It encompasses four “scratch and sniff”

booklets. Odorants are embedded in microcapsules placed on strips at the bottom of the page of booklets. The stimuli are released by scratching the strip with a pencil, and subjects have to choose one of the four proposed descriptors that best correspond to the respective odor, in a multiple forced choice procedure [7, 8]. Several adapted versions have been developed and adapted culturally worldwide.

The Cross-Cultural Smell Identification Test is similar to the UPSIT. In this short test, patients are presented with 12 odors and are asked to perform a multiple forced choice procedure among four descriptors [9].

In Western Europe, the Sniffin's Sticks test [10] is the most frequently used to assess orthonasal olfactory function. It consists of pen-like, odor-dispensing devices that are presented in front of the nose of the patient. The extended version [10] encompasses three different tasks, namely tests for odor threshold, odor discrimination, and odor identification tasks. The odor threshold for n-butanol is assessed using a single staircase, three-alternative forced choice procedure. The odor discrimination is assessed using three-alternative items forced choice procedure: three pens are presented to the subject: two containing the same odorant and one containing a different odorant. Finally, odor identification is assessed for 16 common odors, using a four-item forced choice procedure. The Sniffin' Sticks also exist in a short version, named the Sniffin' Sticks Screening test, consisting in the identification of 12 or 16 pens, based on a four-item forced choice procedure [10, 11].

The European test of olfactory capabilities (ETOC) is based on 12 odors contained in small glass bottles are presented to patients. First, patients are asked to identify one out of four bottles containing an odorant. Secondly, patients have to identify the odorant based on a four-item forced choice procedure [12].

Another validated test is the Connecticut Chemosensory Clinical Research Center Test (CCCRC Test). This test encompasses the evaluation of butanol threshold and identification performances. Butanol threshold is assessed by presenting ascending concentrations of butanol to patients, along with a nonodorous sample. Patients are asked to identify the odorous sample. The threshold is represented by the concentration that is correctly identified in three to five consecutive trials. In the identification task, patients are presented with eight odorants that have to be identified from a 16-item list [13].

The BAST-24 consists of 24 odors contained in hermetic containers and presenting to patients, aiming to test smell detection, identification, and forced choice [14].

The smell diskette test has eight polyester diskettes containing different odorants in a high suprathreshold concentration (coffee, vanilla, smoke, peach, pineapple, rose, coconut, and vinegar). The diskettes are opened to release the odor and closed when the test is done [15].

The T and T test is probably the most frequently used in Japan. This test is based on five odors, presented in eight concentrations. Odorants are presented in ascending

concentrations. First, the detection threshold is assessed; then, the identification threshold is defined [16].

Retronasal Test

Retronasal olfactory function is assessed following a standardized method using a row of 20 items [17]. Powderized substances are applied to the tongue and patients are asked to recognize the substance following a multiple forced choice procedure. Although having the advantage of being easy to use, cheap, and validated, psychophysical testing require the collaboration of the subjects and hence, may be subjected to response bias.

Electrophysiological Testing

On contrast, *electrophysiological recordings* such as electro-olfactogram (EOG) and chemosensory event-related potentials (CSERPs) only require some collaboration of the subject and are considered as more objective.

Electro-olfactograms (EOG) are electrical potentials of the olfactory epithelium that occur in response to olfactory stimulation. The EOG represents the sum of generator potentials of olfactory receptor neurons. Although this technique appears to be attractive, for example, for the functional characterization of the human olfactory epithelium, there are only few reports utilizing the human EOG in clinic (for a review, see [18]).

Event-related potentials (ERP) are EEG-derived signals. They reflect the sum of postsynaptic potentials occurring in a population of similarly oriented cortical pyramidal neurons, activated by a transient “event” (i.e., the onset of a sensory stimulus). Chemosensory ERP may be recorded using a constant flow olfactometer and specific molecules, activating either the olfactory or the trigeminal system [19–21]. Chemosensory ERPs are directly correlated to neuronal activation; they have a high temporal resolution in the range of microseconds, and they can be obtained independently of the subject’s response bias, e.g., they are well-suited for medico-legal investigations [19]. Although this technique is particularly interesting for clinical

diagnosis due to its relative objectivity, it has several drawbacks that are its high cost, its low signal-to-noise ratio, the need of expertise, and the time required for one recording, rendering it poorly available in clinic.

Imagery

Imagery is also very helpful in the clinical work-up of patients with olfactory dysfunction. CT scanner of the nose and of the paranasal sinuses may help to diagnose CRS, diseases in the olfactory cleft, and variation of the normal anatomy. Magnetic resonance imaging adds important informations regarding the cranial base where the olfactory bulbs (OBs) are located. MRI is the imaging modality of choice to evaluate olfactory apparatus, because it allows examining the olfactory bulb, olfactory tract, olfactory sulcus, and central olfactory projection areas (Fig. 1). Moreover, the olfactory bulb volume and the olfactory sulcus depth are well correlated to the olfactory dysfunction in many different diseases, the volume and the depth being smaller when the olfactory dysfunction is more affected. In the context of chronic rhinosinusitis, it has been shown that the olfactory bulb volume is correlated with the sinonasal disease score, and patients having a sinonasal disease score ≥ 12 have significantly larger olfactory bulb volume as compared to patients with a higher score. Interestingly, the olfactory bulb has a high plasticity (for a review, see [22]). For example, it has been shown that olfactory bulb volume significantly increases after surgical treatment of patients with chronic rhinosinusitis with polyps; and this increase of OB volume correlated significantly with the decrease in odor thresholds [23••].

Olfactory Dysfunction and Chronic Rhinosinusitis

In the literature, chronic rhinosinusitis (CRS) is described as the most common cause of olfactory dysfunction, accounting for 14–30 % of cases [24–27]. Inversely, olfactory impairment is a common symptom affecting 61–83 % of patients with CRS



Fig. 1 2-MRI on the coronal plane in **a** a patient suffering from CRS and reporting olfactory dysfunction and **b** a normal control. The olfactory bulb (white arrow) of the patient has a decreased volume as compared to the olfactory bulb of the normal control. **c** An anosmic patient suffering from CRS (TDI=13). The patient received a surgical treatment for CRS

several years ago. We can note on this MRI that the olfactory bulbs are hypoplastic. Moreover, the patients still have CRS lesions and we clearly see opacification of the olfactory cleft, which was cicatricial at rigid endoscope examination

[28, 29, 30, 31]. Nevertheless, up to one quarter of patients with CRS are unaware of their decreased olfactory abilities, probably because the olfactory dysfunction in CRS develops slowly and in consequence, only a few patients note this disorder [32]. Psychophysical tests have shown that patients with CRS have quantitative disorders, between hyposmia and anosmia [24–27, 33]. Patients with CRS may also report qualitative dysfunctions such as parosmia and phantosmia. However, these symptoms are less frequent in sinonasal disease as compared to other etiologies (i.e., post-infectious, post-traumatic). Reden et al. [34] reported incidence of parosmia and phantosmia in patients with CRS of 28 and 7 %, respectively. Typically, the olfactory dysfunction is fluctuant depending on the inflammation present in the nose and the paranasal sinuses, which itself may be dependent on the allergen exposure for patients combining allergic sensitization and CRS [35]. Litvack et al. [29] found that age ≥ 65 years, nasal polyposis, asthma, and smoking were associated with olfactory dysfunction in patients with CRS. Moreover, it has been shown in patients with nasal polyposis that asthma has a further impact on the sense of smell [36]. In patients with bronchiectasis, smell impairment is also present and is higher when associated with CRS (particularly with nasal polyps), as compared to patients with post-infectious and idiopathic bronchiectasis [37]. Interestingly, aspirin intolerance, allergic rhinitis, and history of prior sinus surgery were not significantly associated with olfactory dysfunction in CRS patients. Studies have described that the severity of quantitative olfactory disorders is related to the importance of the sinonasal disease, based on endoscopy and CT scores [38] (Table 1).

In every patients' complaining of olfactory disorder, it is mandatory to perform a complete endoscopic examination, with a particular focus on the middle meatus (edema, inflammation, polyp); the superior meatus; and the olfactory cleft (Fig. 2). The olfactory cleft is a very narrow space, open anteriorly and inferiorly in the nasal fossa. The olfactory cleft is bordered medially by the nasal septum and laterally by the turbinate wall of the ethmoid labyrinth. The olfactory neuroepithelium is located in the olfactory cleft, and the vast majority of the olfactory receptor neurons (ORNs) are found in the olfactory neuroepithelium, although some ORNs can also be found in the supreme, the superior, and the middle turbinates (specially on their medial aspect) and even in the postero-superior aspect of the septum.

Traditionally, olfactory dysfunction in CRS is explained by a conductive olfactory loss, caused by swollen or hypertrophic nasal mucosa or nasal polyps (Fig. 2), inducing an impaired access of odorants to the olfactory cleft. In that sense, some anatomical variations such as septal deviation, concha bullosa, and supreme superior turbinate have also been incriminated in olfactory dysfunction but this remains very controversial.

Indeed, clinical studies have failed to prove this hypothesis, as there is only little correlation between nasal resistance and the degree of olfactory dysfunction [59]. In addition, results of

surgical therapy, although improving the nasal patency, are sometimes uncertain when considering olfactory dysfunction. At present, it is generally agreed that the olfactory disturbance is due to an inflammatory process in the olfactory cleft rather than a pure obstruction. Indeed, biopsies of the olfactory neuroepithelium in patients suffering from CRS reveal inflammatory and apoptotic pathological changes in the nasal mucosa, including the ORNs and olfactory supporting cells [60, 61]; and the degree of inflammation in the neuroepithelium has been shown to be related to the severity of olfactory dysfunction [60]. This could be explained by the fact that inflammatory cells release inflammatory mediators that trigger hypersecretion in respiratory and Bowman's glands [45, 62, 63]. Hypersecretion of Bowman's gland is thought to alter the ion concentration of olfactory mucus, affecting the olfactory transduction process [64, 65]. Also, Kern asserted that chronic inflammation might inhibit olfactory neurogenesis and this inhibition might cause damage to the olfactory mucosa, which is less able to recover from injury [60]. Finally, it has been demonstrated that cytokines and mediators, particularly those released by eosinophils, may be toxic for ORNs [66–69].

Besides these two mechanisms (conductive and inflammatory) originating in the nose, there is another explanation for the decreased olfactory function in CRS patients at the level of the olfactory bulb. The inflammation into the nose and paranasal sinuses probably takes a long time before the symptoms appear and the definition of the CRS assumes that the symptoms last for at least 6 months. During this period of time, it has been speculated that the sensory organ is less stimulated and that the volume of the olfactory bulb slowly decreases in relation to the persistent inflammation [41]. In many other diseases, a clear correlation exists between the olfactory bulb volume shrinkage and the decreased olfactory function [70, 71]. This mechanism probably also exists in CRS patients with or without nasal polyp. This explains why patients with CRS with nasal polyp usually have lower olfactory performances than patients with CRS without nasal polyp.

Finally, patients with previous sinus surgery and persistent symptoms of CRS may demonstrate many endoscopic features explaining why restoring olfactory function is difficult: fibrosis in the olfactory cleft, synechia between the middle turbinate and the septum, crusting in the olfactory cleft, desiccation in the olfactory cleft after turbinate's removal, and damage to the olfactory neuroepithelium (Fig. 1). It has also been demonstrated that inferior total turbinectomy may alter the intranasal trigeminal perception, and hence, have a negative impact on the olfactory perception [72].

Olfactory Function in Chronic Rhinosinusitis Without Nasal Polyps

In the literature, it has been reported that 73 % of patients with CRS without polyps have subjective complaints of smell

Table 1 Results of studies evaluating smell function in patients' chronic rhinosinusitis, using psychophysical measures

Authors	Patients	Risk factors associated with olfactory disorder	Olfactory test	Patient's olfactory function	Imagery	Treatment	Outcome/results
Gudziol et al. [23••]	19 CRSwNP 19C	–	SSTE	Significantly decreased (in the range of hyposmia)	MRI	FESS	Significant increase of the OB volume after FESS Improvement of detection threshold performances after FESS
Seiden et al. [27]	60 nasal sinus disease	–	UPSIT	58 % Anosmia 38 % Hyposmia 35 % Dysosmia	–	–	–
Reden et al. [34]	29 sinus disease	–	SSTE	28 % parosmia 7 % phantosmia	–	–	–
Livack et al. [29•]	367 CRS	Nasal polyps Asthma >65 years Smoking	SIT	18–64 years = 64 % OD >65 years = 91 % OD	–	–	–
Alobid et al. [36]	245 CRSwNP	Asthma (particularly persistent asthma)	BAST-24	Impaired smell detection, identification, and forced choice	CT	–	Asthma and especially persistent asthma has an accumulative impact on the loss of smell in patients with NP The loss of smell is correlated with paranasal sinus opacification Endoscopic and CT severity scores were increased in anosmia and hyposmia
Livack et al. [38•]	367 CRS	Nasal polyps Asthma ASA intolerance	SIT	33 % normosmia 45 % hyposmia 29 % anosmia	CT	–	Worse disease severity (based on endoscopic and CT) was correlated with worse olfaction Correlation between opacification of the olfactory cleft and the frontal sinus and olfactory function
Alt et al. [39••]	445 patients with RARS or CRS w or s NP	Prior surgery Nasal polyps Recalcitrant disease ASA intolerance	BSIT	28.3 % OD	CT	–	Patients with Lund-mas Kay score >12 had significantly lower OB volume as compared to controls
Chang et al. [40•]	210 CRS	–	BTT OIT	–	CT	–	–
Rombaux et al. [41•]	22 sinonasal disease (vs controls)	–	SSTE Retronasal	Decreased olfactory function	CT MRI	–	–
Vento et al. [42]	41 CRSwNP	Gender Total nasal resistance Degree of opacity of the ethmoid Polyps	Threshold	40 % of patients had increased threshold	CT	–	–
Mott et al. [43] Reychler et al. [44]	39 patients 30 CRS (13 CRSwNP)	–	«objective test» SST Retronasal	–	–	Topical steroid Steroids: - topical - nebulized - oral FESS	Significant improvement of olfactory function Improvement in TDI after oral and sonic nebulization
Downey et al. [45]	50 subjects with anosmia and symptoms of CRS	Severity of sinus disease on preoperative CT Persistent mucosal disease in surgical bed	UPSIT	–	CT	–	52 % improvement
Delank et al. [46]	115 CRS	–	Threshold	–	–	FESS	11 % anosmia

Table 1 (continued)

Authors	Patients	Risk factors associated with olfactory disorder	Olfactory test	Patient's olfactory function	Imagery	Treatment	Outcome/results
Klimek et al. [47]	31 CRSwNP		discrimination	31 % anosmia, 52 % hyposmia, 17 % normosmia			57 % hyposmia Normosmia 31 %
Min et al. [48]	80 CRS		CCCRC BTT	Mean score: moderate hyposmia	CT	FESS	3 months after surgery, the mean score showed mild hyposmia Postoperative butanol threshold reduction was more pronounced in severe CRS
Briner et al. [49]	45 CRS		BTT Smell diskette T and T			FESS + topical steroids FESS	Improvement persist after 5 years while using continuous topical steroids after FESS Improvement of T and T recognition Improvement persisted longer in non eosinophilic CRS
Oka et al. [50]	89 CRS (eosinophilic and non eosinophilic)		Intravenous olfactometry olfaction test SIT				
Litvack et al. [51]	111 CRS	Polyps		62.5 % OD before		FESS	Patients with anosmia significantly improved after ESS Improvement was sustained at 12 months of follow up
Vandenhende-Szymanski et al. [52]	30 CRSwNP	Severity of the disease on the CT Opacification of the olfactory cleft	ETOC			FESS	Improvement after surgery CT score and opacification of the OC are predictive factors of surgery
Cantone et al. [53]	69 elderly patients with CRS (vs controls)		SSTE			Clenotherapy	Improvement of TDI score
Minwegen et al. [54]	92 CRS		SSTE		CT	FESS	Olfactory function of patients with more severe disease improved more than that of patients with less severe disease
Kim et al. [55]	50 CRSwNP	Opacification of the olfactory cleft	CCSIT BTT UPSIT			FESS FESS	Favorable wound healing group had greater improvement of olfactory result Improvement of smell after surgery Nasal polyps in the olfactory cleft were associated
Hsu et al. [56]	32 CRS patients with smell disturbance						with better improvement (Improvement rate: 44.8 % after 6–12 months, 47.8 % after 12–24 months)
Baradaranfar et al. [57•]	60 CRSwNP		CCCRC			FESS Medical treatment	Improvement with both treatment but better improvement with surgery
DeConde et al. [58••]	280 CRS		BSIT			FESS Medical treatment	Comparable gain for both treatments

CRSwNP Chronic rhinosinusitis with nasal polyps, CRSwNP Chronic rhinosinusitis without nasal polyps, R4RS recurrent acute rhinosinusitis, SSTE Sniffin' Sticks test (extended version), FESS Functional endoscopic sinus surgery, CT computed tomography, MRI magnetic resonance imaging, OB olfactory bulb, SIT Smell Identification Test, BSIT Brief Smell Identification Test, OD olfactory disorder, UPSIT University of Pennsylvania Smell Identification Test, BTT butanol threshold test, OIT odor identification test, ETOC CSITCCRC

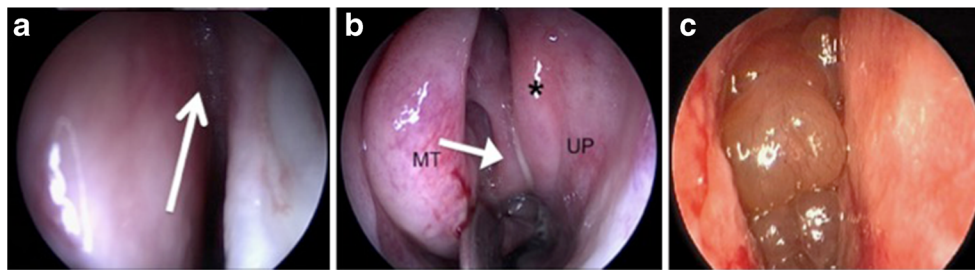


Fig. 2 Endoscopic endonasal view 25°. **a** Olfactory neuroepithelium (left nasal fossa). **b** Left middle meatus with edema (*asterisk*), mucopurulent secretions arrow. *MT* middle turbinate, *UP* uncinate process. **c** Nasal polyposis (right nasal fossa)

disorders [73], although olfactory testing of identification reported altered olfactory function in 17 % of patients [39••].

Some authors found that the severity of olfactory dysfunction in CSR without polyps is associated with the smoking status, the presence of asthma, allergic rhinitis, age and septal deviation [29•], and endoscopy scores, but not with the severity of the CT scan [39••], whereas others reported that severity of olfactory dysfunction seems to be related to the opacity of the olfactory cleft [40•].

Finally, in patients with CRS without polyps, MRI studies have demonstrated that the OB volume is inversely correlated with sinonasal disease scores [41•].

Olfactory Function in Chronic Rhinosinusitis with Nasal Polyps

Olfactory dysfunction is a major feature of CRS with polyps and prevalence of 83–91 % has been reported [29•]. Furthermore, it is well known that the severity of olfactory dysfunction is higher in CRS patients with polyps as compared to CRS patients without polyps, and that patients with polyps have increased risk of hyposmia and anosmia [29•, 74], with odds ratio of, respectively, 2.4 and 13.2 [29•].

This may be explained, at least in part, by the location of the disease and by the higher eosinophilia in CRS with polyps as compared to CRS without polyps. Indeed, eosinophils are known to release several neurotoxic mediators [66], potentially damaging the olfactory receptor neurons. Moreover, blood eosinophilia seems to be correlated with subjective smell reduction [75]. Joe and Thakkar reported that CRS, especially chronic hyper-plastic sinusitis with nasal polyps, has a strong relationship with chronic asthma [76]. The eosinophils perpetuate the inflammation in both disease processes and these two diseases share similar histopathology [76]. It seems that increased systemic inflammatory response in CRS patients with comorbid asthma affect the olfactory cleft and contribute to olfactory dysfunction in CRS [29•, 77, 78].

In patients with polyps, it has been reported that olfactory function was significantly better when odors are applied through the retronasal route as compared to orthonasal route [79]. This is thought to be related, at least in part, to the presence of mechanical obstruction in the anterior portion of the

olfactory cleft, whereas odors are still able to reach the olfactory epithelium through the retronasal route [80]. Moreover, it has been shown that olfactory scores were significantly associated with the severity of the CT scan [42, 81], the location of the disease [81], the polyposis visible in anterior rhinoscopy, total nasal resistance, and gender, whereas no relationship was found with the number of surgeries [42].

Interestingly, in patients with polyps, it has been shown that OB volume significantly increases after surgical treatment and this increase of OB volume correlates significantly with the decrease in odor thresholds [23••].

Treatment

Medical and/or surgical treatment should be proposed to patients suffering from sinonasal related olfactory disorders since (1) the treatments can improve olfaction [43, 82–84], and (2) it has been demonstrated that patients reporting an improvement of their olfactory abilities have a better quality of life than patients reporting no improvement [85].

Type of treatment of CRS with or without nasal polyps is not directly related to the sensory olfactory dysfunction except for those patients for who an intact chemosensory system is mandatory for professional reasons (cook, fireman, perfumer ...). However, the persistence of the olfactory dysfunction despite an adequate treatment may influence the clinician to step up the treatment choosing for a surgical treatment after medical treatment failure.

Corticoids seem to be the most effective drug to restore olfaction in CRS patients. The nature of the compound does not seem to be essential but well the way to deliver the drug. Corticoids may be administered in many different ways: topical, oral, and aerosoltherapy. A recent study compared the efficacy of three-drug delivery modalities on olfactory function in chronic rhinosinusitis. This study showed that sonic nebulized and oral administration significantly improved orthonasal olfactory function, while the effect was not significant with nasal sprays [44]. It is widely admitted that oral corticoids are more effective to restore the olfactory function than topical corticoids [86]. However, a few weeks after an oral corticoid treatment, the olfactory usually declines and

returns to the same previous level of discomfort. Topical corticoid treatment is usually less potent than oral corticoid in restoring the olfactory function in CRS patients but the efficacy seems to remain stable with time with few habituation or tachyphylaxia [82]. Side effects are frequent locally with topical administration (crusting, bleeding ...). Oral corticoid treatment may predispose to internal diseases if given on a regular basis [87]. Aerosoltherapy with corticoid may represent an adequate way to deliver the drug with fewer resorption and fewer internal disease and even so, with a potent activity. Because it is admitted that local corticoids need to reach the olfactory cleft to be effective and because topical administration has revealed that the quantity of corticoid reaching the cleft is very low, some squirt, drop, or inserted cannula inside the nose have been developed to increase the concentration of the drug in the surrounding area of the cleft and to increase the efficacy. However, this method is not yet standardized and not used in the vast majority of the patients. Finally, crenotherapy seems efficient in improving olfactory function in elderly [53].

Endonasal endoscopic surgery is also a standard treatment for patients presenting an olfactory dysfunction related to CRS with or without nasal polyp. The surgical procedure is required after medical treatment failure and is proposed to patients after informed consent and preoperative work-up. The basic procedure encompasses an ethmoidectomy associated to a middle meatotomy and/or a sphenoidotomy. The procedure is performed under general anesthesia (local anesthesia is possible for some patients) and consists of an opening of the paranasal sinuses in order to facilitate drainage and ventilation. The question to radically or functionally remove the pathologic mucosa is still a debate among rhinosurgeons but there is some consensus to be more radical in CRS with nasal polyposis and more functional in CRS without nasal polyps. The middle turbinate and the superior turbinate removal is another debate and it should be kept in mind that these structures have an important role in the normal physiology of olfaction because some ORNs are present in these structures and because they facilitate the airstream to the olfactory cleft where the neuroepithelium is present.

Considering patients' self-reported olfactory function, authors agree that functional endoscopic sinus surgery (FESS) lead to a significant improvement of olfactory dysfunction [83, 84, 88–90]. Only few studies have investigated the effect of FESS on olfactory function using semi-objective olfactory testing (Table 1). They have also shown that FESS as a significant positive effect on olfactory function [45, 47–50, 52, 54–56, 57•, 58••, 91]. Hence, it can be concluded that FESS seems to significantly improve olfactory function in patients with CRS with or without polyps. However, it is important to note that although endoscopic sinus surgery has the potential to improve olfaction, long-term results of surgery are still debated [49, 50] and authors agree that it is challenging to

predict improvement following endoscopic sinus surgery in CRS-related olfactory dysfunction (for a review, see [92]). A lot of criticism may be proposed to the vast majority of studies trying to study the effect of surgery on olfactory perception in patients with CRS (for a review, see [93]). Particularly, there are major variations in the selection of patients for the surgery, in the kind of surgery, in the postoperative care, and in the assessment of olfactory function. Indeed, sometimes the type of surgery varies from simple polypectomy to radical surgery, sometimes the olfactory perception is only studied through questionnaire without psychophysical testing, and sometimes the postoperative management is different from no treatment to oral corticoid treatment.

Some studies have compared the results of surgery in comparison to medical therapy for the improvement of smell in CRS; however, the results are conflicting: some saying that surgery gives more improvement than medical therapy, the others suggesting that both treatments give the same improvement [57•, 58••]

Predictors of successful surgery are still debated in the scientific literature. Some authors have studied the correlation between the severity of CRS and surgical outcomes on olfaction. It was reported that the improvement after FESS is significantly better in patients with severe olfactory dysfunction whereas it is not in patients with mild olfactory dysfunction [51, 94]. The degree of nasal obstruction, the extent of the rhinosinusitis disease (evaluated by symptom score or CT scan), and the coexistence of nasal polyps or allergic rhinitis do not predict the possibility of olfactory improvement after FESS [95–97]. Konstantinidis et al. asserted that the site of CRS was a more important factor in olfactory function than CRS severity [65]. In addition, Jankowski et al. [98] demonstrated that there was a correlation between the improvement of subjective olfactory function after oral corticosteroids given preoperatively and olfactory function 1 year after nasalization. Jankowski et al. [99] have also compared the impact of different surgical approaches on olfactory function. Olfaction was evaluated by a 10-point visual analog scale. They reported that improvement of olfaction was similar in both functional ethmoidectomy group and radical ethmoidectomy group 6 months after surgery. Nevertheless, olfaction decreased in the functional ethmoidectomy group after 6 months while it was stable in the radical ethmoidectomy group.

Finally, we should mention the importance of the olfactory cleft in sinonasal-related olfactory dysfunction. Indeed, there are some data revealing that edema, polyp formation or cicatrization in this area may have a dramatic impact on olfactory function (Fig. 1). Patients with CRS without nasal polyposis may have edema and/or inflammation and patients with CRS with nasal polyposis may have polyp formation in the olfactory cleft. Moreover, the histopathological conditions may reveal different diseases in the olfactory cleft. For example,

respiratory epithelial adenomatoid hamartoma (REAH) can be diagnosed in isolated form or associated to CRS with nasal polyposis. Hence, it should be stressed to analyze separately the polyp formation coming from the olfactory cleft and those coming from the remaining sinus cavity because this could have a significant impact on the prognosis if a REAH is diagnosed.

Olfactory Training

For some patients complaining of an olfactory dysfunction, the corticoid therapy is not helpful. For example, there is no real benefit to give corticoid treatment in post-infectious or post-traumatic olfactory loss. Based on the concept that a certain degree of plasticity exists in the olfactory pathways due to some degree of neurogenesis, the idea to stimulate with an olfactory training this plasticity has been tested in different studies [100–102].

These studies confirm that an olfactory training based on the presentation of different odors for some minutes during at least 3 months to the patients is helpful and that these patients with an olfactory training are more prone to show a recovering of their olfactory perception than those not performing this training.

Despite this confirmation, there is no study confirming that an olfactory training has a positive effect in the pre- or in the postoperative period for those patients demonstrating an olfactory dysfunction secondary to a CRS with or without nasal polyposis. It should be stressed that some prospective studies on this topic should be performed in the future.

Conclusions

Patients with CRS with or without nasal polyposis represent a large proportion of the patients demonstrating an olfactory dysfunction. Before starting any medical and/or surgical treatment, the evaluation of the olfactory ability should be done by the physician. This will help to have a baseline value and to assess the variation according to the proposed treatment. Corticoid therapy is very helpful and the way to deliver the drug is important with a balance between the efficacy and the side effects. Although deeply studied, there is no absolute predictor of success of surgery when considering the endoscopic sinus surgery and the olfactory recovering. There is still a debate on the way to perform the surgery in relation to the olfactory function. Finally, the olfactory training should be studied in patients with CRS with or without nasal polyposis as this treatment has proven its efficacy in others causes predisposing to an olfactory dysfunction.

Compliance with Ethical Standards

Conflict of Interest Drs. Rombaux, Huart, Levie, Cingi, and Hummel declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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