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Chronic Rhinosinusitis and Olfactory Dysfunction

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1. Introduction

Chronic rhinosinusitis (CRS) is defined, according to the European Position Paper on Rhinosinusitis and Nasal Polyps (Fokkens et al., 2007), as "presence of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) +/- facial pain/pressure +/- reduction or loss of smell for >12 weeks". Olfactory disorder thus appears to be one of the diagnosis criteria for CRS with or without nasal polyposis, underlining the importance of this specific symptom among patients with CRS. Inversely, CRS appears to be the most common cause of olfactory dysfunction in patients presenting to smell evaluating centers and account for 14-30% of the cases (Holbrook and Leopold, 2006; Landis et al., 2004; Mott and Leopold, 1991; Raviv and Kern 2004; Seiden and Duncan, 2001). What underlines the intimate connection between CRS and olfactory dysfunction.

Several studies have shown that the quality of life is severely impaired in patients suffering from olfactory disorders (Frasnelli and Hummel, 2005; Neuland et al., 2011). It is thus important to detect this symptom and to provide an optimal treatment to patients. Nowadays, we have medical and surgical treatments that may relieve patients but these results are still hazardous.

Good management and good support to patients highly depend on a good knowledge of this entity. We will thus review important issues about CRS and olfactory dysfunction, beginning with generalities about olfactory dysfunction, to continue with pathophysiology of this entity, assessment of olfactory function in patients, the contribution of imaging and finally effects of current treatments on olfactory function.

2. Olfactory dysfunction

The incidence of olfactory dysfunction among the population is still a matter of debate. Authors report an incidence of 1-3% of dysfunction among population (Hoffman et al., 1998; Murphy et al., 2002). Nevertheless a recent study by Landis et al. (2004) reported higher values of olfactory dysfunction among population without sinonasal complaints, with a rate of 4.7% of anosmia and 16% of hyposmia. The most common causes of olfactory disorder are CRS, upper respiratory tract infection and head trauma. It is also mandatory to note that in a significant number of cases the cause of olfactory dysfunction remains unknown, even after investigations. (Table 1)

1	Rhinosinusitis
2	Post upper respiratory tract infection
3	Idiopathic
4	Post traumatic
5	Iatrogen
6	Toxic
7	Congenital
8	Miscellaneous

Table 1. Etiologies of olfactory dysfunction listed in descending order. Rhinosinusitis appears to be the most important cause of olfactory dysfunction in the general population.

In the literature, CRS is described as the most common cause of olfactory dysfunction, accounting for 14-30% of cases (Holbrook and Leopold 2006; Mott and Leopold, 1991; Raviv and Kern 2004; Seiden and Duncan, 2001). Inversely, olfactory impairment is a common symptom affecting 61-83% of patients with CRS (Bhattacharyya, 2003; Litvak et al., 2008; Orlandi and Terrell, 2002; Soler et al., 2008). 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 (Nordin et al., 1995). Psychophysical tests results show that patients with CRS have quantitative disorders, between hyposmia and anosmia (Holbrook and Leopold 2006; Mott and Leopold, 1991; Raviv and Kern 2004; Seiden and Duncan, 2001; Welge-Luessen, 2009) and may report fluctuating symptoms (Apter et al., 1999). Also it is widely known that patients with CRS with polyps have a higher incidence of smell symptoms and anosmia than patients with CRS without polyps (Hellings and Rombaux, 2009).

Some studies have described that the severity of quantitative disorders is related to the importance of the sinonasal disease (Litvack et al., 2008, 2009a). Indeed, the mean endoscopy score and the mean CT score are significantly higher (more abnormal) in patients with hyposmia and anosmia than in patients with normosmia (Litvack et al., 2009a). Also, the opacification of the olfactory cleft on the CT scan seems to have a negative correlation with the olfactory function (Chang et al., 2009).

Patients with CRS not only report quantitative olfactory dysfunction but also qualitative dysfunction such as parosmia and phantosmia. However, these symptoms seem less frequent when related to sinonasal disease than to other etiologies (i.e. post-infectious, post traumatic) and Reden et al. (2007) reported incidence of parosmia and phantosmia in patients with CRS of 28% and 7%, respectively.

It is also mandatory to note that the quality of life of patients suffering from olfactory disorders is severely impaired. Indeed it has been described that patients with olfactory disorders not only complain about daily life problems (cooking, detection of potentially dangerous odors) (Temmel et al., 2002) but also have a higher prevalence of mild to severe depression compared to the general population (Deems et al., 1991). Using questionnaire of olfactory disorder and psychometric tests some authors reported that patients suffering from quantitative olfactory impairment significantly more complaints that patients with normosmia and this was even more important if they had associated parosmia (Frasnelli and Hummel, 2005; Neuland et al., 2011). Finally, since patients reporting an improvement of their olfactory abilities have a better quality of life than patients reporting no improvement (Miwa et al., 2001); it is essential to investigate about the etiology of olfactory dysfunction in instance to provide an optimal treatment to the patients. Particularly in cases of chronic rhinosinusitis, different treatments are available and improve olfactory function. They will be discussed later.

3. Pathophysiology

Traditionally, olfactory dysfunction in CRS is explained by a conductive olfactory loss, caused by swollen or hypertrophic nasal mucosa or nasal polyps, inducing an impaired access of odorants to the olfactory cleft. But clinical studies have failed to prove this hypothesis, as there is only little correlation between nasal resistance and the degree of olfactory dysfunction (Doty and Frye, 1989; Cowart et al., 1992). In addition, results of surgical therapy, although improving the nasal patency, are sometimes uncertain when considering the olfactory dysfunction.

Some studies have shown that the olfactory disturbance might also be explained by inflammatory process in the olfactory cleft (Konstantinidis et al., 2007). Indeed, biopsies of the olfactory neuroepithelium in patients suffering from CRS revealed inflammatory changes in the nasal mucosa and apoptotic pathological changes, including the olfactory receptor neurons and olfactory supporting cells (Hellings and Rombaux, 2009; Naessen, 1971). Also, inflammatory cells release inflammatory mediators, which are known to trigger hypersecretion in respiratory and Bowman's glands (Hellings and Rombaux, 2009; Getchell and Mellert, 1991; Downey et al., 1996). Hypersecretion of Bowman's gland is thought to alter the ion concentrations of olfactory mucus, affecting the olfactory transduction process (Kern et al., 1997; Joshi et al., 1987). In addition, cytokines and mediators, particularly those released by eosinophils, may be toxic to olfactory receptor neurons (Apter et al., 1992; Nakashima et al, 1985), and the degree of inflammation changes in the neuropithelium is related to the severity of olfactory dysfunction (Kern, 2000)

Patients with nasal polyps show a higher incidence of olfactory disturbances and a higher incidence of anosmia than patients with CRS without polyps. This more severe symptomatology may be explained by the conductive olfactory loss induced by polyps but also by degenerative changes associated with recurrent infections, scaring, chronic nasal medication, exotoxins and enhanced secretion of cytokines from Staphylococcus Aureus infection and neurotoxic cytokines released by a huge eosinophilic population (Bernstein et al., 2011; Holcomb et al., 1996; Joshi et al., 1987; Litvack et al., 2008; Vento et al., 2001; Wang et al., 2010).

4. Assessment of olfactory function

Assessment of olfactory function should be considered in the clinical evaluation of patients suffering from chronic rhinosinusitis and complaining of olfactory disorders. Not only this evaluation allows detecting and quantifying olfactory disorders but also it is useful to objectively and reproducibly assess the efficacy of a treatment on olfactory function.

Odorants can reach the olfactory cleft both orthonasally (from the nostrils to the olfactory cleft) and retronasally (from the oral cavity to the olfactory cleft).

The most widely used tests for the evaluation evaluation of the orthonasal function are the Sniffin' Sticks test (Hummel et al., 2007; Burghart Medical Technology, Wedel, Germany) and the UPSIT (University of Pennsylvania smell identification test) (Doty et al., 1984). These semi-objective tests have the advantage of being easy to implement and of having been validated in multicenter studies. The Sniffin' Sticks test consists in felt-tip pens that are presented in front of the nose of the patient. It encompasses three different approaches. First the odor threshold (T) assessment; second the odor discrimination (D) and third odor identification (I). To judge the olfactory function, these three results are added together to provide a total TDI score. The UPSIT test 40 items. It encompasses fours "scratch and sniff" booklets that can be self administrated or applied by a third party. Odorants are embedded in microcapsules positioned on brown strips at the bottom of the page of booklets. The stimuli are released by scratching the strip with a pencil and subjects have to choice one of the four proposed descriptors that best corresponds to odor (Doty et al., 1984; Tourbier and Doty, 2007). These two tests are forced choice, what mean that the subject must provide a response even if no odor is perceived.

Retronasal olfactory performances can also be evaluated following a standardized method using a row of 20 items. Powder substances are applied using squeezable plastic vials in the middle of the tongue inside the oral cavity. Each substance is identified by means of a forced-choice procedure between 4 items. (Heilmann et al., 2002)

Nevertheless these tests have the disadvantage to be semi-objective and might be biased by the patient's response.

The objective evaluation of the olfactory function relies on event-related potentials technique. This technique is based on the fact that brief olfactory stimulus elicit transient changes in the ongoing electrographic activity. To evaluate olfactory function a pure odorant substance (i.e. 2-phenylethanol) is delivered in the nose of the patients (Kobal and Hummel, 1988). Since the magnitude of the transient olfactory-induced EEG deflection is much smaller than the magnitude of the background EEG, the event is repeated several times and recorded responses are the added and averaged into a single waveform to increase the signal to noise ratio. The bulk of olfactory chemosensory event-related potentials consist of a negative component (N1) occurring between 320 and 450 ms after stimulus onset, followed by a positive (P2) component occurring between 530-800 ms (Hummel et al., 1992; Hummel et al., 2003; Hummel and Kobal, 1999, 2002; Rombaux et al., 2006).

In cases of chronic rhinosinusitis, both orthonasal and retronasal scores can be decreased, with scoring of both anosmia and hyposmia. Electrophysiological investigations show abnormal responses with in moderate cases decreased amplitude and an increased latency and in severe cases the absence of olfactory responses (Rombaux et al., 2009). It is interesting to note that while in chronic rhinosinusitis, there is no difference between orthonasal and retronasal score, patients with CRS with polyps have a better retronasal than orthonasal score (Landis et al., 2003). Moreover ortho- and retronasal scores do not have a correlation when patient demonstrate an olfactory dysfunction related to sinonasal disease score proving that ortho- and retronasal scores have a distinct evolution in such cases (Rombaux et al., 2008).

5. Imaging of the olfactory apparatus in CRS

The MRI is the imaging modality of choice for the evaluation of the olfactory apparatus since it allows examining the olfactory bulb, olfactory tract and central olfactory projection areas. The assessment of olfactory bulb volume is particularly useful in the evaluation of olfactory disorder associated with CRS. Rombaux et al. (2008) demonstrated that the olfactory bulb volume is correlated with the sinonasal disease score, and patients having a sinonasal disease score > or = 12 significantly have larger olfactory bulb volume than patients with higher score. Smaller olfactory bulb volume is thus associated with a higher degree of sinonasal pathology. On contrast the olfactory function of the patients assessed with psychophysical testing was only slightly decreased or was even normal, emphasizing the idea that the olfactory bulb volume changes are more sensitive to subtle changes in the olfactory system than results of psychophysical testing. (Figure1)

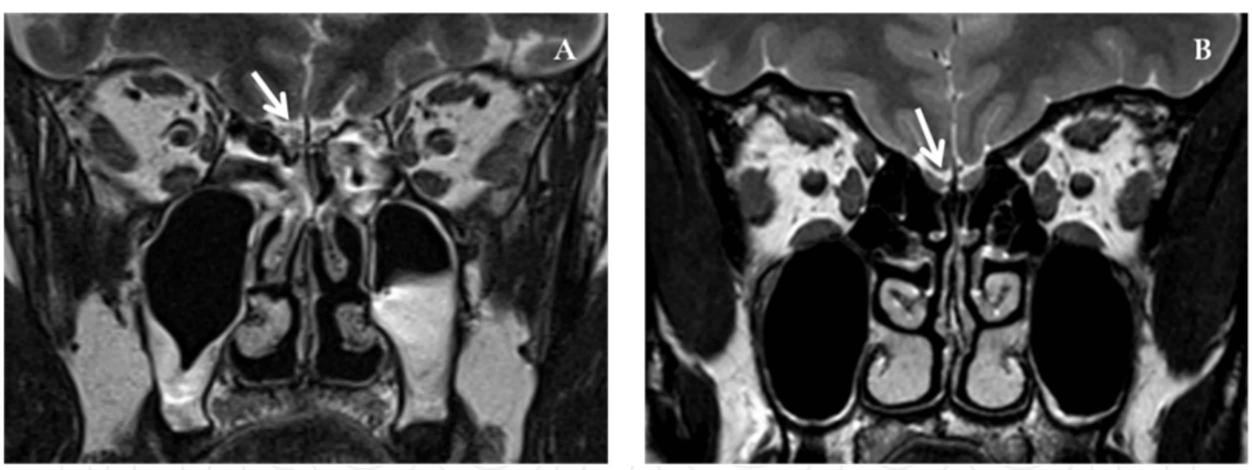


Fig. 1. T2-MRI on the coronal place of patient suffering from CRS (A) and control subject (B). Note that the olfactory bulb (white arrow) of the patient seems smaller than the OB of the control subject.

CT scan can also be useful in the assessment of patients with olfactory dysfunction associated with CRS. Litvack et al. (2009a) have shown that the severity of quantitative olfactory disorder is associated with the importance of the sinonasal disease and that mean CT score is significantly higher in patients with hyposmia and anosmia than in normosmic patient. It was also demonstrated that the opacification of the olfactory cleft has a negative correlation with the olfactory function in patients with CRS and that it is significantly correlated with the postoperative olfactory results; patients with mild opacification having better postoperative results than patients with moderate and severe anterior olfactory cleft result (Kim et al., 2011).

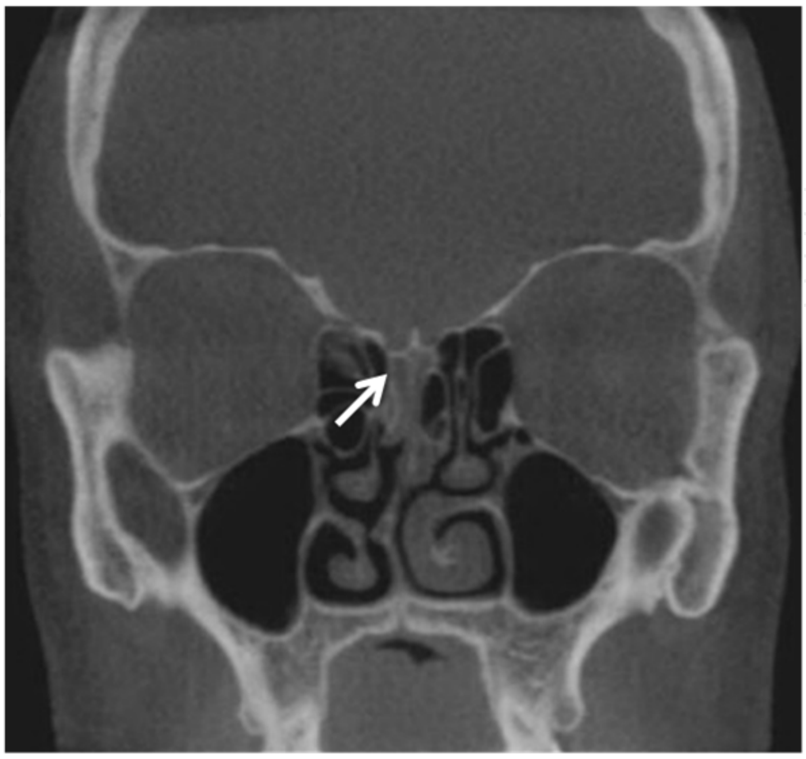


Fig. 2. CT-Scan in the coronal plane of a patient suffering from quantitative olfactory disorder. We can note on this picture an opacification of the olfactory cleft (white arrow) whereas there is no obvious rhinosinusitis. This image represents a so-called "olfactory cleft disease".

6. Predictors of olfactory dysfunction in patients with CRS

As we discuss previously, it is agreed that the severity of olfactory dysfunction is related to the importance of the sinonasal disease (Litvack et al., 2008, 2009a) and that the mean endoscopy and mean CT score are significantly higher in patients with hyposmia and anosmia than in normosmic patients (Litvack et al., 2009a).

But common comorbidities have also been incriminated as severity factors of olfactory loss related to the CRS. Some authors have incriminated age of patients, smoking status, nasal polyposis, asthma, allergic rhinitis, previous endoscopic sinus surgery, septal deviation and inferior turbinate hypertrophy to cause olfactory dysfunction but the results are conflicting (Apter et al., 1999; Damm et al., 2003; Doty and Mishra, 2001; Kimmelman, 1994; Litvack et al., 2008; Simola and Malmberg, 1998). Nevertheless, the majority of authors agree that the age of patients and the presence of nasal polyps are predictors of olfactory dysfunction in CRS (Apter et al., 1999; Doty and Mishra, 2001; Litvack et al., 2008; Simola and Malmberg, 1998). Nasal polyposis is a significant predictor of olfactory dysfunction and it has been showed that there is a negative correlation between the size of the nasal polyps and the olfactory performance. Also, in patients with nasal polyposis, the blood eosinophilia seems to be correlated with subjective smell reduction (Hox et al., 2010).

On contrast, studies agree that semi-objective olfactory testing are not correlated with disease-specific or general health-related quality of life instruments (Litvack et al., 2009a; Hox et al., 2010)

7. Effects of treatment on olfactory function

7.1 Medical therapy and smell dysfunction

Only a few clinical studies have been conducted dealing with the improvement of olfactory function as a primary outcome in sinonasal disease treatment. Clinical trials of medical treatment for smell disorders associated with CRS have evaluated the efficacy of nasal and oral corticosteroid treatment, but we found no studies about other treatments that are currently used in the treatment of CRS (antileukotrienes, antihistamines,…).

Corticosteroids with their potent anti-inflammatory effects are admitted to be the standard treatment for olfactory disorders induced by CRS. Their action mechanism on olfactory function might be explained by an inhibition of the release of proinflammatory mediators (i.e. cytokines, adhesion molecules, mast cells, basophiles, eosinophiles) and a reduction in mucosa swelling (Demoly, 2007; Mygind et al., 2001).

Following EPOS recommendations, nasal steroids are recommended as the first line treatment for CRS with or without nasal polyps (Fokkens et al., 2007). Studies have evaluated the efficacy of different topical corticosteroids such as Betamethasone, Flunisolide, Mometasone Furoate, Fluticasone Propionate, Budesonide, Beclomethasone. Studies show that these drugs appear to be highly effective for most of the symptoms associated with CRS, including smell disorder, with a rapid onset of action and a cumulative effect after several days of use. In addition, they have the advantage of being a local therapy with limited side effects. Nevertheless the improvement in olfaction is frequently transient and incomplete (Blomqvist et al., 2003; Golding-Wood et al., 1996; Hellings and Rombaux, 2009; Lildholdt et al., 1995; Mott et al., 1997; Stuck et al., 2003).

Oral steroids are recommended in the treatment of CRS with nasal polyps as a second line treatment (Fokkens et al, 2007). Several studies have investigated the efficacy of oral steroids in patients with CRS with or without polyps. They have shown that these potent anti-inflammatory drugs increase the olfactory function and they appear to be more effective than nasal steroids (Heilmann et al., 2004; Vaidyanathan et al., 2011). Moreover, an initial oral steroid therapy followed by topical steroid therapy seems to be more effective than topical steroid therapy alone (Vaidyanathan et al., 2011). Nevertheless oral steroids have important side effects if they are frequently administrated or if their administration is prolonged. Bonfils et al. (2006) evaluated the risk of oral steroid treatment in patients with CRS with nasal polyps and showed that almost 50% of patients who received more than three short courses of oral steroid treatment had an asymptomatic adrenal insufficiency. Oral corticosteroids should thus be prescribed only if necessary and should be avoided if possible.

7.2 Surgical therapy and smell dysfunction

Functional endoscopic sinus surgery (FESS) is widely accepted as a treatment for chronic rhinosinusitis with or without nasal polyps after failure of the medical therapy.

The only randomized study to attempt comparison between steroid therapy and polypectomy showed significant improvement of subjective and objective olfactory function in both groups, remaining for one year. However these results should be tempered by the fact that the smell evaluation methodology was not described (Lildholdt, 1989)

Several studies have investigated the effect of FESS on olfactory function (for a review see Bonfils et al., 2009). Nevertheless the literature shows that there are major variations in the selection of patients for the surgery and some studies have poor validity because of poorly defined patient groups, lack of clear inclusion or exclusion criteria, poor description of the surgical procedure and poor description of the olfactory evaluation tool.

In this literature, olfactory function was assessed either by subjective patient self-reported olfactory function or by semi-objective olfactory testing (i.e. UPSIT). Considering patients self reported olfactory function, authors agree that FESS lead to a significant improvement of olfactory dysfunction. Park et al. (1998) showed that olfactory disturbance was reported in 72% of patients with CRS with or without polyps or recurrent acute rhinosinusitis preoperatively compared with 38% following FESS. Lund and Mac Kay (1994) also reported that 79% of patients reported improved olfaction after FESS. Klossek et al. (1997) reported a series of patients with nasal polyposis. 100% of patients had anosmia pre-operatively while after surgery 78% of patients recovered the sense of smell. Levine et al. (1990) reported a series of 250 patients with CRS with or without nasal polyps and noted only 16% of patients complaining of smell disturbance before surgery and 3% patients reporting anosmia after a mean follow-up of one year after surgery. Jakobsen and Svendstrup (2000) reported a series of 237 patients with CRS with or without nasal polyps. Anosmia was present in 48% of the patients with nasal polyps before surgery against 21 % after surgery. Only few studies have investigated the effect of FESS on olfactory function by using semi-objective olfactory testing. They have also shown that FESS as a significant positive effect on olfactory function. For examples, Lund and Scading (1994) evaluated olfactory function of patients with CRS using UPSIT and showed significant UPSIT score improvement after surgery. Downey et al. (1996) also used UPSIT to assess the olfactory function of patients with CRS pre- and post-operatively and showed that after surgery, 52% of patients had higher UPSIT score. Min et al. (1995) tested olfactory thresholds to butanol in patients with CRS. Before surgery, 33 % of patients had anosmia and 45% of patients had hyposmia. After surgery these percentages were 16% and 46% respectively. Delank and Stoll (1998) noted a post operative improvement of olfactory function assessed by olfactory thresholds and discrimination in 70% of patients with CRS. Klimek et al. (1997) reported improved odor identification and discrimination score after FESS in patients with CRS with nasal polyps. Hence, FESS seems to significantly improve olfactory function in patients with CRS with or without polyps.

Gudziol et al. (2009) explored the influence of the treatment of CRS on the olfactory function. They measured olfactory bulb volume and olfactory function of patients suffering from CRS before treatment and 3 months after. They showed that the olfactory bulb volume significantly increases after treatment and that the increase of olfactory bulb volume correlated significantly with an increase in odor thresholds.

Some authors have also 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 (Litvack et al., 2009b, Soler et al., 2010). The degree of nasal obstruction, the extent of the rhinosinusitis disease (evaluate by symptom score or CT scan), the coexistence of nasal polyps or allergic rhinitis do not predict the possibility of olfactory improvement after FESS (Bhattacharyya, 2006; Jiang et al., 2009; Wright and Agrawal, 2007). In addition, Jankowski et al. (Jankowski and Bodino, 2003) demonstrated that there was a correlation between the improvement of subjective olfactory function after oral corticosteroids given preoperatively and olfactory function 1 year after nazalisation.

Jankowski et al. (1997) compared the impact of different surgical approaches on olfactory function. Olfaction was evaluated by a 10-point visual analogue scale. They reported that improvement of olfaction was similar in both functional ethmoidectomy group and radical ethmoidectomy group six months after surgery. Nevertheless olfaction decreased in the functional ethmoidectomy group after six months while it was stable in the radical ethmoidectomy group.

8. Conclusion

CRS is the major cause of olfactory dysfunction among the population. The exact pathophysiology is this entity is still unclear. The olfactory dysfunction in these patients is reversible, as proved by the effect of treatments and MRI studies. Nevertheless, most studies show that the improvement of olfactory function is usually transient and incomplete. Different causes are hypothesized, but this is still a matter of debate. Future studies are necessary to better understand this entity.

9. References

Apter AJ, Gent JF & Frank ME (1999). Fluctuating olfactory sensitivity and distorted odor perception in allergic rhinitis. *Arch Otolaryngol Head Neck Surg,* 125 (9):1005-10

Apter AJ, Mott AE & Cain WS (1992). Olfactory loss and allergic rhinitis. *J Allergy Clin Immun*, 90:670-680

Bernsteins JM, Allen C, Rich G, Dryja D, Bina P, Reiser R, Ballow M & Wilding GE (2011). Further observations on the role of Staphylococcus Aureus exotoxins and IgE in the pathogenesis of nasal polyposis. *Laryngoscope,* 121(3):647-55

Bhattacharyya N (2003). The economic burden and symptom manifestations of chronic rhinosinusitis. *Am J Rhinol*, 17:27-32

Bhattacharyya N (2006). Radiographic stage fails to predict symptom outcomes after endoscopic sinus surgery for chronic rhinosinusitis. *Laryngoscope,* 116(1):18-22

Blomqvist EH, Lundblad L, Bergstedt H & Stjärne P (2003). Placebo-controlled randomized, double-blind study evaluating the efficacy of fluticasone propionate nasal spray for the treatment of patients with hyposmia/anosmia. *Acta Otolaryngol,* 123:862-868

Bonfils P, Halimi P & Malinvaud D (2006). Adrenal suppression and osteoporosis after treatment of nasal polyposis. *Acta Otolaryngol,* 126(11): 1195-1200

Bonfils P, Malinvaud Y, Soudry Y, Devars du Maine M & Laccourreye O (2009). Surgical therapy and olfactory function. *B-ENT,* 5 Suppl 13:77-87

Chang H, Lee HJ, Mo JH, Lee CH & Kim JW (2009). Clinical implication of the olfactory cleft in patients with chronic rhinosinusitis and olfactory loss. *Arch Otolaryngol Head Neck Surg,* 135(10):988-92

Cowart B, Flynn-Rodden K, McGeady S &Lowry LD (1992). Hyposmia in allergic rhinitis. *J Allergy Clin Immunol,* 9:747-751

Damm M, Eckel HE, Jungehulsing M &Hummel T (2003). Olfactory changes at threshold and suprathreshold levels following septoplasty with partial inferior turbinectomy. *Annals Otol Rhinol Laryngol,* 112:91-97

Deems DA, Doty RL, Settle RG, Moore-Gillon V, Shaman P, Mester AF, Kimmelman CP, Brightman VJ & Snow JB (1991). Smell and taste disorders: a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg,* 117:519-528

Delank KW & Stoll W (1998). Olfactory function after functional endoscopic sinus surgery for chronic rhinoinusitis. *Rhinology,* 36:15-19

Demoly P (2008). Safety of intranasal corticosteroids in acute rhinosinusitis. *Am J Otolaryngol,* 29(6):403-13

Doty RL & Frye R (1989). Influence of nasal obstruction on smell function. *Otolaryngol Clin North Am*, 22:397-411

Doty RL & Mishra A (2001). Olfaction and its alteration by nasal obstruction, rhinitis and rhinosinusitis. *Laryngoscope,* 111:409-423

Doty RL, Shaman P & Dann M (1984). Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav,* 32(3):489-502

Downey LL, Jacobs JB &Leibowitz RA (1996). Anosmia and chronic sinus disease. *Otolaryngol Head Neck Surg,* 115:24-28

Fokkens WJ, Lund VJ, Mullol J et al (2007). European Position Paper on Rhinosinusitis and Nasal Polyps 2007. *Rhinology Suppl,* 20:1-139

Frasnelli J & Hummel T (2005). Olfactory dysfunction and daily life. *Eur Arch Otorhinolaryngol,* 262(3):231-235

Getchell M & Mellert T (1991). Olfactory mucus secretion. In: *Smell and taste in health and disease*. Getchell TV, Bartoshuk LM, Doty RL, Snow J, eds, pp.83-95, Raven Press editor, ISBN-10:0881677981, New York

Golding-Wood DG, Holmstrom M, Darby Y, Scadding GK & Lund VJ (1996). The treatment of intranasal hyposmia with intranasal steroids. *J Laryngol Otol,* 110:132-135

Gudziol V, Buschhüter D, Abolmaali N, Gerber J, Rombaux P & Hummel T (2009). Increasing olfactory bulb volume due to treatment of chronic rhinosinusitis – a longitudinal study. *Brain,* 132 (Pt 11):3096-101

Heilmann S, Huettenbrink KB & Hummel T (2004). Local and systemic administration of corticosteroids in the treatment of olfactory loss. *Am J Rhinol*, 18:29-33

Heilmann S, Strehle G, Rosenheim K, Damm M & Hummel T (2002). Clinical assessment of retronasal olfactory function. *Acta Otolaryngol Head Neck Surg,* 128(4):414-8

Hellings PW & Rombaux P (2009). Medical therapy and smell dysfunction. *B-ENT,* 5 Suppl 13:71-5

Hoffman HJ, Ishii EK & MacTurk RH (1998). Age related changes in the prevalence of smell and taste problems among the United States adult population: results of the 1994 Disability Supplement to the National Health Interview Survey (NHIS). *Ann N Y Acad Sci,* 855:716-722

Holbrook EH & Leopold DA (2006). An updated review of clinical olfaction. *Curr Opin Otolaryngol Head Neck Surg,* 14:23-28

Holcomb JD, Graham S & Calof AL (1996). Neuronal homeostasis in mammalian olfactory epithelium: a review. *Am J Rhinol* 10(3):125-134

Hox V, Bobic S, Callebaux I, Jorissen M & Hellings PW (2010). Nasal obstruction and smell impairment in nasal polyp disease: correlation between objective and subjective parameters. *Rhinology,* 48(4):426-32

Hummel T & Kobal G (1999). Differences in human evokes potentials to trigeminal stimuli change in relation to the interval between repetitive stimulation of the nasal mucosa. *Eur Arch Otorhinolaryngol,* 256:16-21

Hummel T & Kobal G (2002). Olfactory event-related potentials. In: *Methods and New frontiers in Neurosciences,* Simon SA editor, pp. 123-148, CRC Press, Boca Raton

Hummel T, Futschik T, Frasnelli J & Hüttenbrink KB (2003). Effects of olfactory function, age, and gender on trigeminally mediated sensations: a study based on the lateralization of chemosensory stimuli. *Toxicol Lett,* 140-141:173-80

Hummel T, Kobal G, Gudziol H & Mackay-Sim A (2007). Normative data for the Sniffin Sticks including test of odor identification, odor discrimination and odor thresholds: an upgrade based on a group of more than 3000 subjects. *Eur Arch Otorhinol,* 264:237-243

Hummel T, Livermore A, Hummel C & Kobal G (1992). Chemosensory event-related potentials in man; relation to olfactory and painful sensations elicited by nicotine. *Electroencephalogr Clin Neurophysiol,* 84(2):192-5

Jakobsen J & Svendstrup F (2000). Functional endoscopic sinus surgery in chronic sinusitis – a series of 237 consecutively operated patients. *Acta Otolaryngol Suppl,* 543:158-161

Jankowski R & Bodino C (2003). Olfaction in patients with nasal polyposis: effects of systemic steroids and radical ethmoidectomy with middle turbinate resection (nazalisation). *Rhinology,* 41(4):220-30

Jankowski R, Pigret D & Decroocq F (1997). Comparison of functional results after ethmoidectomy and nazalisation for diffuse and severe nasal polyposis. *Acta Otolaryngol.* 117: 601-608

Jiang RS, Su MC, Liang KL, Shiao JY, Hsin CH, Lu FJ & Chen WK (2009). Preoperative prognostic factors for olfactory change after functional endoscopic sinus surgery. *Am J Rhinol Allergy,* 23(1):64-70

Joshi H, Getchell ML, Zielinski B & Getchell TV (1987). Spectrophotometric determination of cation concentrations in olfactory mucus. *Neurosci Lett,* 82 (3): 321-326

Kern RC, Foster JD& Pitovski DZ (1997). Glucocorticoid (type II) receptors in the olfactory mucosa of the guinea pig: RU 28362. *Chem sens,* 22:313-319

Kern RC. Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. Laryngoscope 2000; 110(7):1071-7

Kim DW, Kim JY & Jeon SY (2011). The status of the olfactory cleft may predict postoperative olfactory function in chronic rhinosinusitis with nasal polyposis. *Am J Rhinol Allergy,* 25(2):90-4

Kimmelman CP (1994).The risk of olfaction from nasal surgery. *Laryngoscope,* 104:981-988

Klimek L, Moll B, Amedee RG & Mann WJ (1997). Olfactory function after microscopic endonasal surgery in patients with nasal polyps. *Am J Rhinol,* 11:251-255

Klossek JM, Peloquin L, Friedman WH, Ferrier JC & Fontanel JP (1997). Diffuse nasal polyposis: post-operative long-term results after endoscopic sinus surgery and frontal irrigation. *Otolaryngol Head Neck Surg.* 117:355-361

Kobal G & Hummel T (1988). Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa. *Electroencephalogr Clin Neurophysiol,* 71:241-50

Konstantinidis I, Triaridis S, Printza A, Vital V, Ferekidis E & Constantinidis J (2007). Olfactory dysfunction in nasal polyposis: correlation with computed tomography findings. *ORL J Otorhinolaryngol Relat Spec,* 69(4):226-232

Landis BN, Giger R, Richchetti A, Leuchter I, Hugentobler M, Hummel T & Lacroix JS (2003). Retronasal olfactory function in nasal polyposis. *Laryngoscope,* 113(11):1993-7

Landis BN, Konnerth CG & Hummel T (2004). A study on the frequency of olfactory dysfunction. *Laryngoscope,* 114(10):1764-9

Levine HL (1990). Functional endoscopic sinus surgery: evaluation, surgery and follow-up of 250 patients. *Laryngoscope,* 100:79-84

Lildholdt T (1989). Surgical versus medical treatment of nasal polyps. *Rhinol Suppl,* 8:31-33

Lildholdt T, Rundcrantz H & Lindqvist N (1995). Efficacy of corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. *Clin Otolaryngol Allied Sci,* 20:26-30

Litvack JR, Fong K, Mace J, James KE & Smith TL (2008). Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. *Laryngoscope*, 118(12): 2225-2230

Litvack JR, Mace J & Smith TL (2009b). Does olfactory function improve after endoscopic sinus surgery? *Otolaryngol Head Neck Surg,* 140:312-319

Litvack JR, Mace JC & Smith TL (2009a). Olfactory function and disease severity in chronic rhinosinusitis. *Am J Rhinol Allergy,* 23(2):139-144

Lund VJ & MacKay IS (1994). Outcome assessment of endoscopic sinus surgery. *J R Soc Med,* 87:70-72

Lund VJ & Scadding GK (1994). Objective assessment of sinus surgery in the management of chronis rhinosinusitis: an update. *J Laryngol Otol,* 108:749-753

Min YG, Yun YS, Song BH, Cho YS & Lee KS (1995). Recovery of nasal physiology after functional endoscopic sinus surgery: olfaction and mucociliary transport. *ORL J Otorhinolaryngol Relat Spec,* 57:264-268

Miwa T, Furukawa M, Tsukatani T, Costanzo RM, DiNardo LJ & Reiter ER (2001). Impact of olfactory impairment on quality of life and disability. *Arch Otolaryngol Head Neck Surg,* 127(5):497-503

Mott AE & Leopold DA (1991). Disorders in taste and smell. *Med Clin North Am,* 75:1321-1353

Mott AE, Cain WS, Lafreniere D, Leonard G, Gent JF & Frank ME (1997). Topical corticosteroid treatment of anosmia associated with nasal and sinus disease. *Arch Otolaryngol Head Neck Surg,* 123:367-372

Murphy C, Shubert CR, Cruickshanks KJ, Klein BE, Klein R & Nondahl DM (2002). Prevalence of olfactory impairment in older adults. *JAMA,* 288:2307-2312

Mygind N, Nielsen LP, Hoffmann HJ, Shukla A, Blumberga G, Dahl R & Jacobi H (2001) Mode of action of intranasal corticosteroids. *J Allergy Clin Immunol,* 108 (1Suppl):S16-25

Naessen R (1971). An inquiry on the morphological characteristics and possible changes with age in the olfactory regions of man. *Acta Otolaryngol,* 71:49-62

Nakashima T, Kimmelman C & Snow JB (1985). Immunohistopathology of human olfactory nerve epithelium, nerve and bulb. *Laryngoscope,* 95:391-398

Neuland C, Bitter T, Marschner H, Gudziol H & Gutinas-Lichius O (2011). Health-related and specific olfaction-related quality of life in patients with chronic functional anosmia or severe hyposmia. *Laryngoscope,* 121(4):867:72

Nordin S, Monsch AU & Murphy C (1995). Unawareness of smell loss in normal aging and Alzheimer's disease: discrepancy between self-reported and diagnosed smell sensitivity. *J Gerontol B Psychol Sci Soc Sci,* 50(4):187-82

Orlandi RR & Terrell JE (2002). Analysis of the adult chronic rhinosinusitis working definition. *Am J Rhinol*, 16:7-10

Park AH, Lau J, Stankiewicz J & Chow J (1998). The role of functional endoscopic sinus surgery in asthmatic patients. *J Otolaryngol,* 27:275-280

Raviv JR & Kern KC (2004). Chronic rhinosinusitis and olfactory dysfunction. *Otolaryngol Clin North Am,* 37:1143-1157

Reden J, Maroldt H, Fritz A, Zahnert T & Hummel T (2007). A study on the prognostic significance of qualitative olfactory dysfunction. *Eur Arch Otorhinolaryngol,* 264(2):139-44

Rombaux P, Mouraux A, Bertrand B, Guerit JM & Hummel T (2006). Assessment of olfactory and trigeminal function using chemosensory event-related potentials. *Neurophysiol Clin,* 36(2):53-62

Rombaux P, Mouraux A, Collet S, Eloy P & Bertrand B (2009). Usefulness and feasibility of psychophysical and electrophysiological olfactory testing in rhinology clinic. *Rhinology,* 47(1):28-35

Rombaux P,Potier H, Bertrand B, Duprez T & Hummel T (2008). Olfactory bulb volume in patients with sinonasal disease. *Am J Rhinol,* 22(6):598-601

Seiden AM & Duncan HJ (2001). The diagnosis of conductive olfactory loss. *Laryngoscope,* 111:9-14

Simola M & Malmberg H (1998). Sense of smell in allergic and non-allergic rhinitis. *Allergy,* 53:190-194

Soler ZM, Mace J & Smith TL (2008). Symptom-based presentation of chronic rhinosinusitis before and after functional endoscopic sinus surgery. *Am J Rhinol,* 22:297-301

Soler ZM, Sauer DA, Mace JC & Smith TL (2010). Ethmoid histopathology does not predict olfactory outcomes after endoscopic sinus surgery. *Am J Rhinol Allergy,* 24(4):281-5

Stuck BA, Blum A, Hagner AE, Hummel T, Klimek L & Hörmann K (2003). Mometasone furoate nasal spray improves olfactory performances in seasonal allergic rhinitis. *Allergy*, 58:1195

Temmel AF, Quint C, Schickinger-Fischer B, Klimek L, Stoller E & Hummel T (2002). Characteristics of olfactory disorders in relation to major causes of olfactory loss. *Arch Otolaryngol Head Neck Surg,* 128:635-641

Tourbier IA & Doty RL (2007). Sniff magnitude test: relationship to odor identification, detection and memory tests in a clinic population. *Chem Sens,* 32(6):515-23

Vaidyanathan S, Barnes M, Williamson P, Hopkinson P, Donnan PT & Lipworth B (2011). Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: and randomized trial. *An Intern Med,* 154(5):293:302

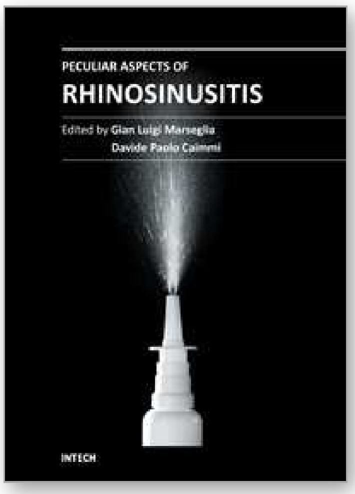
Vento SI, Simola M, Ertama LO & Malmberg CHO (2001). Sense of smell in longstanding nasal polyposis. *Am J Rhinol,* 15:159-163

Wang JH, Kwon HJ & Jang YJ (2010). Staphylococcus aureus increases cytokine and matrix metalloproteinase expression in nasal mucosa of patients with chronic rhinosinusitis and nasal polyps. *Am J Rhinol Allergy*, 24(6):422-7

Welge-Luessen A (2009). Psychophysical effects of nasal and oral inflammation. *Ann N Y Acad Sci*, 1170:585-9

Wright ED & Agrawal S (2007). Impact of perioperative systemic steroids on surgical outcomes in patients with chronic rhinosinusitis with polyposis: evaluation with novel perioperative sinus endoscopy (POSE) scoring system. *Laryngoscope*, 117 (11 Pt 2 Suppl 115): 1-28

Yee KK, Pribitkin EA, Cowart BJ, Vainius AA, Klock CT, Rosen D, Feng P, Mc Lean J, Hahn CG & Rawson NE (2010). Neuropathology of the olfactory mucosa in chronic rhinosinusitis. *Am J Rhinol Allergy*, 24(2):110-20



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Rhinosinusitis has both a great practical interest and a broad significance due to the scientific complexity of the pathogenetic problems related to the disease, not yet completely resolved, and their implications for clinical treatment. This book highlights certain specific topics that usually are not clarified in other resources. The first chapter is devoted to the impoverished quality of life experienced by patients suffering from rhinosinusitis. The second chapter focuses on the microbiological aspects of rhinosinusitis, while the two subsequent chapters explain the peculiar aspects of chronic rhinosinusitis and of recurrent chronic rhinosinusitis. The first chapter of the second section of the book is dedicated to the imaging techniques used to visualize the nasal sinuses and the other to a medical topical type of treatment.

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