Chem. Senses 27: 617–622, 2002

Anti-inflammatory and Surgical Therapy of Olfactory Disorders Related to Sino-nasal Disease

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Abstract

Olfactory loss may be caused by mechanical obstruction or inflammation of the olfactory epithelium due to allergic/non-allergic rhinitis and chronic sinusitis with or without polyps. Treatment of olfactory loss related to sino-nasal disease is possible. Apart from surgical approaches and/or treatment with antibiotics, both systemic and topical steroids are effectively used in the therapy of olfactory loss related to sino-nasal disease. In most cases improvement of olfactory function appears to relate to the anti-inflammatory actions of the steroids used. While some details of therapeutic effect and dose regimen are not clear, systemic steroids are often helpful even in patients without nasal obstruction due to polyps or obvious inflammatory changes.

Introduction

A free nasal passage is the prerequisite of olfactory function. Olfactory loss is encountered when this passage is mechanically blocked or when the intranasal air flow is altered such that the transport of odor molecules to the olfactory epithelium is affected (Mott and Leopold, 1991; Smith and Duncan, 1992; Knecht *et al*., 1999). In this context it is important to point out that the olfactory epithelium is mainly localized in the olfactory cleft (von Brunn, 1892; Read, 1908; Leopold *et al*., 2000) with a typical width of 1–2 mm. The cleft is easily obstructed by mucosal congestion or polypoid changes of the mucosa. The nasal airway, however, may remain intact despite this congestion within the nasal vault.

In addition to mechanical obstruction, inflammation of the olfactory epithelium also appears to affect olfactory function (Jafek *et al*., 1987; Klimek and Eggers, 1997; Stevens, 2001). Finally, olfactory magnitude also depends on the perceived effort associated with a sniff, which is frequently increased in sino-nasal disease (SND) (Teghtsoonian and Teghtsoonian, 1984; Youngentob *et al*., 1986; Hornung *et al*., 1997). For example, perceived odor strength is reduced when subjects sniff against increasing resistances while the nasal flow rate remains constant (Youngentob *et al*., 1986). Consequently, olfactory loss is a characteristic complication of SND which is related to both nasal obstruction and inflammatory changes of the olfactory epithelium.

Causes of SND-related olfactory loss

Olfactory loss following SND has different causes (Doty and Frye, 1989; Mott and Leopold, 1991). Among them are inflammatory conditions (allergic and non-allergic rhinitis and chronic sinusitis with or without polyps), neoplasms and scars following surgery, (Duncan and Smith, 1995; Cullen and Leopold, 1999; Seiden and Duncan, 2001). In a study of 53 patients with SND-related olfactory loss 21 had chronic sinusitis with nasal polyps, 19 had chronic sinusitis without polyps, eight had allergic rhinitis, two had post-surgical trauma, one had atrophic rhinitis and one had an inverting papilloma [cited from Seiden (Seiden, 1997)]. In patients with allergic rhinitis it has been shown that the degree of olfactory loss is correlated with the presence of eosinophilic cationic protein, which is known to be a sensitive marker of allergies found in the mucus. This correlation (r = 0.83) was significantly higher than the correlation between olfactory loss and nasal obstruction assessed by means of rhinomanometry (r = 0.65) (Klimek and Eggers, 1997). It is unclear, however, how inflammation can affect olfactory function so dramatically in some patients that it leads to an almost complete suppression of olfactory function (Kern, 2000).

Frequency of SND-related olfactory loss

Olfactory loss is found in approximately one quarter of patients with chronic sinusitis without polyps but in up to

83% of patients with chronic sinusitis with polyps (Delank and Stoll, 1994; Lund and Scadding, 1994; Bonfils *et al*., 1998). In allergic rhinitis approximately 15% present with olfactory loss (Cowart *et al*., 1993) [compare Seiden *et al*. (Seiden *et al*., 1989)]. Considering that 10–15% of the general population suffer from allergic rhinitis (Cowart *et al*., 1993) and ~14% of the population report chronic sinusitis (Lieu and Feinstein, 2000), an impressive number of people are compromised by SND-related olfactory dysfunction.

Subjective symptoms

Common characteristics of SND-related olfactory loss include a gradual decrease in olfactory function over several years and fluctuations of olfactory function, e.g. temporary improvement through physical exercise or the spontaneous restoration of olfactory sensitivity for a few moments (Mott and Leopold, 1991; Smith and Duncan, 1992) [compare Hill and Jafek (Hill and Jafek, 1989)]. Such fluctuations are seen in ~45% of patients with SND-related olfactory loss (Seiden, 1997). The presence of parosmia or phantosmia has also been described in SND-related olfactory loss. This seems to be much more characteristic of olfactory dysfunction following upper respiratory tract infections (Nordin *et al*., 1996; Hummel and Knecht, 2001; Seiden and Duncan, 2001). Some patients with SND-related olfactory loss may have no other nasal symptoms, e.g. respiratory dysfunction. This is due to the fact that, in healthy subjects, the largest portion of the respiratory airstream primarily passes through the middle and some of the inferior meatus of the nasal cavity; it is estimated that only 10–15% of the respiratory air reaches the olfactory cleft (Masing, 1967; Scherer *et al*., 1989).

It is interesting to note that many people with SND-related olfactory loss are apparently not disturbed by this sensory impairment (Hosemann *et al*., 1993). Only one third of SND patients with confirmed olfactory loss complain of decreased olfactory function. When specifically asked for the presence of olfactory loss, half of SND patients report hyposmia; the other half of SND patients are not aware of this olfactory loss, even when anosmia is present (Doty and Frye, 1989; Delank and Stoll, 1994). This situation is comparable to age-related loss of olfactory function where many elderly people are not aware of an impaired sense of smell. In both scenarios olfactory function decreases gradually over several years (Nordin *et al*., 1995). Thus it appears that many people adjust to the slow onset of olfactory loss. In addition, there are preliminary data indicating that these adjustments also include changes in sensitivity in the gustatory and trigeminal systems (Hummel, 2000; Hummel *et al*., 2001). In contrast, adjusting to sudden olfactory loss seems to be much more difficult, e.g. in olfactory loss following upper respiratory tract infections (post-URTI) or head trauma (Hendriks, 1988) where, in the majority of cases, the olfactory loss is clearly recognized.

This may also influence estimates of the relative frequency of SND-related olfactory loss (Douek, 1970; Doty, 1979; Henkin *et al*., 1981; Fikentscher *et al*., 1983; Davidson *et al*., 1987; Hendriks, 1988; Deems *et al*., 1991; Mott and Leopold, 1991; Temmel *et al*., 2001). Of all patients who present themselves to specialized centers ~10–77% suffer from an olfactory loss due to SND, 3–33% from post-traumatic olfactory loss, 14–40% from post-URTI olfactory loss and 1–30% from olfactory loss related to other causes (e.g. congenital olfactory loss, olfactory loss through toxic substances, drug-induced olfactory loss and olfactory loss through neurodegenerative disease). In up to 26% of the cases impairment of the sense of smell is diagnosed as idiopathic. When contemplating these figures it must be kept in mind that most of these statistics are based on highly selected populations. It can be assumed that many people with olfactory loss are first counseled/treated by a general practioner, an otorhinolaryngologist or a neurologist. As there are therapeutic opportunities in SND-related olfactory loss, it can be assumed that many ORL specialists are able to effectively counsel SND patients and that SND-related olfactory loss may be treated effectively in many cases (see below). Consequently, the number of patients with SND-related olfactory loss is probably grossly underestimated.

Objective symptoms

The dominant symptom of the putrid form of chronic sinusitis is mucosal discharge, particularly post-nasal drip. In contrast, the polypoid form of chronic sinusitis is dominated by decreased respiratory air flow. Both forms of chronic sinusitis are often accompanied by pain and/or sensations of pressure.

In SND patients the degree of olfactory loss is correlated with the degree of nasal obstruction (Damm *et al*., 2000). Interestingly, however, there is only a weak correlation between duration of nasal obstruction and degree of olfactory loss (Min *et al*., 1995; Apter *et al*., 1999). Olfactory loss is found in only 25–29% of patients with chronic sinusitis without polyps, but in 76–83% of patients with chronic sinusitis with polyps (Delank and Stoll, 1994; Lund and Scadding, 1994; Bonfils *et al*., 1998). In addition, in patients with chronic sinusitis without polyps only 4% are diagnosed as anosmic, whereas 31% of patients with polyps are anosmic (Bonfils *et al*., 1998; Delank and Stoll, 1998).

Patients with perennial rhinitis have been reported to exhibit decreased olfactory thresholds, odor discrimination and odor identification throughout the entire year; in contrast, when patients with seasonal allergic rhinitis are tested during the symptom-free interval only thresholds have been found to be altered (Klimek and Eggers, 1997; Moll *et al*., 1998). More recent work indicates that the degree of olfactory loss is related to the degree of the allergic

condition. Specifically, it has been suggested that olfactory loss is related to the number of items patients are allergic to (Schickinger *et al*., 2000).

Work-up of patients with SND should include a detailed endoscopic examination of the nasal cavity. This is superior to anterior rhinoscopy, which has a false negative rate of ~50% in patients with SND-related olfactory loss (Seiden, 1997). In addition, a coronal CT scan should be performed even in cases where endoscopy is unremarkable (Seiden and Duncan, 2001). Other investigations may include bacteriological and/or cytological analyses, allergy testing (Simola and Malmberg, 1998), measurements of nasal air flow using anterior rhinomanometry (McCaffrey, 1991), measurements of nasal volume, e.g. acoustic rhinometry, or, in highly specialized centers, biopsies from the respiratory and/or olfactory epithelium (Lovell *et al*., 1982; Roithmann *et al*., 1994; Hamilton *et al*., 1995; Min and Jang, 1995).

Therapy of SND-related olfactory loss

Therapy of typical SND-related olfactory loss follows a step-wise procedure. In cases of purulent chronic sinusitis antibiotics may be tried. Steroids, used either systemically or locally, are prescribed in patients with chronic sinusitis. Finally, when medical therapy fails, surgical tretament is indicated (Mott and Leopold, 1991).

Conservative therapy of SND-related olfactory loss

Antibiotics

Most frequently putrid acute siunusitis is governed by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, which are relativley sensitive to antibiotic therapy. However, in the chronic form of putrid sinusitis *Staphylococcus aureus* and *Pseudomonas aeruginosa* are much more important. Whenever possible antibiotic therapy should only be started after the bacteria have been identified and tested for resistance to antibiotics. It is important to note that in chronic putrid sinusitis antibiotic treatment is not always succesful.

Steroids

Among many other effects corticosteroids act as anti-inflammatory drugs, the effects of which are produced via a number of different pathways, including inhibition of phospholipase A2 through induction of lipocortin (Fong *et al*., 1999). They reduce submucosal edema and mucosal hypersecretion and thereby increase nasal patency. Although not yet proven in an appropriate double blind study, steroids are of help in many SND patients (Golding-Wood *et al*., 1996; Mott *et al*., 1997; Tos *et al*., 1998; Seiden and Duncan, 2001). For example, most recently Stevens reported that systemic administration of steroids was effective in 12 of 24 patients with SND-related olfactory loss (Stevens, 2001). In addition to the anti-inflammatory activity it has been postulated that corticosteroids directly improve olfactory function (Mott and Leopold, 1991; Klimek and Eggers, 1997) by modulating the function of olfactory receptor neurons through effects on olfactory Na,K-ATPase (Fong *et al*., 1999). In fact, also based on our own experience, systemic steroids are often helpful even in patients without nasal obstruction due to polyps or obvious inflammatory changes (compare Jafek *et al*., 1987; Stevens, 2001).

Steroids may be administered systemically or topically. With regard to olfactory dysfunction, systemic administration is often applied for diagnostic purposes. If systemic steroids improve olfactory function, treatment is continued with locally administered steroids. Although systemic steroids are usually more effective than locally administered steroids (Mott and Leopold, 1991; Ikeda *et al*., 1995), prescription of systemic steroids over an extended period of time is rarely warranted (Hotchkiss, 1956; Jafek *et al*., 1987). Side effects such as diabetes, gastric ulceration, osteoporosis, hypertonia, depression or sleeping disorders clearly limit the systemic use of steroids for the treatment of olfactory disorder (Scott, 1989). While exact recommendations are missing, it is possible, however, to repeatedly administer short courses of systemic steroids with an interval of 6–12 months between courses. In fact, some of our patients regularly ask for a course of steroids over christmas (which in Germany and Switzerland is a truly olfactory period).

A number of studies indicate the usefulness of topical steroids (Golding-Wood *et al*., 1996; Mott *et al*., 1997; Tos *et al*., 1998), however, the role of topical steroids in the treatment of SND-related olfactory loss has not been clearly established (Mott and Leopold, 1991; El Naggar *et al*., 1995; Ikeda *et al*., 1995). So far, no factors predicting a favorable response to topical stroids have been identified. Finally, little information is available on the efficacy of this treatment over an extended period of time.

Systemic steroids are more effective than locally administered steroids (Mott and Leopold, 1991; Ikeda *et al*., 1995). For example, 30 of 36 patients experienced an improvement in their sense of smell when put on systemic steroids, however, this was the case in only 13 of 52 patients following application of topical steroids (Seiden and Duncan, 2001). For locally administered steroids one double blind study has been performed in patients with seasonal allergy using mometasone (n = 80) or placebo (n = 41) (Meltzer *et al*., 1998). Upon assessment with tests for odor identification and *n*-butanol odor thresholds baseline levels before treatment were found to be normal, which may have contributed to the lack of significant differences between placebo and mometasone. It is not entirely clear why systemic steroids have a higher therapeutic efficacy compared with topical steroids (Ikeda *et al*., 1995; Seiden and Duncan, 2001). One reason may relate to the deposition of the spray in the nasal cavity. In fact, it has been shown that only a small volume of nasally applied sprays reach the olfactory epithelium, which is situated in an effectively protected area of the nasal cavity (Hardy *et al*., 1985; Newman *et al*., 1987; McGarry and Swan, 1992). Considering that the dominant function of the

nose is heating, humidification and filtering inspired air it becomes clear that little or nothing of applied sprays reach the olfactory epithelium. This situation can be improved by the application of sprays in a 'head-down forward position' (Mott and Leopold, 1991). Other reasons for the greater efficacy of systemic steroids may relate to the site of action of steroids in SND patients. It has been speculated that the site of inflammation relevant to olfactory loss may not always be in the mucosa but in the area of the cribriform plate or the olfactory bulb (Wolf, 1998; Roob *et al*., 1999). This hypothesis appears particularly attractive in patients who respond to systemic steroids, have no apparent signs of nasal inflammation and do not respond to locally administered steroids.

In addition to the use of steroids there are still other therapeutic approaches to restoration of olfactory loss. They include the use of antileukotrienes (Parnes and Chuma, 2000), saline lavage (Bachmann *et al*., 2000) or approaches which have received less vigorous scientific investigation, e.g. diet changes (Rundles, 1946), anti-allergy immunotherapy (Stevenson *et al*., 1996) and herbal treatments.

Surgical therapy

Surgical therapy aims at both elimination or reduction of nasal obstruction and removal of inflamed mucosa or polyps (Jafek and Hill, 1989). Today this type of surgery is routinely performed endonasally under endoscopic or microscopic control.

Most of the patients undergo surgery to remedy decreased nasal patency, a feeling of pressure or recurrent infections of the nasal sinuses. Surgery is rarely performed to specifically treat olfactory dysfunction. In spite of this, post-operative improvement of olfactory function has been reported by 50–100% of patients (Lund and Scadding, 1994; Min *et al*., 1995; Downey *et al*., 1996; Delank and Stoll, 1998). Frequently, however, olfactory recovery is incomplete (Lund and Scadding, 1994). When olfactory function is measured, one study found an improvement in 25% of patients with pre-operative hyposmia and 5% with pre-operative anosmia (Delank and Stoll, 1998). Following surgery, others (Min *et al*., 1995) reported the percentage of normosmic patients increased from 22 to 36%.

In addition, a study reported severe impairment of olfactory acuity in 24 patients prior to excision of the inferior turbinates (Ophir *et al*., 1986). Post-operative improvements of olfactory acuity were statistically significant. None of the patients exhibited elevated thresholds compared with pre-operative results; in two anosmic patients olfactory loss could not be remedied.

Predictors of treatment outcome in terms of improvement of olfactory function have not been identified. Neither the degree of pre-operative obstruction nor the duration of olfactory loss correlate with therapeutic success. Similarly, findings of post-operative endoscopical investigations do not correlate with the improvement in the sense of smell (Hosemann *et al*., 1993). This is not altogether surprising, since polypoidal mucosa is usually not removed from areas superior to the upper turbinate/olfactory cleft underlying the cribriform plate.

While beneficial in most cases, surgery may also pose a certain risk to olfactory function. Formation of synechiae (mucosal adhesions), crusting or damage to the olfactory epithelium may all compromise the success of the intervention. Kimmelman (Kimmelman, 1994) reported a risk of 1.1% of becoming anosmic after nasal surgery [compare Damm *et al*. (Damm *et al*., 2001)]. However, a number of other researchers did not see a post-operative decrease in olfactory acuity (Elwany and Harrison, 1990; Ophir *et al*., 1986; Friedman *et al*., 1999), indicating that the risk to olfaction from nasal surgery is low.

Conclusions

Effective treatment of SND-related olfactory loss is possible, although not always successful. Apart from surgical approaches and/or treatment with antibiotics, both systemic and topical steroids are effectively used in the therapy of SND-related olfactory loss. In most cases an improvement in olfactory function appears to relate to the anti-inflammatory actions of the steroids used. While some details of therapeutic effect and dose regimen are not clear, systemic steroids are often helpful even in patients without nasal obstruction due to polyps or obvious inflammatory changes.

Acknowledgement

The present manuscript resulted from a session on 'clinical aspects of olfaction' held during the ECRO meeting 2000 in Brighton, UK.

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Accepted May 25, 2002