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Chapter 18

Diseases of the nasal cavity

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Abstract

Despite garnering minimal attention from the medical community overall, olfaction is indisputably critical in the manner in which we as humans interact with our surrounding environment. As the initial anatomical structure in the olfactory pathway, the nasal airway plays a crucial role in the transmission and perception of olfactory stimuli. The goal of this chapter is to provide a comprehensive overview of olfactory disturbances as it pertains to the sinonasal airway. This comprises an in-depth discussion of clinically relevant nasal olfactory anatomy and physiology, classification systems of olfactory disturbance, as well as the various etiologies and pathophysiologic mechanisms giving rise to this important disease entity. A systematic clinical approach to the diagnosis and clinical workup of olfactory disturbances is also provided in addition to an extensive review of the medical and surgical therapeutic modalities currently available.

INTRODUCTION

Albeit largely neglected by the medical community overall, olfaction is indisputably critical in the manner in which we as humans interact with our environment. Our ability to recognize environmental dangers, such as fires, gas leaks, or ingested toxins, depends heavily on the existence of an intact olfactory pathway such that any disturbance thereof may engender significant safety concerns (Miwa et al., 2001; Santos et al., 2004; Bonfils et al., 2008; Pence et al., 2014). Olfactory disturbances may also alter our qualitative appreciation of our environment with olfaction being shown to play an influential role in the human emotional response and memory processing (Croy et al., 2011). It is, therefore, not surprising that individuals afflicted with a disordered sense of smell report significant reductions in quality of life (QOL) as a result of adverse influences on one's daily life and mental health (Deems et al., 1991; Gopinath et al., 2011).

As the initial anatomical structure in the olfactory pathway, the nasal airway plays a crucial role in the transmission and perception of olfactory stimuli. Sinonasal pathology, in turn, makes up a critical proportion of etiologies underlying olfactory disturbances. Among patients presenting for clinical evaluation of olfactory impairment, rhinitis and/or rhinosinusitis comprises the most frequent etiology (Cowart et al., 1997). Chronic rhinosinusitis (CRS) is also among the most epidemiologically significant chronic inflammatory disease processes affecting up to an estimated 16% of the American adult population annually and generating approximately $10 billion per year in U.S. national healthcare costs (Halawi et al., 2013; Caulley et al., 2015; Smith et al., 2015). In sum, the nasal cavity and its associated diseases represent an essential component in the diagnostic and therapeutic approach of olfactory disturbances. The aim of this chapter is to provide an in-depth review of sinonasal diseases contributing to olfactory dysfunction with particular attention given to the differential diagnosis, physiopathology, clinical approach, treatment strategies, and prognostic factors of sinonasal hyposmia or anosmia.

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NASAL OLFACTORY ANATOMY AND PHYSIOLOGY

The nasal contribution to olfaction is closely related to nasal airflow and nasal mucosa integrity. Odorants within inspired air travel through the nasal passageway, traversing the nasal vestibule and nasal cavity to eventually interface with olfactory receptors situated in the olfactory neuroepithelium located on the superior nasal septum, olfactory cleft, and portions of the superior and middle turbinates (Cullen and Leopold, 1999; Leopold et al., 2000; Raviv and Kern, 2004; Zhao and Frye, 2015). Along this route, air passes through regions of restricted cross-sectional area such as the internal nasal valve and nasal turbinates that render the airflow turbulent, thereby facilitating odorant delivery to the olfactory epithelium. Approximately 15% of inspired air will be diverted to the olfactory cleft in this fashion (Hahn et al., 1993; Wrobel and Leopold, 2004b). This sequence of airflow, termed orthonasal olfaction, is what has been traditionally conceptualized as the principle mechanism for mediating olfaction (Heilmann and Hummel, 2004). Odorants may also be perceived through retrograde passage of odorants from the oral cavity and oropharynx into the nose via the nasopharynx, termed retronasal olfaction (Ni et al., 2015). This process is thought to be an important mediator of flavor appreciation and likely contributes to the perception of gustatory loss expressed by patients with a primarily olfactory disturbance (Hadley et al., 2004).

CLASSIFICATION OF OLFACTORY DISTURBANCES

Olfactory disturbances of sinonasal origin may broadly be classified mechanistically into one of two categories: conductive or neurosensorial. Conductive olfactory loss signifies an underlying airflow etiology. This commonly arises in the setting of sinonasal disease, wherein various pathologies may anatomically obstruct nasal airflow to the olfactory cleft and other mucosal regions lined with olfactory neuroepithelium. The spectrum of pathologies that may give rise to this form of olfactory dysfunction includes CRS particularly among those with nasal polyposis, sinonasal neoplasms, allergic rhinitis, and septal deviations. A neurosensorial olfactory loss signifies damage or dysfunction at any point along the olfactory neural pathway from the olfactory receptors through to the central olfactory processing centers in the brain. The latter category may include local etiologies such as upper respiratory viral illness and toxin inhalation injury to central processes such as neurodegenerative disease, congenital anomalies, and head trauma (Wrobel and Leopold, 2004a; Daramola and Becker, 2015). In some instances, both mechanisms of olfactory loss may be contributory as in the case of nasal inflammatory diseases such as CRS (Kern, 2000; Allis and Leopold, 2012), which will be elaborated upon elsewhere in this chapter.

A descriptive classification of olfactory disturbance is also widely employed to further qualify the nature of the olfactory disturbance. This may take the form of a quantitative classification in which a partial loss is termed hyposmia and a complete loss is referred to as anosmia. Qualitative olfactory disturbances (also known as dysosmia) include parosmia, a distortion in olfactory perception in the presence of an odorant, and phantosmia, a perception of odor in the absence of exposure to an odorant stimulus. The exact pathophysiologic mechanism for qualitative distortions in olfaction has yet to be clearly elucidated though both peripheral and central theories have been proposed corresponding to a dysfunction at either the level of the olfactory neurons or central olfactory processing centers, respectively (Leopold, 2002).

CAUSES OF SINONASAL HYPOSMIA AND ANOSMIA

Postviral olfactory loss

Upper respiratory tract viral infection (URTI) is among the most common etiologies of olfactory loss accounting for up to 43% of cases of neurosensorial olfactory disorders (Cain et al., 1988; Deems et al., 1991; Quint et al., 2001; Seiden and Duncan, 2001; Temmel et al., 2002). Women and people over the age of 65 appear to be more likely afflicted with an olfactory loss following a URTI although the exact reason for this observed predilection remains unclear (Temmel et al., 2002). Some authors have hypothesized a gerontologic predisposition may be due in part to a cumulative damage sustained by the olfactory epithelium (Dalton, 2004). Others have suggested a female predilection may result from increased viral exposure possibly due to more frequent contact with children (Seiden, 2004). Olfactory loss arising in a postviral setting is more often described as partial (hyposmia) than complete (anosmia) compared to other common etiologies of disturbed olfaction (Cain et al., 1988; Deems et al., 1991; Wrobel and Leopold, 2004a). A postviral olfactory disturbance may also manifest as dysosmia, with patients more often presenting with parosmia compared to phantosmia (Leopold, 2002).

The exact viral pathogen responsible for this clinical entity continues to elude researchers, with evidence equally lacking regarding a viral etiology altogether (Seiden, 2004; Wrobel and Leopold, 2004a, b). Pathogens identified within the nasal discharge of patients with

postviral olfactory dysfunction include rhinovirus, coronavirus, parainfluenza virus, and Epstein–Barr virus (Suzuki et al., 2007). Nonetheless, an extensive body of literature has furnished histopathologic evidence of disruption at various levels along the olfactory pathway following a viral insult. Biopsy specimens obtained in patients with olfactory loss have revealed distinct olfactory epithelial changes compared to specimens from normal controls. Changes observed include both a reduction and complete absence of olfactory receptors, replacement of olfactory epithelium by respiratory or metaplastic epithelium, morphologic changes to the olfactory receptors, and disrupted epithelial neural connections (Yamagishi et al., 1988, 1990, 1994; Moran et al., 1992; Jafek et al., 2002). Some evidence in this patient population suggests a correlation between the severity of olfactory loss and observed reductions in olfactory receptor density (Seiden, 2004), although other researchers have failed to replicate this finding (Yamagishi et al., 1994). Various animal models have also shown degeneration of the central olfactory pathways including the olfactory bulb following intranasal viral inoculation (Mohammed et al., 1990; Perlman et al., 1990; Schwob et al., 2001). These data are further supported by radiologic studies of postviral olfactory loss in humans revealing both anatomical and functional changes to central olfactory structures. Magnetic resonance imaging (MRI) of the olfactory bulb in patients presenting with a postinfectious olfactory loss has revealed significant reductions in olfactory bulb volume that correlate both with the degree and duration of olfactory loss (Rombaux et al., 2006, 2009). Moreover, functional brain imaging in these patients employing ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) has demonstrated significant reductions in basal metabolism within specific brain regions responsible for reception and integration of olfactory information (Kim et al., 2012).

Traditionally, the prognosis of olfactory recovery in postviral olfactory loss has been described as poor, with only one-third of patients demonstrating a recovery in olfactory ability (Hendriks, 1988). Moreover, the length of dysfunction has been reported to correlate with the likelihood of recovery (Wrobel and Leopold, 2004b). In the largest and most definitive study on the recovery of olfactory function from any cause (~38% of which were postviral olfactory loss), the strongest positive predictor of olfactory recovery was the degree of initial dysfunction (London et al., 2008). However, long-term follow up of these patients has proved more promising, with improvements in objective olfactory function observed in patients with postviral olfactory loss followed for over 1 year (Duncan and Seiden, 1995). In a recent study of the long-term prognosis of postviral olfactory loss for which subjects were followed for a mean length of over two and a half years, subjective improvement in olfactory ability was reported by over 85% of subjects. Interestingly, an increased length in follow up (>2 years) was found to be predictive of improvement in subjective olfactory function. The latter finding would appear to suggest that either the regenerative process of the olfactory pathway continues long after the initial viral insult or that patients merely become accustomed to the olfactory dysfunction over time (Lee et al., 2014).

Sinonasal surgery

A variety of surgical interventions within the sinonasal cavity may inadvertently alter olfactory function. Landis et al. proposed four mechanisms in which surgical interventions of the sinonasal tract may yield an olfactory disturbance: scar tissue, granulation tissue, persistent mucosal edema, and inflammation or damage of the olfactory neuroepithelium (Landis et al., 2005). Wrobel and Leopold have since modified this scheme to better encompass the spectrum of pathophysiologic processes arising in a perioperative setting. The authors broadly classified mechanisms of olfactory injury following sinonasal surgery into one of four categories: mechanical injury, airflow modifiers, vascular/neural injury, and others. Mechanical injuries allude to direct trauma of the olfactory epithelium (e.g., thermal injury from electrocautery, olfactory fila traction with superior septoplasty and/or osteotomies), scarring, or atrophic rhinitis-related crusting due to overaggressive resection of intranasal structures (e.g., turbinates). Airflow modifiers include any anatomical sequelae (e.g., scarring) that may alter airflow to the olfactory neuroepithelium. Vascular comprise may arise with surgically created ischemia of the olfactory epithelium with neural injury resulting from postoperative URTI. Other mechanisms include topical or locally infiltrated medications in addition to previously unrecognized olfactory disturbances (Wrobel and Leopold, 2004b). Olfactory loss has also been described in association with general anesthesia, although the exact mechanism of this relationship remains unclear (Adelman, 1995).

Despite the manifold means by which olfactory disturbances may arise following sinonasal surgery, the literature would suggest that this complication is rare overall. In a review of over 90 cases encompassing a variety of sinonasal procedures, Kimmelman reported a transient olfactory loss in one-third of patients with a permanent loss occurring in a single patient (1%) (Kimmelman, 1994). These findings parallel those reported by Stevens and Stevens, wherein the vast majority of patients expressed either no change or an

improvement in olfactory ability following sinonasal surgery with a single patient manifesting anosmia following a septorhinoplasty (Stevens and Stevens, 1985). Though a postoperative reduction in olfactory ability may infrequently occur following sinonasal surgery, over 10% of patients may report a smell loss preoperatively, prompting a need to document this fact to avoid postoperative accusations of a surgical complication (Briner et al., 2003).

The risk of permanent olfactory loss appears to be equally infrequent when evaluating specific sinonasal procedures. Given the presence of olfactory epithelium on the superior portion of the middle turbinates, there exists a potential risk of inducing an olfactory loss, following their partial or complete resection. In a cohort of over 100 patients undergoing partial middle turbinate resection during endoscopic sinus surgery (ESS), a single patient endorsed postoperative anosmia accounting for an overall incidence of 0.9% (Biedlingmaier et al., 1996). Despite there being no mention of pre and postoperative objective olfactory testing, this reported rate of anosmia compares favorably to that of an ESS cohort wherein the middle turbinates were preserved (0.8%) (Wigand, 1990).

Permanent postoperative changes in olfaction following septal surgery likewise manifests in a minority of patients both in so far as olfactory improvement and unanticipated olfactory loss. Pade and Hummel evaluated both pre and postoperative olfactory function in a cohort of 150 patients undergoing septoplasty and noted that the overwhelming majority of patients (81%) endorsed no change in olfaction when assessed at a mean interval of 4 months postoperatively. Improvement in olfaction was related by 13% and only 7% of patients reported decreased function. A separate group of patients who underwent ESS demonstrated a tendency to derive significantly greater olfactory benefit when compared to patients who underwent septoplasty alone. Interestingly, septoplasty patients reporting a loss of smell postoperatively had significantly higher preoperative olfactory scores. These findings suggest that while an olfactory sequela is relatively rare following septal surgery, the potential for this outcome should nonetheless factor into the preoperative counseling of patients undergoing this surgical intervention (Pade and Hummel, 2008). It is also worthwhile informing patients of the potential for a transient olfactory loss in the acute postoperative setting as a result of mucosal edema and obstructed airflow.

Impairment in olfaction has also been described following rhinoplasty though most of this literature represents lower grades of evidence. In one of the first studies to address this question, Champion published a series of 200 cases whereby subjective evaluation of smell loss was performed for up to 18 months following surgery. A single patient (0.5%) experienced permanent anosmia with 11% of patients reporting temporary olfactory loss (Champion, 1966). Shortly thereafter, Goldwyn and Shore published their series of just under 100 patients for which objective olfactory testing was performed both prior to and following rhinoplasty or submucous resection. The reported incidence of decreased olfactory function was 3% (Goldwyn and Shore, 1968).

Skull base surgery

Anterior skull base approaches for the extirpation of both sinonasal and intracranial pathology carry a significant risk of olfactory complications given the proximity of critical olfactory structures to the surgical field. With the introduction of ESS in the 1980s, minimally invasive endoscopic skull base approaches have increasingly been adopted with the aim of circumventing potential morbidities associated with the traditional open craniofacial approach. While these approaches are conceptually minimally invasive, they frequently require maximal surgical exposure of the endonasal skull base, which entails sacrificing significant portions of peripheral olfactory structures, such as the olfactory epithelium and potentially the olfactory bulb in the case of a transcribriform approach (Schwartz et al., 2016a). Reconstruction of the skull base defect typically entails harvesting a vascularized, pedicled tissue flap known as a nasoseptal flap, which is largely derived from the mucosa of the nasal septum and may further alter olfactory function.

Although, in theory, endoscopic approaches to the skull base are expected to significantly alter olfactory function, the literature would appear to disagree on the extent of its olfactory impact. Some evidence suggests that contemporary endoscopic approaches may be more favorable insofar as preserving olfactory function compared to the more traditional transseptal microscopic approach that was once widely employed prior to the advent of the endoscope. These two surgical approaches were the subject of a comparative analysis in a prospectively recruited patient cohort undergoing pituitary surgery, wherein olfaction was objectively evaluated preoperatively in addition to 1 and 6 months postoperatively. Patients subjected to a microscopic approach were statistically more likely to sustain an olfactory disturbance compared to the endoscopic group (Kahilogullari et al., 2013). This is not to say that endoscopic pituitary approaches are without olfactory sequela with some groups describing both a subjective and objective decline in olfactory function 6 months postoperatively (Kim et al., 2014). This observation is not however uniform, with other authors reporting no significant change in objective olfactory function following endoscopic pituitary surgery, irrespective of the employment of nasoseptal flaps (Chaaban et al., 2015).

Furthermore, statistically significant changes both in three-dimensional volume and cross-sectional nasal passage dimensions observed in patients undergoing an endoscopic transphenoidal approach have not been shown to correlate with a corresponding decline in olfactory function (Kim et al., 2016a, b). Yet more extensive endoscopic skull base approaches, commonly termed expanded endonasal approaches (EEAs), do appear to carry a higher risk of engendering an olfactory disturbance. When compared to more limited transphenoidal approaches to the pituitary, EEA patients report significantly greater loss in smell postoperatively though this finding has not replicated with objective olfactory evaluation.

Though olfactory preserving techniques have previously been described for open skull base approaches (Spetzler et al., 1993; Dare et al., 2001; Honeybul et al., 2001; Feiz-Erfan et al., 2005), an increasing awareness regarding potential olfactory sequela following endoscopic skull base surgery has prompted a plethora of literature describing endoscopic techniques for sparing olfactory dysfunction in these patients. These techniques include preservation of the septal olfactory strip (Griffiths et al., 2014; Harvey et al., 2015) and use of the cold knife (Kim et al., 2013; Hong et al., 2014) (vs electrocautery) during nasoseptal flap harvest in addition to curtailing the routine resection of normal sinonasal structures such as the middle turbinates (Thompson et al., 2014).

Neoplasms

Olfactory dysfunction may occasionally arise in the setting of a sinonasal or intracranial neoplasm. An olfactory deficit in this context may be either conductive or neurosensorial in origin, with the latter resulting from tumoral involvement of the olfactory epithelium and/or olfactory bulbs (Allis and Leopold, 2012). Intranasal tumors are typically unifocal in nature and more often present with unilateral symptoms more so than bilateral symptoms (Bachar et al., 2008). The most commonly occurring intranasal tumors include squamous cell carcinoma, inverting papilloma, adenomas, and esthesioneuroblastoma (Allis and Leopold, 2012). The classic example of a nasal tumor giving rise to olfactory dysfunction is an esthesioneuroblastoma, also known as olfactory neuroblastoma (see Fig. 18.1). Esthesioneuroblastomas comprise approximately 5% of all sinonasal malignancies and are thought to originate from basal progenitor cells of the olfactory neuroepithelium (Dulguerov et al., 2001). These tumors often grow insidiously with delays in diagnosis of up to 1 year. They most commonly present with nasal airway obstruction and epistaxis (Zafereo et al., 2008), though they often create disturbances in olfaction due to their anatomical origin within the olfactory cleft. Intracranial neoplasms, particularly those located or involving the anterior cranial fossa, may also produce olfactory deficits. Examples of pathologies commonly encountered in this location include olfactory groove meningiomas (see Fig. 18.2), frontal lobe gliomas, pituitary adenomas, and craniopharyngiomas (Bakay, 1984; Allis and Leopold, 2012). Neoplasms within the temporal lobe may impair olfaction with up to 25% of such cases presenting as such (Wrobel and Leopold, 2004a). Tumors in this location are also known to produce olfactory hallucinations (Li et al., 1994).

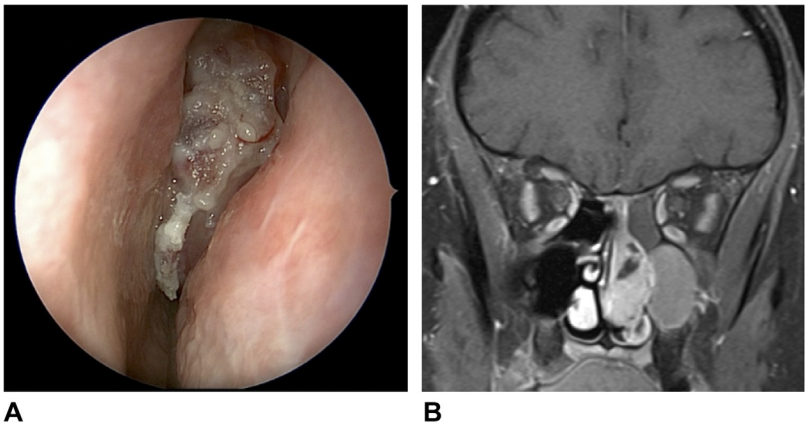

Fig. 18.1. Esthesioneuroblastoma. Endoscopic (A) and radiologic (B) appearance of an esthesioneuroblastoma. T1-weighted, contrast-enhanced MRI with coronal views (B) demonstrates a hyperintense lesion within the left nasal cavity, contiguous with the olfactory cleft from which this lesion is known to originate. Adjacent sinus opacification is seen within the left maxillary and ethmoid sinuses due to obstruction of the outflow drainage pathway by the tumor.

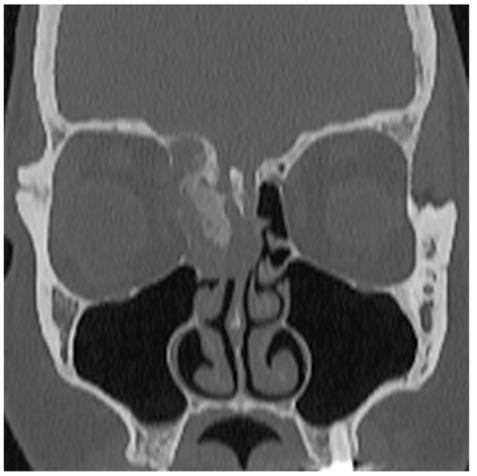

Fig. 18.2. CT scan of an anterior cranial fossa meningioma. Coronal cut, bone window, noninfused CT scan of the paranasal sinuses demonstrates a soft tissue mass epicentered within the right ethmoid cavity and olfactory cleft with attenuation of the right medial orbital wall indicative of orbital dehiscence. Marked hyperostosis, which is typical of meningiomas involving the skull base, is present.

Chronic rhinosinusitis (CRS)

CRS is an epidemiologically important inflammatory condition of the paranasal sinuses with well documented, wide reaching economic implications (Halawi et al., 2013; Caulley et al., 2015; Smith et al., 2015; DeConde and Soler, 2016). As per the most recent 2012 European position paper on rhinosinusitis (EPOS), CRS may be defined as the presence of two or more symptoms, one of which must include nasal obstruction or nasal discharge, with or without facial pain/pressure and/or smell disturbance for a period exceeding 12 weeks (Fokkens et al., 2012). Clinically, CRS is broadly classified into two subtypes, CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP) on the basis of presence or absence of bilateral nasal polyps as identified on nasal endoscopy (Schwartz et al., 2016b). Despite an exhaustive body of literature dedicated to this disease process, the exact mechanism underlying the pathophysiology of CRS continues to elude researchers in the field. The medical management of CRS, therefore, remains empiric, with a variety of oral and topical therapies proposed directed at combatting both inflammatory and potential microbial contributions to the disease. In the absence of a clinical response, ESS is undertaken with an estimated 450, 000 cases performed annually in the United States alone (Meltzer et al., 2004). In addition to restoring mucociliary drainage pathways for the paranasal sinuses, ESS optimizes CRS disease control by optimizing sinonasal mucosal distribution of topical therapies (Harvey et al., 2008, 2010; Abouali et al., 2012; Snidvongs et al., 2013; Thomas 3rd et al., 2013; Bahmanzadeh et al., 2015; Wofford et al., 2015; Barham et al., 2016; Zhao et al., 2016).

Impaired olfaction is a frequent complaint among patients afflicted with CRS, with a reported incidence of up to 80% in these patients (Raviv and Kern, 2004; Rosenfeld et al., 2007; Jiang et al., 2008; Soler et al., 2008; Litvack et al., 2009b). The degree and likelihood of impairment, however, appears to vary based on CRS disease subtype with the most severely and frequently impaired patients comprising those with nasal polyposis (CRSwNP) (Apter et al., 1995; Simola and Malmberg, 1998; Vento et al., 2001; Wolfensberger and Hummel, 2002) (see Figs. 18.3 and 18.4). Employing a regression model, Alt et al. (2014) identified nasal polyposis as the strongest predictor of olfactory impairment in a multicenter cohort of patients with CRS or recurrent acute sinusitis. CRS disease severity, as measured by standardized radiologic and endoscopic scoring systems, was also shown to correlate strongly with the severity of olfactory dysfunction, which concurs with findings reported elsewhere in the literature (Gupta et al., 2014). Soler et al. recently reported a novel endoscopic scoring system entitled the olfactory cleft endoscopic scale that demonstrated high intrarater and interrater reliability in addition to correlating strongly with both self-reported olfaction and objective olfactory evaluation (Soler et al., 2016a). In addition to traditional CT staging systems for CRS, radiologic evaluations of key anatomical sinonasal subsites have also proved valuable in predicting the degree of olfactory burden in CRS patients. Quantitative assessment of olfactory

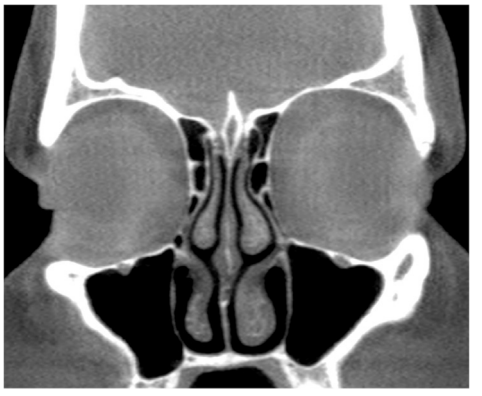

Fig. 18.3. Normal CT scan of the paranasal sinuses. Coronal cut, bone window, noninfused CT scan of the paranasal sinuses demonstrates normal sinus aeration with absence of sinus mucosal thickening as well as a patent nasal airway and olfactory cleft. Healthy appearing paranasal sinuses are characterized radiologically by an immediate transition from the bone (*white*) of the sinus wall to the air (*black*) of the sinus cavity without any intermediating soft tissue (*gray*) as seen in Fig. 18.1.

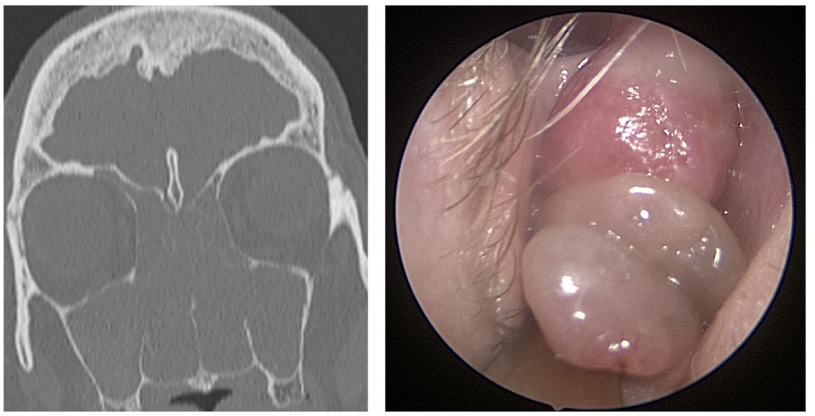

Fig. 18.4. Chronic rhinosinusitis (CR) with nasal polyposis. Radiologic (A) and endoscopic (B) appearance of CR with nasal polyposis (CRSwNP). Coronal cut, bone window, noninfused CT scan of the paranasal sinuses (A) demonstrates complete opacification of the nasal airway, frontoethmoidal recess, ethmoid and maxillary paranasal sinuses consistent with severe CRSwNP. Complete opacification of the olfactory cleft bilaterally is also noted. Endoscopic view (B) of the same patient reveals a significant burden of nasal polyposis extending to the nasal floor and to the anterior most limit of the nasal cavity known as the nasal vestibule, which is lined by hair bearing skin.

cleft opacification employing three-dimensional computerized volumetric analysis was recently demonstrated to significantly correlate with objective measures of olfaction (Soler et al., 2015). Additional clinical predictors of olfactory impairment in CRS-identified patients in the literature include comorbid asthma, smoking history, advanced age, recalcitrant disease, and aspirin intolerance (Litvack et al., 2008; Alt et al., 2014). Histologic and serologic correlates of olfactory impairment in CRS patients include mucosal and serum eosinophilia as well as ethmoid mucosa basement membrane thickening (Soler et al., 2009; Hox et al., 2010).

The pathophysiology of CRS-related smell dysfunction has historically been conceived as being conductive in nature. This concurs with the aforementioned predisposition for olfactory impairment among patients with CRSwNP due to restricted nasal airflow. Clinically, this is best reflected by the transient improvement in nasal airflow and olfaction associated with a reduction in nasal polyp burden frequently observed in these patients following the administration of a high dose corticosteroid taper. In accordance with these observations, several studies have demonstrated the impact of regional nasal anatomy and airflow on olfactory function. Damm et al. demonstrated a significant correlation between olfactory thresholds and the volume of specific intranasal subsites (olfactory cleft and internal nasal valve) as assessed by MRI (Damm et al., 2002). Employing a computational fluid dynamics (CFD) model to simulate nasal airflow, Zhao et al. demonstrated significant variations in airflow and odorant transport when the same two anatomical regions were altered. While nasal airflow overall did not vary, airflow to the olfactory region and odorant uptake rose dramatically when airway patency at these two subsites were improved (Zhao et al., 2004). Zhao expanded on these findings by demonstrating a significant correlation between olfactory thresholds and odorant absorption within the olfactory region when CFD simulations were applied to a CRS patient cohort (Zhao et al., 2014).

Increasingly, findings have come to light providing evidence in favor of a neurosensorial contribution to the olfactory impairment observed in CRS patients. The earliest evidence in support of this mechanism was a study by Kern in which olfactory mucosa of CRS patients undergoing sinus surgery was histopathologically analyzed for inflammatory changes. The majority of patients manifesting objective olfactory deficits were found to exhibit pathologic inflammatory cellular infiltrate within the olfactory neuroepithelium (Kern, 2000). Further work by Kern et al. provided additional histologic evidence in which increased apoptotic activity was identified within the olfactory neuroepithelium of CRS patients manifesting an olfactory deficit (Kern et al., 2004). The findings mentioned earlier are confirmed by additional research demonstrating pathologic alterations to olfactory epithelial architecture in CRS patients with olfactory impairment. Histologic findings of olfactory mucosa noted in CRS patients with persistent olfactory loss included epithelial atrophy, squamous metaplasia, reduction in olfactory receptor density, and loss of orderly cell arrangement characteristic of normal olfactory epithelium (Lee et al., 2000; Konstantinidis et al., 2010). A neurosensorial mechanism of smell loss in CRS for which surgical palliation of the nasal airway following ESS fails to improve olfactory function resonates clinically in those patients. Taken together, the literature to date suggests that a combination of both conductive and neurosensorial mechanisms in CRS likely exists. This may account for the variability in olfactory recovery

observed in these patients following medical and surgical management despite objective endoscopic and radiologic improvements in disease burden.

SINONASAL CLINICAL EVALUATION OF OLFACTORY DISTURBANCES

The initial approach to a patient presenting with diminished olfaction demands, above all, a thorough clinical history and physical examination. Patients will often describe altered taste perception but, upon further review, will acknowledge intact taste (sweet, salty, sour, bitter, and umami) with impaired flavor perception. Only rarely will impaired flavor perception represent a true gustatory dysfunction. The vast majority of such complaints will be olfactory in etiology (Wrobel and Leopold, 2004a) due to the olfactory system's contribution to flavor perception through retronasal airflow (Hadley et al., 2004). A detailed history begins with a temporal analysis of the olfactory disturbance, including symptom onset, duration, and evolution. It is essential to quantify the degree of olfactory impairment (hyposmia or anosmia) in addition to probing for any qualitative disturbances in olfactory ability (parosmia or phantosmia).

The three most common etiologies associated with olfactory impairment are head trauma, URTI, and sinonasal disease (Seiden and Duncan, 2001), and a proper history should explicitly elicit the occurrence of such predisposing factors in relation to symptom onset. Contemporary diagnostic criteria for CRS include a history of facial pressure/pain, nasal obstruction/congestion, and purulent/discolored rhinorrhea in association with smell disturbance. Many CRS patients, particularly those with nasal polyps, present with an atopic history, and a review of the patient's past medical history should inquire regarding comorbid asthma and allergic rhinitis. Transient olfactory improvement following administration of a high dose corticosteroid taper or topical corticosteroids is commonly seen in patients with CRS. Smell disturbances in this context are typically conductive in nature with olfactory recovery resulting from improved nasal patency following steroid administration.

Neoplastic etiologies (sinonasal or intracranial) may be suspected in the presence of prior epistaxis, unilateral nasal obstruction, or neurologic symptoms such as cranial neuropathies. Foster Kennedy syndrome describes the triad of ipsilateral optic nerve atrophy, contralateral papilledema, and anosmia. It was first described in association with tumors of the anterior cranial fossa causing direct compression of the ipsilateral optic nerve, olfactory bulbs, and intracranial hypertension, resulting in edema of the contralateral optic nerve. It has since been described in association with a variety of other nonneoplastic causes resulting in the same constellation of symptoms and termed pseudo Foster–Kennedy syndrome (Massey and Schoenberg, 1984). Patients should also be questioned regarding a personal or familial history of neurodegenerative conditions such as Alzheimer's or Parkinson's disease. Olfactory dysfunction is a cardinal feature of both of these conditions with up to 90% of patients affected within the early stages of the disease despite most being unaware of this deficit prior to olfactory testing (Doty, 2009, 2012a, b). Olfactory deficits are also seen in Huntington's disease, though such symptoms are primarily reported in patients who already manifest traditional signs of the disease (Moberg and Doty, 1997). A potential psychiatric history should be explored given the well-established association between olfactory impairment and schizophrenia (Moberg and Turetsky, 2003; Turetsky et al., 2003a, b; Nguyen et al., 2010; Rupp, 2010; Moberg et al., 2014). A history of delayed puberty or infertility may be indicative of idiopathic hypogonadotropic hypogonadism (IHH). The confluence of the latter and anosmia characterizes Kallman's syndrome, a rare genetic condition with variable inheritance. Abnormal intrauterine development in these patients results in both an altered hypothalamic–pituitary–gonadal axis and hypoplasia/aplasia of the olfactory bulb/tracts (Ottaviano et al., 2015). The olfactory deficit in patients with IHH varies along a continuum from complete anosmia (Kallman syndrome) to hyposmia to normosmia, with about one-third of patients displaying each phenotype as reported in a recent study of a large IHH cohort (Lewkowitz-Shpuntoff et al., 2012).

Additional relevant points to be addressed upon review of the patient's past medical history include any oncologic history or prior external beam radiation to the head and neck region. Patients must be questioned regarding past surgical history including prior sinonasal, facial, or neurosurgical interventions. Prior environmental toxin or fume exposure may be elicited upon review of the patient's occupational history (Doty, 2015). The patient's social history should be assessed for illicit intranasal drug use, topical decongestant abuse, and cigarette smoke, the latter of which is known to adversely affect olfactory function in a dose-related manner (Frye et al., 1990; Katotomichelakis et al., 2007).

Following a comprehensive clinical history, it behooves the consulting physician to perform a complete head and neck examination in the evaluation of a patient of a patient complaining of olfactory dysfunction. Particular importance should be directed toward a thorough endonasal examination in view of identifying a conductive etiology of olfactory loss. This should not merely entail an anterior rhinoscopic examination. The latter has been deemed insufficiently sensitive in discerning conductive pathology with over 50% of such cases missed when a nasal speculum examination was

employed in isolation. This figure is reduced to just under 10% when nasal endoscopy is performed in conjunction (Seiden and Duncan, 2001). Elements of the endoscopic examination worth highlighting include a nasal septum deflection, turbinate hypertrophy, mucosal edema, purulent or tenacious secretions, synechia, nasal polyps, and masses. Patency of the olfactory cleft should be evaluated, should the patient's anatomy allow for it, with visualization of the air space between the middle turbinate and nasal septum. Assessment of cranial nerve function should also be performed in addition to a fundoscopic examination in view of identifying papilledema. Should the history elicit suspicions of a neurodegenerative condition or dementia, a complete neurologic exam is recommended, including a Mini-Mental Status examination (Wrobel and Leopold, 2004a, b).

TREATMENT OF QUANTITATIVE SINONASAL OLFACTORY DISTURBANCES

Medical therapy

The vast majority of literature pertaining to the treatment of sinonasal-attributed olfactory impairment has been conducted in patients with CRS. Despite the enigma of CRS pathophysiology, current American (Rosenfeld et al., 2015) and European (Fokkens et al., 2012) guidelines support the empiric use of medical therapies in the management of CRS, with surgical intervention reserved for those patients who fail to respond to "maximal medical therapy (MMT)." Though a consensus regarding what exactly MMT entails is notably lacking in the literature, a recent systematic review of MMT protocols prior to ESS identified that the most common therapeutic regimen consisted of an 8-week course of topical intranasal corticosteroids, a 3-week course of broad spectrum or culture directed antibiotics, and a 2-week course of systemic corticosteroids (Dautremont and Rudmik, 2015).

The administration of corticosteroids in CRS is widely practiced consistent with a consensus in the literature regarding a local inflammatory basis for CRS. Corticosteroids are potent antiinflammatory agents with multiple previously described mechanisms of action including the modulation of inflammatory gene transcription, inflammatory cell infiltration and proinflammatory mediators (Mullol et al., 2009). Corticosteroids are employed both topically and systemically in the management of CRS, with the former preferred as long-term maintenance therapy given its concentration of drug delivery locally with limited systemic absorption and adverse effects. Topically delivered corticosteroids have long been a workhorse in the daily, long-term management of CRS with a plethora of evidence demonstrating its effectiveness in this regard. Topically administered steroids may vary based on mode of delivery, classified as either a standard or nonstandard formulation. A standard delivery topical corticosteroid entails a dose-metered spray that has been approved for nasal use by the Food and Drug Administration (Rudmik et al., 2013). This therapy has been assigned the highest level of evidence and grade of recommendation for the management of both CRSwNP and CRSsNP by EPOS 2012 (Fokkens et al., 2012) with a recent evidence-based review (Rudmik et al., 2013) reiterating these conclusions. Significant improvements in both objective and subjective clinical outcomes of CRS have been consistently demonstrated with this treatment modality. The strength of evidence of systemic (oral) corticosteroids differs considerably, however, based on the presence or absence of nasal polyposis. Recommendations for the use of oral corticosteroids in CRSwNP is founded upon well established, high levels of evidence, whereas a lack of well-controlled studies demonstrating its efficacy in CRSsNP has curtailed support for its use in this patient subset (Poetker et al., 2013).

While the value of the aforementioned therapies have been well established in the overall symptomatic management of CRS, their efficacy in so far as olfactory-specific outcomes is concerned has received comparatively less attention. The most recent and comprehensive review of olfactory outcomes in CRS following medical therapy comprised a systematic review and meta-analysis by Banglawala et al. (2014). Unfortunately, only randomized control trials (RCTs) evaluating treatment efficacy in CRSwNP were included in the analysis. A total of 28 RCTs were evaluated with only five trials providing sufficient data for meta-analysis. A meta-analysis of the five studies evaluating oral corticosteroids demonstrated statistically significant improvements in subjective and objective olfactory outcomes compared to placebo. Of note, all of these studies included limited follow up periods (2–8 weeks) consistent with clinical observations concerning the transient olfactory benefit of oral corticosteroids. The evidence in favor of an olfactory benefit following topical steroid administration was comparatively weaker. Insufficient study data precluded data pooling for the purposes of a meta-analysis. A majority of studies (16/22) demonstrated significant improvement in subjective olfactory outcomes following a trial of topical steroids compared to placebo, whereas only a single study (1/8) reported a significant improvement in objective olfactory outcomes. When studies comprising a combination treatment of oral and topical corticosteroids were evaluated, half the studies (3/6) demonstrated a significant subjective olfactory benefit, whereas a single study (1/3) reported a significant improvement in objective olfactory outcomes. Other

studies included in this review evaluating alternative medical therapies for CRSwNP received little scientific support for olfactory-specific improvements. These therapies included oral antibiotics (doxycycline and azithromycin), topical antifungals (amphotericin B), herbal therapies, and anti-IgE (omalizumab) (Banglawala et al., 2014). A more recent study compared three different modalities of corticosteroid administration (oral corticosteroids, dose-metered budesonide nasal spray, and sonic nebulized budesonide) in CRS for which both disease subsets (CRSwNP and CRSsNP) were equally represented. Interestingly, oral and nebulized corticosteroids yielded equivalent, clinically relevant improvements in objective olfactory measures, which were significantly higher than the standard intranasal formulation. While the latter proved ineffective, the authors noted that the abbreviated duration of therapy (16 days) compared to what is ordinarily employed in clinical practice could have contributed to the absence of effect (Reychler et al., 2015).

Despite representing the most common cause of olfactory dysfunction, there is likewise a limited body of literature demonstrating effective pharmacologic therapies for the treatment of postviral olfactory loss. In a systematic review by Harless and Liang, 8 articles out of a possible 445 abstracts were identified as meeting the study inclusion criteria totaling 563 patients. The various treatments investigated included oral corticosteroids, local corticosteroid injections, zinc sulfate, α lipoic acid, caroverine, vitamin A, Gingko Biloba, and minocycline. The majority of included studies were unfortunately of poor quality with only three studies comprising RCTs. Benefit in objective olfactory outcomes was noted in four of the studied therapies (oral corticosteroid, injected corticosteroid, α lipoic acid, and caroverine), with a single study (caroverine) employing a controlled methodology. Unfortunately, the latter study sample comprised a variety of neurosensorial etiologies with no details regarding the etiologic makeup of each treatment group. It was therefore unclear what benefit patients with postviral olfactory loss specifically derived, given that treatment response was not stratified based on etiology. In all of the studies mentioned so far, the proportion of study patients manifesting objective olfactory improvement represented a minority of the study sample with the highest response rate seen with local corticosteroid injection (49.6%). While promising, the reported frequency and duration of the therapy (every 2 weeks for 8–10 weeks) of locally injected corticosteroids raises serious concerns regarding the clinical feasibility and cost-effectiveness of this treatment modality. Finally, no evidence was identified in support of topical corticosteroids either alone or adjunctive to systemic corticosteroid therapy (Harless and Liang, 2016).

Surgical interventions

Surgical intervention in the form of ESS is frequently employed as part of the algorithmic approach for the symptomatic management of medically refractory CRS. A wealth of literature has demonstrated that ESS confers significant clinical benefit both in terms of subjective and objective CRS-related outcomes, with a maintenance of these outcomes observed long term (Smith et al., 2005, 2010, 2011, 2014; Bhattacharyya, 2007; Litvack et al., 2007; Hopkins et al., 2009, 2015; Tan and Lane, 2009; DeConde et al., 2014; Georgalas et al., 2014). Olfactory-specific outcomes following ESS have proved to be less uniform with disparate findings reporting either a significant, minimal, or absent olfactory benefit (Jiang et al., 2008; Soler et al., 2008; Chester, 2009; Chester et al., 2009). The variability in olfactory benefit following surgical intervention for CRS has been attributed to the complex and multifactorial pathophysiology underlying CRS, which is likely both obstructive and neurosensory in etiology (Rudmik and Smith, 2012). This has led to an interesting wave of research bent on further elucidating our understanding of the role of ESS in improving CRS-related olfactory dysfunction through the identification of predictive factors associated with olfactory improvement. While some authors have failed to identify such factors (Jiang et al., 2009), others have demonstrated significant associations between postoperative olfactory outcomes and patient demographics, clinical variables, and preoperative imaging.

In a prospective, multiinstitutional trial comprising over 100 CRS patients who underwent ESS, Litvack et al. identified preoperative olfactory function as a significant predictor of postoperative olfactory improvement. Contrary to their initial hypothesis, patients with severe olfactory dysfunction (anosmia) experienced significant recovery of olfaction, which was sustained at 1-year follow up, whereas patients with milder olfactory dysfunction (hyposmia) did not. Nasal polyposis was also determined to be a significant predictor of improved postoperative olfactory outcome at 12-month follow up. Interestingly, a statistically significant effect modification was noted between preoperative olfactory status and nasal polyposis following a multivariate linear regression analysis. The authors reasoned that the difference in olfactory outcomes observed might have been attributed to complete obstruction of the olfactory cleft in anosmics with nasal polyposis. An obstructive etiology would thereby be amenable to olfactory optimization following surgical extirpation. In contrast, the olfactory impairment in hyposmics without nasal polyposis may have been multifactorial, with ESS less likely to confer improvement in the setting of inflammation-induced

neurosensory involvement (Litvack et al., 2009a). The value of preoperative olfactory function and/or nasal polyposis as predictors of postoperative olfactory recovery has since been replicated by several other studies (Pade and Hummel, 2008; Soler et al., 2010; DeConde et al., 2015; Kim et al., 2015; Andrews et al., 2016). Moreover, these two variables have also been shown to be independent preoperative predictors of postoperative improvements in QOL outcomes (Katotomichelakis et al., 2014).

Despite considerable symptomatic improvements attributed to ESS, a significant proportion of patients will require revision sinus surgery. This appears to be an ongoing area of concern despite the advent of multiple technological advances since the initial inception of ESS. In a recent UK based epidemiologic study of CRS, 20% of CRSwNP patients reported undergoing multiple ESS, with this figure rising to 23% when including patients with allergic fungal rhinosinusitis. The estimated cost burden of repeated surgeries is likewise significant, with a total cost to the U.K. National Health Service likely to be upwards of £30 million annually (Philpott et al., 2015). While both objective and surgical outcomes of CRS appear to improve following revision ESS (McMains and Kountakis, 2005; Lee et al., 2008; Shen et al., 2011), the exact impact on olfactory recovery is less well known. A recent prospective study of 32 patients who underwent revision sinus surgery determined the rate of objective olfactory improvement between 12 and 24 months postoperatively to be 48% (Hsu et al., 2013). Other authors have highlighted the prognostic significance of prior surgery in determining the likelihood of olfactory improvement with repeat interventions. The overall consensus among these studies is that prior sinus surgery is a strong predictor of poor olfactory outcomes following subsequent revision sinus surgery (Danielides et al., 2009; Katotomichelakis et al., 2010; Nguyen et al., 2013, 2015). Furthermore, the likelihood of olfactory function recovery appears to diminish with each subsequent surgical revision with those patients undergoing more procedures experiencing less improvement than those with fewer repeat surgeries. A possible explanation for this finding is surgery-induced injury to the olfactory epithelium with subsequent replacement by nonfunctional respiratory epithelium (Nguyen et al., 2015). Coupled with this observation is the influence of the duration of the olfactory deficit and age on olfactory improvement following sinus surgery. Increases in both of these variables have similarly been shown to portend a poor prognosis in so far as olfactory recovery following ESS (Danielides et al., 2009; Katotomichelakis et al., 2010; Nguyen et al., 2013). This finding is perhaps not surprising given the potential relationship between these three variables: patients subjected to a greater number of surgeries might experience an olfactory deficit for a longer duration of time and may, in turn, be older in age.

Radiologic markers of CRS have also proved informative as it relates to postoperative olfactory recovery. In a prospective study by Soler et al., only baseline CT scores, as graded by a standardized radiologic CRS grading system, were determined to significantly predict postoperative improvement in olfactory-specific QOL (Soler et al., 2016b). Additional studies have provided further insight into the role of preoperative imaging in this regard by evaluating disease severity within various anatomical subsites of the sinonasal cavity. Kim et al. investigated the relationship between the radiologic status of the olfactory cleft and postoperative olfactory outcomes in CRSwNP. The authors determined that preoperative opacification of the anterior olfactory cleft had the strongest negative correlation with postoperative olfactory assessment than any other anatomical region evaluated. This region, the authors reasoned, is a significant determinant of olfactory cleft airflow. Moreover olfactory epithelium appears to be more densely distributed anteriorly than previously assumed. Altogether, disease involvement of this region, given its previously stated role in the olfactory pathway, would appear to significantly influence the potential for olfactory recovery following surgical intervention (Kim et al., 2011). In a related study, Kim et al. evaluated the relationship between postoperative olfactory performance and radiologic disease severity within various regions of the sinonasal cavity. Individuals demonstrating the greatest olfactory benefit were those with preoperative evidence of partial anterior ethmoid opacification. The authors provided a limited explanation for this finding, speculating only that the olfactory impairment in such individuals may have been more conductive in nature and, therefore, more amenable to surgical intervention (Kim et al., 2015).

Additional investigations regarding the impact of histologic markers of CRS on olfactory outcomes have been comparatively less fruitful. In a study by Soler et al., a positive correlation was observed between olfactory impairment, basement membrane thickening, and tissue eosinophilia. Yet, once nasal polyposis was controlled, these and other histopathology inflammatory markers failed to predict the likelihood of postoperative olfactory recovery (Soler et al., 2010). Two other studies that accounted for the histopathology of obstructive lesions within the olfactory cleft (eosinophlic polyps vs respiratory epithelial adenomatoid hamartoma) in CRS patients likewise failed to predict postoperative olfactory outcomes on the basis of this variable (Nguyen et al., 2013, 2015).

TREATMENT OF QUALITATIVE OLFACTORY DISTURBANCES

Medical therapy

Qualitative olfactory disturbance is a poorly understood clinical entity with an elusive pathophysiology for which both central and peripheral theories have been proposed (Leopold, 2002; Hong et al., 2012). Qualitative olfactory impairment often occurs in conjunction with a quantitative olfactory loss, with one series reporting a partial or complete loss in up to 100% of patients manifesting a distortion in smell perception (Bonfils et al., 2005). Many patients will report a gradual decrease in symptoms over time, with over 50% of phantosmia patients and close to 30% of parosmic patients experiencing a relief in symptoms within a 12-month observation period according to one series (Reden et al., 2007). This has led some authors to advocate in favor of a watchful waiting approach as an initial management strategy for patients reporting an olfactory distortion (Hong et al., 2012). Wherein the olfactory distortion persists, a variety of medical interventions have been proposed, though none of them are supported by particularly high levels of scientific evidence, nor do they convey long-term normalization of olfactory function. The simplest and most economical medical therapy involves the application of nasal saline drops in the head down and forward position (otherwise known as Moffet's position), which may be placed at frequent intervals in limitless quantity. While this is not deemed to be effective in all instances, it may provide a short-lived symptom reduction for those patients whose olfactory distortion can be inhibited with nasal occlusion, which is the same effect produced with the application of nasal saline drops (Leopold, 2002; Hong et al., 2012). Oxymetazoline, a topical decongestant in which a rebound mucosal edema (termed rhinitis medicamentosa) ensues when applied long term, may be similarly effective by obstructing nasal airflow (Leopold, 2002). An additional conservative strategy involves the withdrawal and/or replacement of medications suspected of being causally related to the olfactory distortion (Hong et al., 2012).

The employment of α lipoic acid in patients with postviral olfactory dysfunction was the subject of a prospective noncontrolled trial by Hummel et al., for which the incidence of parosmia at the time of study's onset approached 50%. The compound is a commonly consumed nutritional supplement that has been employed in the treatment of diabetic neuropathy. The therapy was administered for an average period of 4.5 months and was deemed beneficial, given the reduction in the incidence of parosmia (22%) observed at the conclusion of the treatment period (Hummel et al., 2002). Topical application of cocaine solution, first proposed by Zilstorff (1966), has also been the subject of a recent retrospective case series of six phantosmia patients. As a topical anesthetic, topical cocaine was initially theorized to counter olfactory distortions by temporarily anesthetizing peripheral olfactory neurons. The study set out to confirm Zilstorff's initial observation of a 100% cure rate of parosmia following topical cocaine application. Although all patients in the current study reported anosmia with absence of the phantom smell following cocainization, this effect was transient and a majority of patients reported a return in olfactory distortion within 1.5 days. Moreover, when questioned over a year and a half after initial cocainization, all patients reported ongoing phantosmia more than 95% of the time. The majority of patients' symptoms were either unchanged or intensified compared to pretreatment levels. The authors thereby rejected this therapy as a long-term treatment strategy for distorted olfaction (Leopold and Hornung, 2013).

Surgical intervention

Medically refractory distortions in olfactory perception may be addressed surgically, with a variety of techniques described with high reported rates of success. Though open neurosurgical approaches have been successfully reported (Kaufman et al., 1988; Markert et al., 1993), the significant risks and morbidity resulting from a craniotomy have ultimately limited their widespread use. With the advent of ESS in the 1980s, minimally invasive, endoscopic approaches to the skull base have increasingly been adopted as standard of practice in view of circumventing potential morbidities associated with traditional external approaches (Schwartz et al., 2016a). In 1991, Leopold et al. described the first case report of a young, 26-year-old female patient who underwent transnasal endoscopic excision of the olfactory neuroepithelium for a debilitating, medically refractory phantosmia. The procedure was deemed a resounding success, yielding both a resolution in the phantosmia in addition to preserving the patient's baseline olfactory function (Leopold et al., 1991). The authors subsequently followed this up with a retrospective case series of eight patients who underwent the procedure. Complete resolution of the phantosmia was achieved in seven of eight patients with an improvement or maintenance of the patients' preoperative olfactory function. The authors stated inclusion criteria for the procedure involved chronic (>2 years) unilateral phantosmia, which could be eliminated following application of topical cocaine. The procedure involves stripping the olfactory mucosa along the length of the cribriform plate with severing of the underlying olfactory fila. A free mucoperiosteal graft is then placed overlying the surgical defect to limit the potential for a postoperative

cerebrospinal fluid leak. Overall, the procedure offers significant promise for symptomatic management of medically refractory olfactory distortions without comprising underlying olfactory ability (Leopold et al., 2002).

CONCLUSIONS AND FUTURE DIRECTIONS

Olfaction represents a critical chemosensory human function in its ability to alert individuals regarding potential environmental dangers in addition to serving as an important determinant of daily QOL. Though olfactory disturbances have historically not garnered widespread interest within the medical community, the last decade has been witness to an increasing awareness and sensitivity to the considerable handicap engendered by the loss of this sense. This has translated into an increasingly diverse body of scientific literature determined to advance our understanding of the etiologic mechanisms of olfactory injury, prognostic determinants of olfactory recovery, and effective treatment modalities for olfactory disturbances. Increasing healthcare reform in the developed world and the anticipated transition to healthcare payment models that reward quality outcomes will no doubt serve to catalyze further interest in this poorly understood yet clinically significant disease entity.

As one of the cardinal symptoms of CRS, olfactory dysfunction contributes considerably to the extraordinary disease burden afflicting this patient cohort. Unfortunately, it is among the most refractory to contemporary medical and surgical therapies, with limited scientific evidence at present supporting viable therapeutic alternatives. Future research must be directed at furthering our understanding of the pathophysiologic mechanisms of olfactory dysfunction in this clinical context with the hope of promoting therapeutic modalities that either preserve and/or restore olfaction. This will also enhance our ability as clinicians to counsel patients regarding the nature of their disability and better orient their expectations regarding the likelihood of olfactory improvement.

References

Abouali O, Keshavarzian E, Farhadi Ghalati P et al. (2012). Micro and nanoparticle deposition in human nasal passage pre and post virtual maxillary sinus endoscopic surgery. Respir Physiol Neurobiol 181: 335–345.

Adelman BT (1995). Altered taste and smell after anesthesia: cause and effect? Anesthesiology 83: 647–649.

Allis TJ, Leopold DA (2012). Smell and taste disorders. Facial Plast Surg Clin North Am 20: 93–111.

Alt JA, Mace JC, Buniel MC et al. (2014). Predictors of olfactory dysfunction in rhinosinusitis using the brief smell identification test. Laryngoscope 124: E259–E266.

Andrews PJ, Poirrier AL, Lund VJ et al. (2016). Outcomes in endoscopic sinus surgery: olfaction, NOSE scale and quality of life in a prospective cohort study. Clin Otolaryngol 41: 798–803.

Apter AJ, Mott AE, Frank ME et al. (1995). Allergic rhinitis and olfactory loss. Ann Allergy Asthma Immunol 75: 311–316.

Bachar G, Goldstein DP, Shah M et al. (2008). Esthesioneuroblastoma: the Princess Margaret hospital experience. Head Neck 30: 1607–1614.

Bahmanzadeh H, Abouali O, Faramarzi M et al. (2015). Numerical simulation of airflow and micro-particle deposition in human nasal airway pre- and post-virtual sphenoidotomy surgery. Comput Biol Med 61: 8–18.

Bakay L (1984). Olfactory meningiomas. The missed diagnosis. JAMA 251: 53–55.

Banglawala SM, Oyer SL, Lohia S et al. (2014). Olfactory outcomes in chronic rhinosinusitis with nasal polyposis after medical treatments: a systematic review and meta-analysis. Int Forum Allergy Rhinol 4: 986–994.

Barham HP, Ramakrishnan VR, Knisely A et al. (2016). Frontal sinus surgery and sinus distribution of nasal irrigation. Int Forum Allergy Rhinol 6: 238–242.

Bhattacharyya N (2007). Progress in surgical management of chronic rhinosinusitis and nasal polyposis. Curr Allergy Asthma Rep 7: 216–220.

Biedlingmaier JF, Whelan P, Zoarski G et al. (1996). Histopathology and CT analysis of partially resected middle turbinates. Laryngoscope 106: 102–104.

Bonfils P, Avan P, Faulcon P et al. (2005). Distorted odorant perception: analysis of a series of 56 patients with parosmia. Arch Otolaryngol Head Neck Surg 131: 107–112.

Bonfils P, Faulcon P, Tavernier L et al. (2008). Home accidents associated with anosmia. Presse Med 37: 742–745.

Briner HR, Simmen D, Jones N (2003). Impaired sense of smell in patients with nasal surgery. Clin Otolaryngol Allied Sci 28: 417–419.

Cain WS, Gent JF, Goodspeed RB et al. (1988). Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. Laryngoscope 98: 83–88.

Caulley L, Thavorn K, Rudmik L et al. (2015). Direct costs of adult chronic rhinosinusitis by using 4 methods of estimation: results of the US Medical Expenditure Panel Survey. J Allergy Clin Immunol 136: 1517–1522.

Chaaban MR, Chaudhry AL, Riley KO et al. (2015). Objective assessment of olfaction after transsphenoidal pituitary surgery. Am J Rhinol Allergy 29: 365–368.

Champion R (1966). Anosmia associated with corrective rhinoplasty. Br J Plast Surg 19: 182–185.

Chester AC (2009). Symptom outcomes following endoscopic sinus surgery. Curr Opin Otolaryngol Head Neck Surg 17: 50–58.

Chester AC, Antisdel JL, Sindwani R (2009). Symptom-specific outcomes of endoscopic sinus surgery: a systematic review. Otolaryngol Head Neck Surg 140: 633–639.

Cowart BJ, Young IM, Feldman RS et al. (1997). Clinical disorders of smell and taste. Occup Med 12: 465–483.

Croy I, Olgun S, Joraschky P (2011). Basic emotions elicited by odors and pictures. Emotion 11: 1331–1335.

Cullen MM, Leopold DA (1999). Disorders of smell and taste. Med Clin North Am 83: 57–74.

Dalton P (2004). Olfaction and anosmia in rhinosinusitis. Curr Allergy Asthma Rep 4: 230–236.

Damm M, Vent J, Schmidt M et al. (2002). Intranasal volume and olfactory function. Chem Senses 27: 831–839.

Danielides V, Katotomichelakis M, Balatsouras D et al. (2009). Evaluation of prognostic factors for olfaction in nasal polyposis treated by endoscopic sinus surgery. Rhinology 47: 172–180.

Daramola OO, Becker SS (2015). An algorithmic approach to the evaluation and treatment of olfactory disorders. Curr Opin Otolaryngol Head Neck Surg 23: 8–14.

Dare AO, Balos LL, Grand W (2001). Olfaction preservation in anterior cranial base approaches: an anatomic study. Neurosurgery 48: 1142–1145: discussion 1145–1146.

Dautremont JF, Rudmik L (2015). When are we operating for chronic rhinosinusitis? A systematic review of maximal medical therapy protocols prior to endoscopic sinus surgery. Int Forum Allergy Rhinol 5: 1095–1103.

DeConde AS, Soler ZM (2016). Chronic rhinosinusitis: epidemiology and burden of disease. Am J Rhinol Allergy 30: 134–139.

DeConde AS, Mace JC, Bodner T et al. (2014). SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. Int Forum Allergy Rhinol 4: 972–979.

DeConde AS, Mace JC, Alt JA et al. (2015). Investigation of change in cardinal symptoms of chronic rhinosinusitis after surgical or ongoing medical management. Int Forum Allergy Rhinol 5: 36–45.

Deems DA, Doty RL, Settle RG et al. (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.

Doty RL (2009). The olfactory system and its disorders. Semin Neurol 29: 74–81.

Doty RL (2012a). Olfaction in Parkinson's disease and related disorders. Neurobiol Dis 46: 527–552.

Doty RL (2012b). Olfactory dysfunction in Parkinson disease. Nat Rev Neurol 8: 329–339.

Doty RL (2015). Neurotoxic exposure and impairment of the chemical senses of taste and smell. Handb Clin Neurol 131: 299–324.

Dulguerov P, Allal AS, Calcaterra TC (2001). Esthesioneuroblastoma: a meta-analysis and review. Lancet Oncol 2: 683–690.

Duncan HJ, Seiden AM (1995). Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. Arch Otolaryngol Head Neck Surg 121: 1183–1187.

Feiz-Erfan I, Han PP, Spetzler RF et al. (2005). Preserving olfactory function in anterior craniofacial surgery through cribriform plate osteotomy applied in selected patients. Neurosurgery 57: 86–93: discussion 86–93.

Fokkens WJ, Lund VJ, Mullol J et al. (2012). European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl 23: 1–298. 3 p preceding table of contents.

Frye RE, Schwartz BS, Doty RL (1990). Dose-related effects of cigarette smoking on olfactory function. JAMA 263: 1233–1236.

Georgalas C, Cornet M, Adriaensen G et al. (2014). Evidence-based surgery for chronic rhinosinusitis with and without nasal polyps. Curr Allergy Asthma Rep 14: 427.

Goldwyn RM, Shore S (1968). The effects of submucous resection and rhinoplasty on the sense of smell. Plast Reconstr Surg 41: 427–432.

Gopinath B, Anstey KJ, Sue CM et al. (2011). Olfactory impairment in older adults is associated with depressive symptoms and poorer quality of life scores. Am J Geriatr Psychiatry 19: 830–834.

Griffiths CF, Cutler AR, Duong HT et al. (2014). Avoidance of postoperative epistaxis and anosmia in endonasal endoscopic skull base surgery: a technical note. Acta Neurochir (Wien) 156: 1393–1401.

Gupta D, Gulati A, Singh I et al. (2014). Endoscopic, radiological, and symptom correlation of olfactory dysfunction in pre- and postsurgical patients of chronic rhinosinusitis. Chem Senses 39: 705–710.

Hadley K, Orlandi RR, Fong KJ (2004). Basic anatomy and physiology of olfaction and taste. Otolaryngol Clin North Am 37: 1115–1126.

Hahn I, Scherer PW, Mozell MM (1993). Velocity profiles measured for airflow through a large-scale model of the human nasal cavity. J Appl Physiol (1985) 75: 2273–2287.

Halawi AM, Smith SS, Chandra RK (2013). Chronic rhinosinusitis: epidemiology and cost. Allergy Asthma Proc 34: 328–334.

Harless L, Liang J (2016). Pharmacologic treatment for post-viral olfactory dysfunction: a systematic review. Int Forum Allergy Rhinol 6: 760–767.

Harvey RJ, Goddard JC, Wise SK et al. (2008). Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. Otolaryngol Head Neck Surg 139: 137–142.

Harvey RJ, Psaltis A, Schlosser RJ et al. (2010). Current concepts in topical therapy for chronic sinonasal disease. J Otolaryngol Head Neck Surg 39: 217–231.

Harvey RJ, Winder M, Davidson A et al. (2015). The olfactory strip and its preservation in endoscopic pituitary surgery maintains smell and sinonasal function. J Neurol Surg B Skull Base 76: 464–470.

Heilmann S, Hummel T (2004). A new method for comparing orthonasal and retronasal olfaction. Behav Neurosci 118: 412–419.

Hendriks AP (1988). Olfactory dysfunction. Rhinology 26: 229–251.

Honeybul S, Neil-Dwyer D, Lang DA et al. (2001). Extended transbasal approach with preservation of olfaction: an anatomical study. Br J Oral Maxillofac Surg 39: 149–157.

Hong SC, Holbrook EH, Leopold DA et al. (2012). Distorted olfactory perception: a systematic review. Acta Otolaryngol 132(Suppl. 1): S27–S31.

Hong SD, Nam DH, Park J et al. (2014). Olfactory outcomes after endoscopic pituitary surgery with nasoseptal "rescue" flaps: electrocautery versus cold knife. Am J Rhinol Allergy 28: 517–519.

Hopkins C, Slack R, Lund V et al. (2009). Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Laryngoscope 119: 2459–2465.

Hopkins C, Rudmik L, Lund VJ (2015). The predictive value of the preoperative sinonasal outcome test-22 score in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope 125: 1779–1784.

Hox V, Bobic S, Callebaux I et al. (2010). Nasal obstruction and smell impairment in nasal polyp disease: correlation between objective and subjective parameters. Rhinology 48: 426–432.

Hsu CY, Wang YP, Shen PH et al. (2013). Objective olfactory outcomes after revision endoscopic sinus surgery. Am J Rhinol Allergy 27: e96–100.

Hummel T, Heilmann S, Hüttenbriuk KB (2002). Lipoic acid in the treatment of smell dysfunction following viral infection of the upper respiratory tract. Laryngoscope 112: 2076–2080.

Jafek BW, Murrow B, Michaels R et al. (2002). Biopsies of human olfactory epithelium. Chem Senses 27: 623–628.

Jiang RS, Lu FJ, Liang KL et al. (2008). Olfactory function in patients with chronic rhinosinusitis before and after functional endoscopic sinus surgery. Am J Rhinol 22: 445–448.

Jiang RS, Su MC, Liang KL et al. (2009). Preoperative prognostic factors for olfactory change after functional endoscopic sinus surgery. Am J Rhinol Allergy 23: 64–70.

Kahilogullari G, Beton S, Al-Beyati ES et al. (2013). Olfactory functions after transsphenoidal pituitary surgery: endoscopic versus microscopic approach. Laryngoscope 123: 2112–2119.

Katotomichelakis M, Balatsouras D, Tripsianis G et al. (2007). The effect of smoking on the olfactory function. Rhinology 45: 273–280.

Katotomichelakis M, Gouveris H, Tripsianis G et al. (2010). Biometric predictive models for the evaluation of olfactory recovery after endoscopic sinus surgery in patients with nasal polyposis. Am J Rhinol Allergy 24: 276–280.

Katotomichelakis M, Simopoulos E, Tripsianis G et al. (2014). Predictors of quality of life outcomes in chronic rhinosinusitis after sinus surgery. Eur Arch Otorhinolaryngol 271: 733–741.

Kaufman MD, Lassiter KR, Shenoy BV (1988). Paroxysmal unilateral dysosmia: a cured patient. Ann Neurol 24: 450–451.

Kern RC (2000). Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. Laryngoscope 110: 1071–1077.

Kern RC, Conley DB, Haines 3rd GK et al. (2004). Pathology of the olfactory mucosa: implications for the treatment of olfactory dysfunction. Laryngoscope 114: 279–285.

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: e90–e94.

Kim YK, Hong SL, Yoon EJ et al. (2012). Central presentation of postviral olfactory loss evaluated by positron emission tomography scan: a pilot study. Am J Rhinol Allergy 26: 204–208.

Kim SW, Park KB, Khalmuratova R et al. (2013). Clinical and histologic studies of olfactory outcomes after nasoseptal flap harvesting. Laryngoscope 123: 1602–1606.

Kim BY, Kang SG, Kim SW et al. (2014). Olfactory changes after endoscopic endonasal transsphenoidal approach for skull base tumors. Laryngoscope 124: 2470–2475.

Kim BG, Kang JM, Shin JH et al. (2015). Do sinus computed tomography findings predict olfactory dysfunction and its postoperative recovery in chronic rhinosinusitis patients? Am J Rhinol Allergy 29: 69–76.

Kim DH, Hong YK, Jeun SS et al. (2016a). Anatomic changes caused by endoscopic endonasal transsphenoidal surgery and their effects on nasal functions. Otolaryngol Head Neck Surg 154: 1132–1137.

Kim DH, Hong YK, Jeun SS et al. (2016b). Intranasal volume changes caused by the endoscopic endonasal transsphenoidal approach and their effects on nasal functions. PLoS One 11. e0151531.

Kimmelman CP (1994). The risk to olfaction from nasal surgery. Laryngoscope 104: 981–988.

Konstantinidis I, Witt M, Kaidoglou K et al. (2010). Olfactory mucosa in nasal polyposis: implications for FESS outcome. Rhinology 48: 47–53.

Landis BN, Hummel T, Lacroix JS (2005). Basic and clinical aspects of olfaction. Adv Tech Stand Neurosurg 30: 69–105.

Lee SH, Lim HH, Lee HM et al. (2000). Olfactory mucosal findings in patients with persistent anosmia after endoscopic sinus surgery. Ann Otol Rhinol Laryngol 109: 720–725.

Lee JY, Lee SW, Lee JD (2008). Comparison of the surgical outcome between primary and revision endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. Am J Otolaryngol 29: 379–384.

Lee DY, Lee WH, Wee JH et al. (2014). Prognosis of postviral olfactory loss: follow-up study for longer than one year. Am J Rhinol Allergy 28: 419–422.

Leopold D (2002). Distortion of olfactory perception: diagnosis and treatment. Chem Senses 27: 611–615.

Leopold DA, Hornung DE (2013). Olfactory cocainization is not an effective long-term treatment for phantosmia. Chem Senses 38: 803–806.

Leopold DA, Schwob JE, Youngentob SL et al. (1991). Successful treatment of phantosmia with preservation of olfaction. Arch Otolaryngol Head Neck Surg 117: 1402–1406.

Leopold DA, Hummel T, Schwob JE et al. (2000). Anterior distribution of human olfactory epithelium. Laryngoscope 110: 417–421.

Leopold DA, Loehrl TA, Schwob JE (2002). Long-term follow-up of surgically treated phantosmia. Arch Otolaryngol Head Neck Surg 128: 642–647.

Lewkowitz-Shpuntoff HM, Hughes VA, Plummer L et al. (2012). Olfactory phenotypic spectrum in idiopathic hypogonadotropic hypogonadism: pathophysiological and genetic implications. J Clin Endocrinol Metab 97: E136–E144.

Li C, Yousem DM, Doty RL et al. (1994). Neuroimaging in patients with olfactory dysfunction. AJR Am J Roentgenol 162: 411–418.

Litvack JR, Griest S, James KE et al. (2007). Endoscopic and quality-of-life outcomes after revision endoscopic sinus surgery. Laryngoscope 117: 2233–2238.

Litvack JR, Fong K, Mace J et al. (2008). Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. Laryngoscope 118: 2225–2230.

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

Litvack JR, Mace JC, Smith TL (2009b). Olfactory function and disease severity in chronic rhinosinusitis. Am J Rhinol Allergy 23: 139–144.

London B, Nabet B, Fisher AR et al. (2008). Predictors of prognosis in patients with olfactory disturbance. Ann Neurol 63: 159–166.

Markert JM, Hartshorn DO, Farhat SM (1993). Paroxysmal bilateral dysosmia treated by resection of the olfactory bulbs. Surg Neurol 40: 160–163.

Massey EW, Schoenberg B (1984). Foster Kennedy syndrome. Arch Neurol 41: 658–659.

McMains KC, Kountakis SE (2005). Revision functional endoscopic sinus surgery: objective and subjective surgical outcomes. Am J Rhinol 19: 344–347.

Meltzer EO, Hamilos DL, Hadley JA et al. (2004). Rhinosinusitis: establishing definitions for clinical research and patient care. J Allergy Clin Immunol 114: 155–212.

Miwa T, Furukawa M, Tsukatani T et al. (2001). Impact of olfactory impairment on quality of life and disability. Arch Otolaryngol Head Neck Surg 127: 497–503.

Moberg J, Doty RL (1997). Olfactory function in Huntington's disease patients and at-risk offspring. Int J Neurosci 89: 133–139.

Moberg PJ, Turetsky BI (2003). Scent of a disorder: olfactory functioning in schizophrenia. Curr Psychiatry Rep 5: 311–319.

Moberg PJ, Kamath V, Marchetto DM et al. (2014). Meta-analysis of olfactory function in schizophrenia, first-degree family members, and youths at-risk for psychosis. Schizophr Bull 40: 50–59.

Mohammed AK, Magnusson O, Maehlen J et al. (1990). Behavioural deficits and serotonin depletion in adult rats after transient infant nasal viral infection. Neuroscience 35: 355–363.

Moran DT, Jafek BW, Eller PM et al. (1992). Ultrastructural histopathology of human olfactory dysfunction. Microsc Res Tech 23: 103–110.

Mullol J, Obando A, Pujols L et al. (2009). Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. Immunol Allergy Clin North Am 29: 657–668.

Nguyen AD, Shenton ME, Levitt JJ (2010). Olfactory dysfunction in schizophrenia: a review of neuroanatomy and psychophysiological measurements. Harv Rev Psychiatry 18: 279–292.

Nguyen DT, Gauchotte G, Nguyen-Thi PL et al. (2013). Does surgery of the olfactory clefts modify the sense of smell? Am J Rhinol Allergy 27: 317–321.

Nguyen DT, Bey A, Arous F et al. (2015). Can surgeons predict the olfactory outcomes after endoscopic surgery for nasal polyposis? Laryngoscope 125: 1535–1540.

Ni R, Michalski MH, Brown E et al. (2015). Optimal directional volatile transport in retronasal olfaction. Proc Natl Acad Sci U S A 112: 14700–14704.

Ottaviano G, Cantone E, D'Errico A et al. (2015). Sniffin' sticks and olfactory system imaging in patients with Kallmann syndrome. Int Forum Allergy Rhinol 5: 855–861.

Pade J, Hummel T (2008). Olfactory function following nasal surgery. Laryngoscope 118: 1260–1264.

Pence TS, Reiter ER, Dinardo LJ et al. (2014). Risk factors for hazardous events in olfactory-impaired patients. JAMA Otolaryngol Head Neck Surg 140: 951–955.

Perlman S, Evans G, Afifi A (1990). Effect of olfactory bulb ablation on spread of a neurotropic coronavirus into the mouse brain. J Exp Med 172: 1127–1132.

Philpott C, Hopkins C, Erskine S et al. (2015). The burden of revision sinonasal surgery in the UK-data from the chronic rhinosinusitis epidemiology study (CRES): a cross-sectional study. BMJ Open 5: e006680.

Poetker DM, Jakubowski LA, Lal D et al. (2013). Oral corticosteroids in the management of adult chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. Int Forum Allergy Rhinol 3: 104–120.

Quint C, Temmel AF, Schickinger B et al. (2001). Patterns of non-conductive olfactory disorders in eastern Austria: a study of 120 patients from the Department of Otorhinolaryngology at the University of Vienna. Wien Klin Wochenschr 113: 52–57.

Raviv JR, Kern RC (2004). Chronic sinusitis and olfactory dysfunction. Otolaryngol Clin North Am 37: 1143–1157. v-vi.

Reden J, Maroldt H, Fritz A et al. (2007). A study on the prognostic significance of qualitative olfactory dysfunction. Eur Arch Otorhinolaryngol 264: 139–144.

Reychler G, Colbrant C, Huart C et al. (2015). Effect of three-drug delivery modalities on olfactory function in chronic sinusitis. Laryngoscope 125: 549–555.

Rombaux P, Mouraux A, Bertrand B et al. (2006). Olfactory function and olfactory bulb volume in patients with postinfectious olfactory loss. Laryngoscope 116: 436–439.

Rombaux P, Martinage S, Huart C et al. (2009). Post-infectious olfactory loss: a cohort study and update. B-ENT 5(Suppl. 13): 89–95.

Rosenfeld RM, Andes D, Bhattacharyya N et al. (2007). Clinical practice guideline: adult sinusitis. Otolaryngol Head Neck Surg 137: S1–31.

Rosenfeld RM, Piccirillo JF, Chandrasekhar SS et al. (2015). Clinical practice guideline (update): adult sinusitis executive summary. Otolaryngol Head Neck Surg 152: 598–609.

Rudmik L, Smith TL (2012). Olfactory improvement after endoscopic sinus surgery. Curr Opin Otolaryngol Head Neck Surg 20: 29–32.

Rudmik L, Hoy M, Schlosser RJ et al. (2013). Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. Int Forum Allergy Rhinol 3: 281–298.

Rupp CI (2010). Olfactory function and schizophrenia: an update. Curr Opin Psychiatry 23: 97–102.

Santos DV, Reiter ER, Dinardo LJ et al. (2004). Hazardous events associated with impaired olfactory function. Arch Otolaryngol Head Neck Surg 130: 317–319.

Schwartz JS, Palmer JN, Adappa ND (2016a). Contemporary management of esthesioneuroblastoma. Curr Opin Otolaryngol Head Neck Surg 24: 63–69.

Schwartz JS, Tajudeen BA, Cohen NA (2016b). Medical management of chronic rhinosinusitis—an update. Expert Rev Clin Pharmacol 9: 695–704.

Schwob JE, Saha S, Youngentob SL et al. (2001). Intranasal inoculation with the olfactory bulb line variant of mouse hepatitis virus causes extensive destruction of the olfactory bulb and accelerated turnover of neurons in the olfactory epithelium of mice. Chem Senses 26: 937–952.

Seiden AM (2004). Postviral olfactory loss. Otolaryngol Clin North Am 37: 1159–1166.

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

Shen PH, Weitzel EK, Lai JT et al. (2011). Retrospective study of full-house functional endoscopic sinus surgery for revision endoscopic sinus surgery. Int Forum Allergy Rhinol 1: 498–503.

Simola M, Malmberg H (1998). Sense of smell in allergic and nonallergic rhinitis. Allergy 53: 190–194.

Smith TL, Mendolia-Loffredo S, Loehrl TA et al. (2005). Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope 115: 2199–2205.

Smith TL, Litvack JR, Hwang PH et al. (2010). Determinants of outcomes of sinus surgery: a multi-institutional prospective cohort study. Otolaryngol Head Neck Surg 142: 55–63.

Smith TL, Kern RC, Palmer JN et al. (2011). Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study. Int Forum Allergy Rhinol 1: 235–241.

Smith KA, Smith TL, Mace JC et al. (2014). Endoscopic sinus surgery compared to continued medical therapy for patients with refractory chronic rhinosinusitis. Int Forum Allergy Rhinol 4: 823–827.

Smith KA, Orlandi RR, Rudmik L (2015). Cost of adult chronic rhinosinusitis: a systematic review. Laryngoscope 125: 1547–1556.

Snidvongs K, Kalish L, Sacks R et al. (2013). Sinus surgery and delivery method influence the effectiveness of topical corticosteroids for chronic rhinosinusitis: systematic review and meta-analysis. Am J Rhinol Allergy 27: 221–233.

Soler ZM, Mace J, Smith TL (2008). Symptom-based presentation of chronic rhinosinusitis and symptom-specific outcomes after endoscopic sinus surgery. Am J Rhinol 22: 297–301.

Soler ZM, Sauer DA, Mace J et al. (2009). Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. Otolaryngol Head Neck Surg 141: 454–461.

Soler ZM, Sauer DA, Mace JC et al. (2010). Ethmoid histopathology does not predict olfactory outcomes after endoscopic sinus surgery. Am J Rhinol Allergy 24: 281–285.

Soler ZM, Pallanch JF, Sansoni ER et al. (2015). Volumetric computed tomography analysis of the olfactory cleft in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol 5: 846–854.

Soler ZM, Hyer JM, Karnezis TT et al. (2016a). The olfactory cleft endoscopy scale correlates with olfactory metrics in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol 6: 293–298.

Soler ZM, Smith TL, Alt JA et al. (2016b). Olfactory-specific quality of life outcomes after endoscopic sinus surgery. Int Forum Allergy Rhinol 6: 407–413.

Spetzler RF, Herman JM, Beals S et al. (1993). Preservation of olfaction in anterior craniofacial approaches. J Neurosurg 79: 48–52.

Stevens CN, Stevens MH (1985). Quantitative effects of nasal surgery on olfaction. Am J Otolaryngol 6: 264–267.

Suzuki M, Saito K, Min WP et al. (2007). Identification of viruses in patients with postviral olfactory dysfunction. Laryngoscope 117: 272–277.

Tan BK, Lane AP (2009). Endoscopic sinus surgery in the management of nasal obstruction. Otolaryngol Clin North Am 42: 227–240. vii.

Temmel AF, Quint C, Schickinger-Fischer B et al. (2002). Characteristics of olfactory disorders in relation to major causes of olfactory loss. Arch Otolaryngol Head Neck Surg 128: 635–641.

Thomas 3rd WW, Harvey RJ, Rudmik L et al. (2013). Distribution of topical agents to the paranasal sinuses: an evidence-based review with recommendations. Int Forum Allergy Rhinol 3: 691–703.

Thompson CF, Suh JD, Liu Y et al. (2014). Modifications to the endoscopic approach for anterior skull base lesions improve postoperative sinonasal symptoms. J Neurol Surg B Skull Base 75: 65–72.

Turetsky BI, Moberg PJ, Arnold SE et al. (2003a). Low olfactory bulb volume in first-degree relatives of patients with schizophrenia. Am J Psychiatry 160: 703–708.

Turetsky BI, Moberg PJ, Owzar K et al. (2003b). Physiologic impairment of olfactory stimulus processing in schizophrenia. Biol Psychiatry 53: 403–411.

Vento SI, Simola M, Ertama LO et al. (2001). Sense of smell in long-standing nasal polyposis. Am J Rhinol 15: 159–163.

Wigand ME (1990). Endoscopic surgery of the paranasal sinuses and anterior skull base, Thieme Medical Publishers, New York.

Wofford MR, Kimbell JS, Frank-Ito DO et al. (2015). A computational study of functional endoscopic sinus surgery and maxillary sinus drug delivery. Rhinology 53: 41–48.

Wolfensberger M, Hummel T (2002). Anti-inflammatory and surgical therapy of olfactory disorders related to sino-nasal disease. Chem Senses 27: 617–622.

Wrobel BB, Leopold DA (2004a). Clinical assessment of patients with smell and taste disorders. Otolaryngol Clin North Am 37: 1127–1142.

Wrobel BB, Leopold DA (2004b). Smell and taste disorders. Facial Plast Surg Clin North Am 12: 459–468. vii.

Yamagishi M, Hasegawa S, Nakano Y (1988). Examination and classification of human olfactory mucosa in patients with clinical olfactory disturbances. Arch Otorhinolaryngol 245: 316–320.

Yamagishi M, Nakamura H, Suzuki S et al. (1990). Immunohistochemical examination of olfactory mucosa in patients with olfactory disturbance. Ann Otol Rhinol Laryngol 99: 205–210.

Yamagishi M, Fujiwara M, Nakamura H (1994). Olfactory mucosal findings and clinical course in patients with olfactory disorders following upper respiratory viral infection. Rhinology 32: 113–118.

Zafereo ME, Fakhri S, Prayson R et al. (2008). Esthesioneuroblastoma: 25-year experience at a single institution. Otolaryngol Head Neck Surg 138: 452–458.

Zhao K, Frye RE (2015). Nasal patency and the aerodynamics of nasal airflow in relation to olfactory function. In: R Doty (Ed.), Handbook of olfaction and gustation, Hoboken.

Zhao K, Scherer PW, Hajiloo SA et al. (2004). Effect of anatomy on human nasal air flow and odorant transport patterns: implications for olfaction. Chem Senses 29: 365–379.

Zhao K, Jiang J, Pribitkin EA et al. (2014). Conductive olfactory losses in chronic rhinosinusitis? A computational fluid dynamics study of 29 patients. Int Forum Allergy Rhinol 4: 298–308.

Zhao K, Craig JR, Cohen NA et al. (2016). Sinus irrigations before and after surgery-visualization through computational fluid dynamics simulations. Laryngoscope 126: E90–E96.

Zilstorff K (1966). Parosmia. J Laryngol Otol 80: 1102–1104.