

Disrupted Od

31. Disrupted Odor Perception

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Olfactory loss is frequent. However, in public not many people complain of that, or they are even not (fully) aware of it. This indicates that it is possible to live a life without a sense of smell, albeit it is more dangerous, less pleasant, and food tastes much less interesting. Most common causes for smell loss are sinonasal disease (chronic rhinosinusitis with and without nasal polyps), acute infections of the upper airways, head trauma, and neurodegenerative disorders. In many people smell loss seems to be due to the aging process. Before treatment olfactory disorders are diagnosed according to cause with the medical history being a big portion of the diagnostic process. Olfactory disorders are in principle reversible, with a relatively high degree of spontaneous improvement in olfactory loss following infections of the upper respiratory tract. Medical treatment is according to cause. It also involves surgical approaches as well as conservative treatments including the use of corticosteroids, antibiotics, or *smell training*. Because today olfactory dysfunction seems to receive more attention than in previous years it can be expected that *tomorrow* we will have more specific and effective treatment options available.

31.1	Epidemiology of Olfactory Loss	653
31.2	Definitions of Olfactory Dysfunction	654
31.2.1	Quantitative Olfactory Disorders	654
31.2.2	Qualitative Olfactory Disorders .	654
31.3	Otorhinolaryngological Examination ...	654
31.4	Questionnaires	657
31.5	Psychophysical Methods of Olfactory Testing	657
31.6	Electrophysiological/Imaging Techniques	658
31.6.1	Electroolfactogram (EOG)	658
31.6.2	Chemosensory Event-Related Potentials (CSERP)	658
31.6.3	Functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET)	659
31.7	Causes and Symptoms of Smell Disorders	659
31.7.1	Most Common Causes	659
31.7.2	Less Frequent Causes.....	660
31.8	Symptoms/Quality of Life	661
31.9	Spontaneous Recovery of Smell Disorders	661
31.10	Treatment of Olfactory Disorders	662
31.10.1	Surgical Therapy of SND-Related Olfactory Loss ..	662
31.10.2	Conservative Therapy of SND-Related Olfactory Loss ..	662
31.10.3	Conservative Therapy of Post-URTI/Posttraumatic Olfactory Loss	663
31.11	Concluding Remarks and Outlook	663
	References	664

31.1 Epidemiology of Olfactory Loss

Population-based studies of olfactory loss show a prevalence of olfactory impairment of 22% (25–75 years; [31.1]), 19% (≥ 20 years; [31.2]), or 24% (≥ 53 years; [31.3]), with the highest prevalence in older men. However, unawareness of olfactory loss is common [31.3–5]. It also has to be kept in mind that total loss of the sense of smell is seen much less frequently (3–10%) [31.6].

With regard to patients presenting themselves to specialized clinical centers, the most common etiologies of smell loss are post viral upper respiratory tract infection (URTI) (18–45%) and sinonasal disease (SND) (7–56%), followed by head trauma (8–20%), exposure to toxins/drugs (2–6%), and congenital anosmia (0–4%) [31.7–15]. A survey in Germany, Austria, and Switzerland shows higher results for SND [31.16].

For qualitative disorders, the prevalence is considerably lower. In the general population, the prevalence of phantosmia is estimated between 0.8 and 2.1% [31.17] and parosmia to about 4% [31.18]. Among patients with

olfactory disorders, parosmia frequency ranges from 10 to 60% [31.7, 19, 20] – possibly indicating that the detection of parosmia is critically dependent on how the investigator asks for parosmia.

31.2 Definitions of Olfactory Dysfunction

31.2.1 Quantitative Olfactory Disorders

Normosmia indicates a normal sense of smell; *hyposmia* indicates a decrease in olfactory function and *anosmia* indicates the loss of olfactory function. Next to general anosmia, specific anosmias have been described, where only certain odors cannot be perceived whereas most odors are [31.21]. The term functional anosmia was chosen since many subjects with severe olfactory loss appear to be able to still perceive a few single odors. Nevertheless, those rare and weak olfactory impressions are too poor to be of any help to these patients in daily life.

31.2.2 Qualitative Olfactory Disorders

The term *qualitative olfactory disorder* reflects the qualitatively changed perception of odorous sensation [31.19, 20, 22, 23]. Their diagnosis relies on the patients' complaints [31.23]. They can be graded in four grades 0–III (frequency of occurrence: daily = 1 point; intensity: very intense = 1 point; social/important other consequences (weight loss, change of daily activities) = 1 point; the degree of parosmia/phantosmia is the sum of points).

Qualitative olfactory disorders are frequently, but not necessarily associated with quantitative olfactory disorders. *Parosmia* describes the distorted perception

of smells in the presence of an odor source; parosmias are triggered by odors. They occur particularly often after infections of the URTI or head trauma [31.24]. The distorted odors are mostly perceived as unpleasant (although some exceptions seem to exist [31.25]). Parosmias are thought to be the result of changes at a peripheral or central-nervous level [31.26, 27]; at the moment it is unclear how they are generated. The diagnosis *qualitative olfactory disorder* can be supported by relatively lower scores in an odor identification test [31.19] or the presence of relatively small olfactory bulbs (OB) compared to patients without parosmia/phantosmia [31.28].

Clinically important, most parosmic impressions tend to weaken over months and finally disappear after years [31.24]. Currently it is also not entirely clear whether parosmias are a positive sign in terms of the prognosis of post-URTI and post-traumatic olfactory loss [31.29]. *Phantosmia* describes the distorted perception of smells in the absence of an odor source. Most often phantosmias occur after trauma or URTI [31.24]. Stress-related phantosmias have also been reported [31.30]. Similar to parosmia, the exact explanation of the molecular modifications leading to phantosmia is yet unknown and also the site of its generation remains unclear. Phantosmias also have a tendency to disappear over the course of years.

31.3 Otorhinolaryngological Examination

Evaluation of a patient starts with a thorough history [31.31]. This should include demographics, eating, drinking or smoking habits, listing of major illnesses and injuries, medications taken in relation to symptom onset, history of present illness, endocrine information (thyroid gland, diabetes), general nasal health including obstruction, rhinorrhea, and changes of the sense of smell (Fig. 31.1). Physical examination should include at least the patient's head and neck. Sometimes a neurological examination may be needed. Specific nasal examination should include nasal endoscopy. Radiological evaluation is helpful to rule out the presence of

tumors or vascular malformations [31.32, 33], to judge the volume of the OB [31.34], measure the depth of the olfactory sulcus [31.35, 36], and to investigate the paranasal sinuses. Especially the volume of the OB seems to carry also prognostic information – the larger its volume the more likely recovery [31.37].

Additional diagnostic tests may include the search for other underlying causes of the olfactory disorders, deficiency of vitamin A or B12, or hypothyroidism. Finally, biopsies of the olfactory epithelium may be helpful in the diagnosis of olfactory disorders [31.27, 38, 39].

To be completed by the physician	
Weight loss due to problem?	<input type="checkbox"/> no <input type="checkbox"/> yeskg/.....years
Medication?	<input type="checkbox"/> no <input type="checkbox"/> yes – which?
Chronic diseases?	<input type="checkbox"/> no <input type="checkbox"/> yes – which? <input type="checkbox"/> diabetes <input type="checkbox"/> high blood pressure <input type="checkbox"/> neoplasia <input type="checkbox"/> others:
Head surgery?	<input type="checkbox"/> no <input type="checkbox"/> yes – which? <input type="checkbox"/> sinuses <input type="checkbox"/> nasal septum <input type="checkbox"/> nasal polyps <input type="checkbox"/> nasal turbinates <input type="checkbox"/> palatal tonsils <input type="checkbox"/> adenoids <input type="checkbox"/> middle ear <input type="checkbox"/> left <input type="checkbox"/> right <input type="checkbox"/> dental surgery: <input type="checkbox"/> others
Flue shots?	<input type="checkbox"/> no <input type="checkbox"/> yes – when?
Smoker?	<input type="checkbox"/> no <input type="checkbox"/> yes – extent?
Alcohol?	<input type="checkbox"/> no <input type="checkbox"/> yes – <input type="checkbox"/> occasionally <input type="checkbox"/> regularly
Diagnostic imaging?	CAT <input type="checkbox"/> no <input type="checkbox"/> yes rad.-sinuses <input type="checkbox"/> no <input type="checkbox"/> yes MRI <input type="checkbox"/> no <input type="checkbox"/> yes Findings:
Profession?	Specific exposure to gaseous, powdered, or other chemicals? <input type="checkbox"/> no <input type="checkbox"/> yes If YES , which? duration (years)? hours per day?
If idiopathic etiology is suspected:	Parkinson's disease among relatives <input type="checkbox"/> no <input type="checkbox"/> yes Alzheimer's disease among relatives <input type="checkbox"/> no <input type="checkbox"/> yes
Parosmia <input type="checkbox"/> no <input type="checkbox"/> yes <input type="checkbox"/> left <input type="checkbox"/> right	<input type="checkbox"/> daily <input type="checkbox"/> not daily <input type="checkbox"/> very strong <input type="checkbox"/> mild <input type="checkbox"/> weight loss due to parosmia <input type="checkbox"/> no weight loss
Phantosmia <input type="checkbox"/> no <input type="checkbox"/> yes <input type="checkbox"/> left <input type="checkbox"/> right	<input type="checkbox"/> daily <input type="checkbox"/> not daily <input type="checkbox"/> very strong <input type="checkbox"/> mild <input type="checkbox"/> weight loss due to phantosmia <input type="checkbox"/> no weight loss

Test results

“Sniffin sticks” T: D: I:
Taste strips (x out of 32):
Taste sprays (4 Sprays):
Retronasal (x out of 20):

Nasal findings

Septal deviation left right none
Olfactory cleft visible left right
Polyps left: 0 I II III
right: 0 I II III

Suspected etiology:

- post traumatic
- sinusal
- toxic
- neurodegenerative
- post-infectious
- idiopathic
- congenital
- others



Examiner (name/signature)

Fig. 31.1 (continued)

31.4 Questionnaires

To detect changes related to olfactory loss, several questionnaires have been developed [31.40]. The sinonasal outcome test-16 specifically addresses nasal dysfunction [31.41] (see also [31.42–46]; it is a 16-item measure that assesses the degree of rhinosinusitis based on the presence of symptoms associated with sinusitis. The relatively elaborate questionnaire of olfactory disorders (QOD) [31.47, 48] was designed to assess daily life problems associated with olfactory loss and has been used in a number of studies [31.49, 50]. It consists of 26 items that can be divided into three domains: *negative* statements indicating patients suffering from olfactory impairment and distorted odorous perceptions (parosmia or phantosmia), *positive* statements about coping with the disorder, and statements of social desirability, for control. Another questionnaire asks about the importance of olfaction in daily life [31.51]. This questionnaire does not focus on impairments, but asks how

often and in which circumstances people use their sense of smell.

In addition, questionnaires are available to measure mood states or quality of life (QoL) [31.52], with the short form-36 health survey being the standard QoL questionnaire [31.53]. However, there is a choice of questionnaires that allows the selection of the best suited tool [31.54, 55]. Depressive symptoms are often assessed with the Beck depression inventory (BDI) questionnaire [31.56], or its more modern version [31.57]. However, it has to be kept in mind that olfactory loss is often confounded with comorbidity. In fact, in patients with chronic rhinosinusitis the additional effect of olfactory loss on general QoL seems to be not very high [31.58]. In order to be able to track the patients' ability to cope with the olfactory disorder, *Nordin* et al. introduced an 11-question instrument [31.59].

31.5 Psychophysical Methods of Olfactory Testing

The basic principle of psychophysical testing of olfaction is to expose a patient to an odor and to collect responses to that exposure. These procedures are easy to understand by the patient, but, importantly, they are also easily understood by the investigator. Asking the patient about his/her chemosensory function does not appear to be useful, at least not in all patients [31.60–62]; in addition, may patients confuse taste and retronasal olfactory function (*flavor*).

Numerous tests for olfactory function are available many of which are based on odor identification (for review, see [31.63]). In daily clinical life, these tests serve as quick screening tools for olfac-

tory dysfunction [31.64]. All olfactory tests should be reliable and valid. Tests apart from screening tools should distinguish between anosmic, hyposmic, and normosmic subjects, respectively, which requires availability of normative data acquired and validated on large samples of healthy and diseased subjects, respectively. In addition, it should be known which change of the test score indicates a clinically significant change of function [31.65]. Most of these requirements apply only to a few olfactory tests [31.66–71]. The best-validated olfactory tests include the University of Pennsylvania smell identification test (UPSIT) [31.67], the Connecticut Chemosensory Clinical Research Center test (CC-CRC) [31.72], and the *Sniffin' Sticks* [31.68, 69] (Fig. 31.2).

Most odor identification tests are presented within a forced choice paradigm. The subjects have to identify odors at supra-threshold concentrations from a list of descriptors [31.73, 74]. For example, subjects receive a rose odor, and they are asked whether the odor was *banana, fish, rose, or coffee*; such tasks are no problem for healthy people, but they are very difficult for people with smell loss. The forced-choice procedure controls the patients' response bias. The result of the test corresponds to the sum of the correctly identified items. *Smell identification tests* are most widely used [31.66–71, 75]. The more odors the test contains the more reliable it is [31.76, 77]. Identification tests have to be



Fig. 31.2 *Sniffin' Sticks* and how they are presented to the patient (courtesy of T. Hummel)

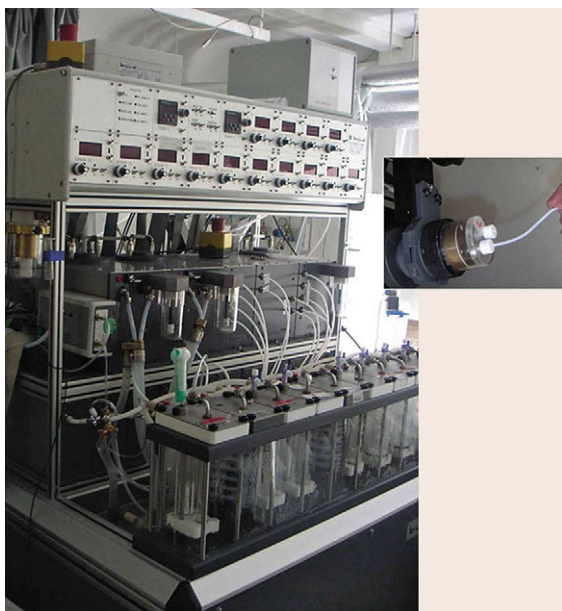


Fig. 31.3 Olfactometer *Omb6* (Burghart, Wedel, Germany) and how stimuli are presented intranasally (courtesy of T. Hummel)

adjusted to the various cultures [31.78, 79], simply because not all odors are known everywhere; for example, many Europeans do not know the smell of *wintergreen* or *root beer*, whereas this is well known in the United States.

Two other widely used test designs are threshold tests and tests of odor discrimination. The idea of threshold tests is to expose a subject repeatedly to ascending and descending concentrations of the same odorant and to identify the least detectable concentration for this individual odor [31.80–82]. Other designs are based on logistic regression [31.83, 84]. Discrimination tasks mainly consist of a three-alternative forced choice technique [31.68, 85]. Two of the administered odors are identical, one is different. The subjects' task is to find out the different one. Tests for odor threshold/odor discrimination can be easily used repetitively, which is more difficult with odor identification tests.

Generally, identification and discrimination tests are believed to reflect central olfactory processing while thresholds are thought to reflect peripheral olfactory function to a stronger degree [31.86–88]. For example, in patients with chronic rhinosinuitis a low threshold score and normal identification and discrimination are frequently seen [31.89].

In order to investigate retronasal function, simple and inexpensive flavor identification tests have been investigated for their test–retest reliability and their validity [31.90–92]. One test, the *taste powders* (*Schmeckpulver*), is also validated on a multinational level [31.93]. Other tests of olfactory function include the investigation of pupillary reflexes [31.94, 95], blinking reflexes [31.96], psychogalvanic skin reactions [31.97], or changes in respiratory/sniffing pattern [31.98, 99].

31.6 Electrophysiological/Imaging Techniques

31.6.1 Electroolfactogram (EOG)

Electroolfactograms (EOG) are electrical potentials of the olfactory epithelium that occur in response to olfactory stimulation. The EOG represents the sum of generator potentials of olfactory receptor neurons (ORNs) [31.100]. Although this technique appears to be attractive [31.101], for example, for the functional characterization of the human olfactory epithelium [31.102], there are only a handful of reports utilizing the human EOG [31.103–108]. Notably there are no published investigations in patients.

31.6.2 Chemosensory Event-Related Potentials (CSERP)

Event-related potentials are EEG-derived signals. They are due to the activation of cortical neurons, which generate electromagnetic fields [31.109]. To extract

event-related potentials (ERP) from the background electroencephalogram (EEG) activity, stimuli are presented repeatedly and the individual recordings are then averaged, which improves the signal-to-noise ratio (random activity would cancel itself out; non-random activation would remain). In addition, stimuli are presented with a steep onset (< 20 ms) in a monotonous environment such that stimulus onset synchronizes the activity of as many cortical neurons as possible. Olfactory ERP are direct correlates of neuronal activation; they have a high temporal resolution in the range of microseconds, and they can be obtained independently of the subject's response bias, they are well-suited for medico-legal investigations [31.110].

Based on a system developed by *Kobal* [31.104, 111], odors are applied intranasally (Fig. 31.3). Presentation of odorous stimuli does not produce mechanical or thermal sensations because odor pulses are embed-

ded in a constantly flowing air stream [31.104, 112, 113]. ERP peaks are either early or late. Earlier peaks like N1 encode exogenous stimulus characteristics to a larger extent (*What is the nature of this stimulus?*) than later, so-called endogenous components (*What is the meaning of this stimulus?*) [31.114, 115]. Although there is a very clear concept available as to how to record and analyze olfactory ERP [31.116, 117] recently there have been a number of attempts to improve the signal-to-noise ratio [31.118–120] and to extract additional information from the stimulus-related EEG [31.121, 122].

Using magneto-encephalographic techniques [31.123] cortical generators of the responses to trigeminal stimulation with CO₂ were localized in the secondary somato-sensory cortex [31.124], sources in response to olfactory stimulation were found in the anterior-central parts of the insula, the para-insular cortex, and the superior temporal sulcus [31.125–127]. More recent work based on EEG [31.128] suggests that olfactory information in humans is processed first ipsilaterally to the stimulated nostril and then

sequentially activates the major relays in olfactory information processing in both hemispheres.

Other EEG-related tests are based on the contingent negative variation (CNV), which occurs in response to an expectation [31.129, 130] or more general EEG changes [31.131] (Fig. 31.4).

31.6.3 Functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET)

Brain imaging allows to study the human olfactory system in detail [31.132–139]. In contrast to electroencephalogram (EEG) and magneto-encephalogram (MEG), PET and fMRI largely reflect blood-flow related changes. In addition, PET and fMRI have a relatively low temporal resolution whereas they exhibit a better spatial resolution than EEG and MEG. Although there are some data available on fMRI and PET in patients with olfactory loss [31.140–142], it seems that the use of these techniques in individual patients with smell or taste disorders is difficult.

31.7 Causes and Symptoms of Smell Disorders

31.7.1 Most Common Causes

Olfactory Loss Following Infections of the URTI

The patients' history typically starts with an episode of a cold during, which they lose their sense of smell [31.20, 143–147]. Some authors claim viral (influenza, parainfluenza viruses type III, rhinovirus, coronavirus, and Epstein Barr) rather than bacterial infections to be responsible for olfactory disturbances [31.148, 149] and observed a higher incidence of dysosmias after spring and summer URTI [31.144]. Furthermore, women above 45 years of age seem to be affected at a higher percentage than men [31.7, 10, 144] – which brings up the potential olfactory protective effect of estrogens [31.150]. Nevertheless, the effect of estrogen on olfactory function remains an open debate [31.17, 151]. It is important to inform patients with post-URTI olfactory loss about the possibility of parosmia (see above). It tends to occur 1–3 months after the URTI, although it appears sometimes to occur directly after the URTI. The frequency of parosmia is in the range of 25% [31.152, 153].

Posttraumatic Olfactory Disorders

Posttraumatic olfactory disorders are said to occur after occipital trauma. The current explanation is that *coup-contre-coup* lesions or tearing of the filae ol-

factoriae leads to anosmia or hyposmia. Although the entity of posttraumatic olfactory loss has already been described at the end of the last century it has received little systematic attention, like most olfactory disorders [31.154]. Olfactory loss seems to correlate with the severity of the trauma [31.155–157], although several authors pointed out the fact that there is considerable individual variability in terms of the vulnerability of olfactory structures [31.157, 158]. The injured parts of the olfactory system are most often the filae olfactoriae which cross the cribriform plate. However, central structures such as the orbitofrontal cortex and gyrus rectus have also been found to be affected from head trauma [31.147, 155]. Similar to post-URTI olfactory impairment, these patients are prone to develop parosmia and phantosmia several months after the trauma. Clinical experience shows that most patients with posttraumatic olfactory disturbance realize the alteration with some latency [31.159].

Sinunasal Disorders

Sinunasal disorders constitute the most frequent causes of olfactory loss [31.16]. This is due to mechanical obstruction of nasal cavity (septal deviation, nasal polyposis, congested mucosa) and/or the inflammatory component of chronic rhinosinusitis [31.160–165]. Mild

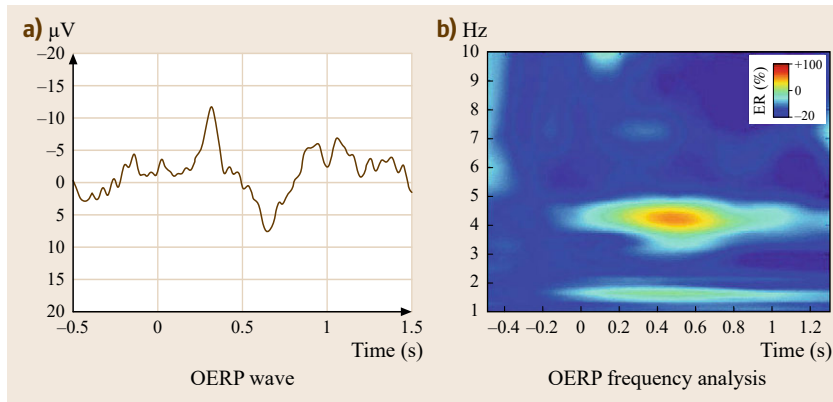


Fig. 31.4a,b Olfactory event-related activity shown in the time domain (a): negativity upward or the frequency domain (b). Stimulus presentation (phenylethylalcohol: PEA) started at time 0 for 200 ms

olfactory impairments could also be identified in other groups of patients with SNDs such as allergic and uncomplicated chronic rhinosinusitis [31.147, 166, 167]. In contrast to posttraumatic and post-URTI olfactory dysfunctions, these patients rarely exhibit parosmia or phantosmia.

Neurodegenerative Causes

Olfactory loss is common in patients with idiopathic Parkinson's disease (IPD) [31.168–170]. While a decreased sniff volume seems to add to the decrease in olfactory function [31.171], electrophysiological recordings in response to passive olfactory stimulation clearly established the presence of olfactory impairment in IPD [31.172, 173]. This olfactory deficit is so reliable that it can be used as a marker of IPD [31.170, 174]. In other words: If a patient with normal olfactory function presents with IPD symptoms the diagnosis should be re-investigated. Olfactory loss precedes the onset of motor symptoms by 4–6 years [31.175–177]. Olfactory loss is also observed regularly in Alzheimer's disease, and at a much lower frequency/less pronounced in multiple system atrophy, Huntington's disease, and motor neuron disease [31.178].

Idiopathic Olfactory Loss

Idiopathic olfactory loss seems to reflect the poor understanding of factors interfering with olfaction [31.147]. With further insight and research this percentage should decrease. A considerable number of these idiopathic causes might be due to SND, post-URTI dysosmias following an almost undetected URTI, or neurodegenerative diseases [31.165].

31.7.2 Less Frequent Causes

Diabetes is probably among the best investigated endocrine diseases concerning olfactory disorders [31.2, 179, 180]. Most studies reveal slight olfactory defi-

ciencies in diabetic patients especially at threshold levels indicating a peripheral patho-mechanism compatible with a possible diabetic micro-angiopathy or peripheral polyneuropathy. However, olfactory impairment in diabetes is relatively mild. Two recent studies conducted with identification tests in large study samples could not find diabetic patients to exhibit a decreased ability to identify odors compared to healthy controls [31.2, 17]; there is evidence showing that olfactory loss is most prominent in complicated diabetes II [31.181]. Several other endocrine diseases like hypothyroidism [31.182] or adrenocortical insufficiency (Addison's disease) [31.183] have been reported to cause olfactory loss.

Affections of the kidney [31.184] and liver [31.17, 185, 186] have been associated with decreased olfactory function. Olfactory disturbances in those pa-

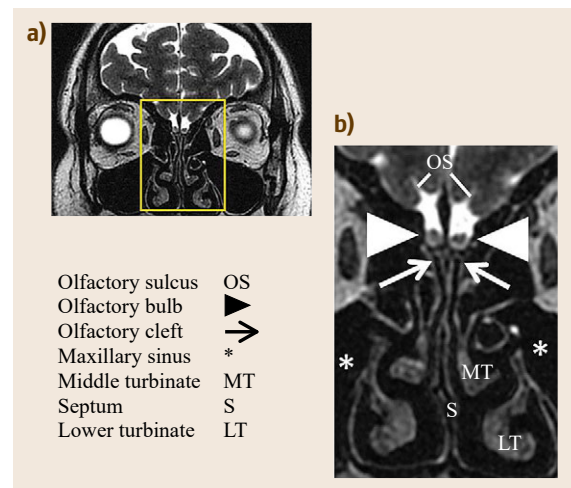


Fig. 31.5a,b Coronal sections (MR-scans) of the head including olfactory bulbs: (a) section through whole head; (b) magnification of rectangular section indicated in the whole head section

tients are of special importance because they are discussed as a potential cause of malnutrition [31.187]. Olfactory loss may be induced by drugs [31.188]. Among these cardiovascular drugs [31.189], anti-hypertensive drugs [31.190, 191], antibiotics [31.192], and chemotherapeutic agents [31.193] are frequently mentioned. However, most information has been accumulated on the basis of case reports [31.194, 195]. Typically, the chemosensory side effects disappear when the medication is discontinued.

Isolated congenital anosmia seems to appear at a frequency of approximately 1 : 8000. Only magnetic resonance (MR) imaging leads to a more definitive di-

agnosis [31.35, 36, 196]. In the frontal imaging planes just tangential to the eye bulbs hypoplastic or aplastic olfactory bulbs (OLB) can be visualized (Fig. 31.5). This plane also allows an evaluation of the olfactory sulcus which is flattened in case the OLB is absent or hypoplastic. This is a useful indicator of congenital anosmia, especially because the bulb is not always easy to identify. Congenital/inborn anosmia as part of a syndrome is the Kallmann syndrome [31.197, 198] – here decreased olfactory function is associated with hypogonadotropic hypogonadism meaning the missing/slowed development of the gonads because of decreased levels of hormones, so-called gonadotropins [31.199].

31.8 Symptoms/Quality of Life

Patients with olfactory disorders are impaired in areas of food intake, safety, personal hygiene, and in their sexual life [31.200, 201]. Most often, difficulties related to eating are reported [31.202], also reduced appetite [31.8, 59] and difficulties in preparing food/cooking [31.40]. Many patients have problems detecting spoiled food [31.203]. Interestingly, however, these eating problems do not lead to a general pattern of reduced food intake [31.204]. In a study by *Ferris and Duffy*, 18% of the smell patients described an increase in food consumption, 20% a decrease, and the majority reported no change in food consumption [31.202].

No significant weight difference and no difference in food preferences was found in patients who were born without a sense of smell in comparison to an age-matched control group [31.198]. This is also supported from observations indicating that congenital absence of olfaction does not result in markedly aberrant food preferences [31.205]. As patients with acquired olfactory disorders, congenitally anosmic people report enhanced problems with burning food and detecting spoiled food [31.198].

Another common problem is worry about failure to detect fire, gas, or smoke [31.40]. The failure to detect fire or smoke is a main risk associated with olfactory disorder [31.59, 206]. Patients also express problems related to personal hygiene and also social relations are reported to be affected by olfactory disorders [31.59]. Impaired sex life has been reported inconsistently [31.42, 207–209]. Problems in working life have been reported to various degrees [31.62].

Olfactory dysfunction also affects QoL [31.210]. However, in SND, for example, it is difficult to separate the effects of olfactory disorders from those of decreased nasal patency. A similar situation is present in posttraumatic olfactory loss, where patients not only exhibit olfactory loss, but often more severe trauma-related disorders.

Finally, most patients also suffer from a feeling of not being recognized as being sensory disabled since both healthcare professionals and peers often lack any knowledge about smell disorders. This non recognition of the smell-impaired person is reported to generate a lot of frustration and has been overlooked in the past [31.211, 212].

31.9 Spontaneous Recovery of Smell Disorders

Age-related anosmia does not seem to exhibit spontaneous recovery. Sinusnasal smell disorders have a tendency to become worse over time – typical is a gradual loss of the sense of smell. This leads to a situation that the entire process may not be noticed or that patients only complain of orthonasal loss but not of loss of retronasal olfactory function. Toxic and drug-induced

smell disorders may recover once the drug intake is interrupted [31.192, 193].

Several authors described recovery rates for post-URTI and posttraumatic disorders to be highest within the first year [31.20, 213–215]. This is probably due to the ability of olfactory neurons to regenerate [31.216, 217]. Post-URTI disorders have a better prognosis com-

pared to posttraumatic disorders, probably (at least in part) owing to the fact that they often cause hyposmia rather than anosmia [31.146]. In approximately 5% of the cases total recovery can be observed, while up to 60% of all patients experience partial recovery of some olfactory function over the following years [31.145].

Positive predictors of spontaneous recovery include: short duration of disease, young age, viral cause of olfactory loss better than trauma, presence of parosmia, women better than men, higher olfactory function (also indicated in the presence of olfactory/trigeminal ERP and larger volume of the OLB), and nonsmoking [31.29, 34, 146, 218]. In contrast to quantitative olfactory disorders, qualitative disorders seem

to have a better prognosis of spontaneous disappearance. Parosmias tend to decrease to a bearable level after approximately one year [31.152]. However, recent work revealed that more than 50% of the parosmias still are present after 2 years [31.210]. Over time, parosmia seems to lose its devastating effect on QoL. To summarize, the best current therapeutic attitude toward post-URTI and posttraumatic olfactory disorders is to correctly inform the patient, without taking any hope of recovery nor promising quick and complete recovery. The patients should receive satisfactory olfactory testing. Follow-up investigations give both the physician and the patient the possibility to observe improvements.

31.10 Treatment of Olfactory Disorders

31.10.1 Surgical Therapy of SND-Related Olfactory Loss

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. However, when asked, postoperative improvement of olfactory function is reported by a majority of the patients [31.219–221]. When olfactory function is measured, a different picture emerges with 25% of patients with preoperative hyposmia and 5% with preoperative anosmia [31.222] (compare [31.223]). In terms of the sense of smell, nasal surgery produced the highest success rates in patients with eosinophilia and a high degree of polyposis [31.223]; in addition, higher success rates were found in women, and patients with aspirin-intolerance [31.224]. Neither age, presence of asthma, nor the number of preoperative surgical interventions had a major impact on the outcome of surgery [31.223, 224]. Findings of endoscopic investigations do not correlate with improvement of the sense of smell [31.225]. While beneficial in many cases, surgery may also pose a certain, albeit low risk to olfactory function [31.223, 226].

31.10.2 Conservative Therapy of SND-Related Olfactory Loss

Antibiotics

In the chronic form of putrid sinusitis *Staphylococcus aureus* and *Pseudomonas aeruginosa* are of high significance. Whenever possible antibiotic therapy should only be started after the bacteria have been identified and tested for resistances to antibiotics. It is important

to note that in chronic putrid sinusitis, antibiotic treatment is not always successful.

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 [31.227]. They reduce submucosal edema and mucosal hypersecretion and thereby increase nasal patency. Systemically administered steroids are of help in many SND patients [31.9, 228–232]. In addition to the anti-inflammatory activity it has been postulated that corticosteroids directly improve olfactory function [31.233, 234] by modulating the function of ORN through effects on olfactory Na, K-ATPase [31.227]. In fact, systemic steroids are often helpful even in patients without nasal obstruction due to polyps or obvious inflammatory changes [31.165, 231, 235].

Steroids may be administered systemically or topically. With regard to idiopathic olfactory dysfunction systemic administration is often applied for diagnostic purposes [31.165]. If systemic steroids improve olfactory function treatment is typically continued with locally administered steroids [31.167, 228, 230, 236]; however, the role of topical steroids in the treatment of SND-related olfactory loss has been questioned [31.165, 237, 238]. One reason why systemic steroids have a higher therapeutic efficacy compared to topical steroids [31.9, 239] may relate to the deposition of the spray in the nasal cavity with only few droplets reaching the olfactory cleft [31.238, 240]. In fact, it has been shown that only a small amount of nasally applied drugs reaches the olfactory epithelium which is situated in an effectively protected area of

the nasal cavity [31.241–243]. This situation can be remedied by the use of longer applicators [31.244], which allow to reach further into the nasal cavity so that the spray can reach the olfactory epithelium more effectively.

Other Treatments

Other treatments include the use of antileukotrienes [31.245,246], saline lavages [31.247], dietary changes [31.248], acupuncture [31.249], anti-allergy immunotherapy [31.250], or herbal treatments [31.251].

31.10.3 Conservative Therapy of Post-URTI/ Posttraumatic Olfactory Loss

Post-URTI smell dysfunction seems to be due to an impairment of ORN, both in function and in numbers [31.252,253]. While numerous treatments have been tried in post-URTI anosmia no pharmacological therapy has been clearly established so far [31.254–257].

However, there are numerous candidates for the conservative treatment of olfactory dysfunction. One of them is alpha-lipoic acid (ALA) which is used in the treatment of diabetic neuropathy [31.258]. The effect of ALA is well described both in experimental animals and in humans (for review see [31.259]). It is known to stimulate the expression of nerve growth factor, substance P, and neuropeptide Y [31.260,261]. It enhances motor nerve conduction velocity as well as microcirculation [31.262]. Further, ALA also has neuroprotective capabilities [31.263]. Preliminary work indicated that it may be useful in post-URTI olfactory loss [31.264]. Other encouraging pilot studies have been performed with the NMDA-antagonist *caroverine* (NMDA: *N*-methyl-D-aspartate) [31.265]. Potential mechanisms for the hypothesized effect included both reduced feedback inhibition in the OLB as a consequence of NMDA-antagonistic actions or antagonism of an excitotoxic action of glutamate.

Although frequently mentioned as a therapeutic option, studies on olfactory dysfunction with *zinc* have produced negative results [31.254,266]. It may, however, be of therapeutic value in patients with severe zinc deficiency, in hemodialysis. In studies in postmenopausal women, *estrogens* have been reported to provide a certain protection against olfactory disturbances [31.7]. However, as mentioned above, recent studies [31.151] indicate that estrogens are probably ineffective in the treatment of olfactory loss. Finally, although discussed frequently, the potential therapeutic use of orally administered *vitamin A* [31.255,267] is questionable; at least doses as high as 10 000 IU do not seem to be effective [31.268].

A different approach to the treatment of olfactory disorders is the detection and treatment of underlying causes. This approach may also involve the replacement of drugs suspect to affect the sense of smell [31.194,269–271]. Among the nonpharmacological treatments acupuncture has been mentioned frequently [31.249,272,273] although its effectivity is a matter of discussion [31.274].

The use of phosphodiesterase inhibitors has been described in several studies, none of which was double-blinded, throwing some doubt on the results [31.275–280]. In addition, animal studies indicated a decreased amplitude of responses recorded from the olfactory epithelium after topical administration [31.281].

Numerous studies indicate the usefulness of *olfactory training*, which is typically performed over a period of 12 or more weeks [31.282]. Patients expose themselves twice daily to four intense odors (phenyl ethyl alcohol: *rose*, eucalyptol: *eucalyptus*, citronellal: *lemon*, eugenol: *cloves*). A number of studies, from different laboratories [31.283–285], one of them performed in a blinded way [31.286], indicate that patients training with odors experience a significant improvement in olfactory function over patients who do not perform such a training. One idea about the effectivity of that training relates to the possible stimulation of regenerative capacities of the olfactory epithelium [31.287].

31.11 Concluding Remarks and Outlook

Olfactory dysfunction receives more attention than in previous years probably because modern societies not only care about simple survival but much about QoL. It can be expected that soon we will (1) have

a better understanding of the processes leading to smell loss and (2) have more specific and effective treatment options available for people with olfactory disorders.

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