Olfaction

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Huart Caroline, Philippe Eloy, and Philippe Rombaux

Core Message

- This chapter reviews the physiology and the pathology of the olfactory system. The aim is to provide adequate information to clinicians in order to improve their understanding about olfaction and its troubles and to promote adequate management of patients with olfactory disorders.

30.1 Introduction

Olfaction is one of the most ancient senses. Nevertheless, the field of olfaction has received far less attention as compared to other sensory modalities. This is notably due to the technical challenge of working with odorous stimuli and the difficulties of measuring brain activity induced by a chemosensory stimulus.

Although a majority of people consider it as one of the less important senses, this sense plays a major role in our interaction with the environment. Not only olfactory system acts for the detection of potential danger in the environment, such as smoke or gas, but also it influences our nutrition, social behavior, well-being, and memory processes.

This chapter proposes a global view of human olfaction. First we will extend on physiology of olfaction, paying a particular interest to olfactory pathways. Then, we will study pathological situations associated with olfactory dysfunction. More particularly, we will see into detail post-infectious olfactory loss, post-traumatic olfactory loss, and sinonasal-related olfactory disorder.

30.2 Physiology

30.2.1 Embryology

The olfactory placode is induced at the end of the fourth week of pregnancy when the local ectoderm makes direct contact with the prosencephalic vesicle. Some cells of the olfactory placode will differentiate into primary neurosensory cells, further constituting the olfactory neuroepithelium. At the end of the fifth week, these cells will develop axons, reaching the neurons from the anterior wall of the prosencephalon, which becomes the telencephalon. This will induce the

H. Caroline (✉) · P. Rombaux
Department of Otorhinolaryngology, Cliniques universitaires Saint-Luc, Brussels, Belgium

Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium
e-mail: caroline.huart@saintluc.uclouvain.be

P. Eloy
Department of Otorhinolaryngology, Cliniques universitaires Saint-Luc, Brussels, Belgium

Department of Otorhinolaryngology, CHU Dinant-Godinne (Site Godinne), Yvoir, Belgium
e-mail: philippe.rombaux@uclouvain.be

Ö. Ö. Celebi, T. M. Önerci (eds.), *Nasal Physiology and Pathophysiology of Nasal Disorders*,
https://doi.org/10.1007/978-3-031-12386-3_30

development of the olfactory bulb which begins to differentiate from the telencephalon. At the seventh week, the olfactory bulb individualizes at the tip of each hemisphere. It will then lengthen and come to lie on the cribriform plate of the ethmoid bone at the 12th week of pregnancy. Secondary neurosensory cells will differentiate inside the olfactory bulb and their dendrites synapse with axons of the primary neurosensory cells. Axons of secondary neurosensory cells will group to form the olfactory tract and synapse with cortical olfactory areas of the entorhinal paleocortex and archicortex [1, 2].

30.2.2 Olfactory Pathways

The olfactory system detects odorant molecules dissolved in air and trapped in the airflow passing through the nasal cavity. Nasal turbinates will guide the airflow to the olfactory cleft, allowing the odorant molecules to reach the olfactory neuroepithelium.

30.2.2.1 The Olfactory Neuroepithelium

The olfactory neuroepithelium is located in the upper part of the nasal vaults. It covers the cribriform plate of the ethmoid bone, medially to the middle turbinate and can extend to the superior turbinate, the superior part of the septum, and the middle turbinate [3]. In adult humans, its surface area is 2.5 cm^2 per nasal fossa. The location of the olfactory epithelium is dependent on individual factors and is thought to change with age, resulting from a conversion of olfactory neuroepithelium to respiratory epithelium or due to loss of olfactory neurons with age or from damages (smoke, toxics, chemicals, chronic infection).

The olfactory neuroepithelium is a pseudostratified columnar epithelium covering a lamina propria. It is composed of (1) olfactory receptor neurons (ORNs), (2) supporting cells, (3) basal cells, some of which serve as ORN stem cells for the regeneration of new olfactory sensory neurons throughout life, and (4) the duct of the Bowman's glands (which are located in the lamina propia) (Fig. 30.1).

The ORNs are bipolar cells, with their dendritic extensions directed toward the olfactory cleft and carrying on its surface several cilia that project into the mucus. Odorants are carried through the mucus layer by olfactory binding proteins, and bind to olfactory receptors located on the ORNs. In 1991, Axel and Buck [4] discovered a family of approximately 1000 genes that encode for an equivalent number of olfactory receptors, corresponding to the largest fam-

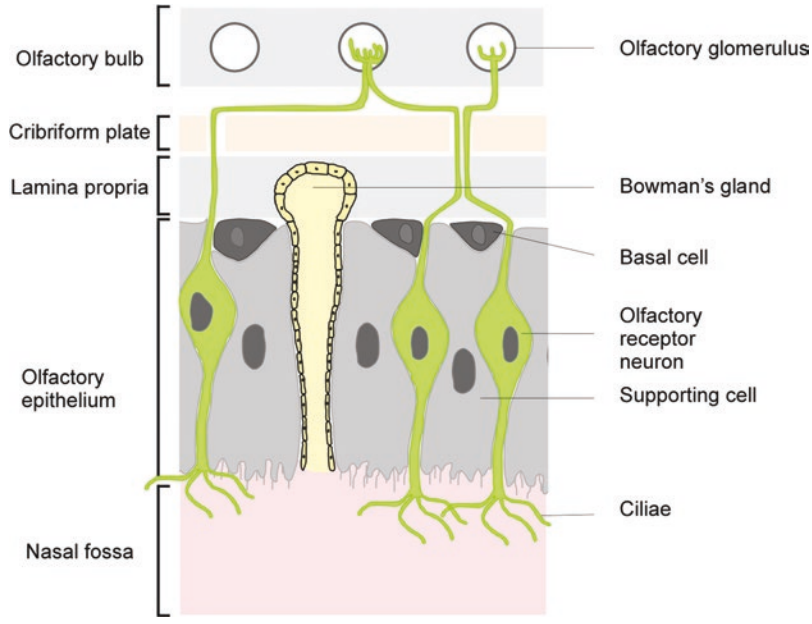

Fig. 30.1 Schematic representation of olfactory neuroepithelium. The olfactory neuroepithelium is composed by olfactory receptor neurons, supporting cells, and basal cells. The dendritic extension of olfactory receptor neurons carries on its surface several cilia, where are located the olfactory receptors. The axons run through the cribriform plate of the ethmoid bone and reach the olfactory bulb where they synapse with mitral cells in spherical structures named glomerulus

ily of genes in the mammalian genome [5], highlighting their important role in physiology. In the majority of mammals most of these genes are functional, but in primate the number of functional genes decreases and is to about 350 in humans [6]. Axel and Buck found that each ORN possesses only one type of odor receptor and each receptor is specialized for a small number of odors. Hence, a given odorant will bind a typical pattern of olfactory receptors. The binding results in the activation of G proteins. The activation of G proteins stimulates the formation of cyclic AMP. Increased levels of cAMP open cyclic nucleotide-gated channels. This causes the opening of the channels and Ca^{2+} influx. This influx activates chloride channels, opening them up, causing Cl^{-}leaves, and finally depolarizing the ORN and generating the action potential.

ORNs axons converge into the olfactory nerves, passing through the cribriform plate of the ethmoid bone and projecting directly to the ipsilateral olfactory bulb where they synapse into spherical structures known as the glomerulus.

30.2.2.2 The First Olfactory Structure: The Olfactory Bulb

The olfactory bulb is ovoid in shape and located in the anterior cranial fossa, above the cribriform plate of the ethmoid bone, and under the frontal lobe. It contains a major structure that is considered as the first olfactory structure: the glomerulus. The glomerulus is the only relay between the periphery and the cortex. Each glomerulus collects ORN axons from the same type of odorant receptor (Fig. 30.2). ORNs axons and dendrites of mitral cells synapse in the glomerulus.

The olfactory bulb has a multilayered cellular architecture. It encompasses 6 different layers: (1) the external layer is composed of ORNs axons; (2) the glomerular layer is composed by glomeruli wherein axons of ORNs synapse with dendrites of mitral cells; (3) the external plexiform layer consists of dendrites of mitral and

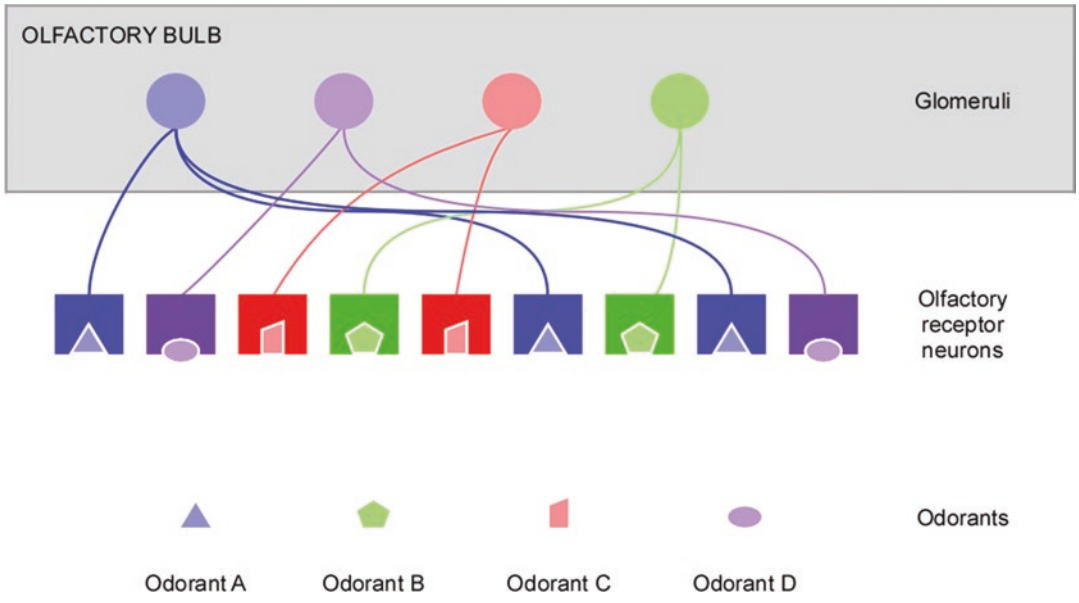

Fig. 30.2 Basic schematic representation of odor coding at the level of neuroepithelium and glomeruli. Odorant molecules bind with specific olfactory receptor neurons. Each olfactory receptor neuron possesses only one type of odorant receptor. Olfactory receptor neurons carrying the same type of receptor send their axon to the same glomerulus at the level of the olfactory bulb

tufted cells; (4) the mitral and tufted cells layer contains cell bodies of mitral and tufted cells (second-order olfactory neuron); (5) the internal plexiform layer; and (6) the granule cell layer contains rows of mitral and tufted axons and granule cells which are interneurons.

Axons of the mitral cells and tufted cells coalesce to form the olfactory tract, located at the base of the forebrain.

Centripetal information is secondary to neuronal activation, with glutamate as the principal neurotransmitter.

30.2.2.3 The Second Olfactory Structure: The Primary Olfactory Cortex

As compared to all other senses, olfaction is particular in that second-order olfactory neurons send information directly to primary olfactory cortex. In humans, the olfactory bulb is connected to the primary olfactory cortex by the fibers of the lateral olfactory tract (LOT). The LOT conveys olfactory information to a wide number of brain areas within the frontal lobe and the dorsomedial surface of the temporal lobe, often referred to primary olfactory cortex.

The primary olfactory cortex comprises the piriform cortex, which covers the uncus, the entorhinal cortex, the anterior olfactory nucleus, the periamygdaloid cortex, the olfactory tubercle, and nucleus. These projections are mainly ipsilateral, but there are also contralateral connections via the anterior commissure [7–9]. Some of the structures of the primary olfactory cortex then project to tertiary highest cognitive centers of the brain. The major projection of the piriform cortex is the thalamus, but it will also project to the insular cortex, the orbitofrontal cortex (neocortex), and the hypothalamus. The entorhinal cortex supplies afferent input to the hippocampus, while the olfactory tubercle connects to the thalamus. The amygdala is the major source of afferents to the hypothalamus (Fig. 30.3). Interestingly, there are many interactions between the secondary olfactory structures: between the anterior olfactory nucleus and the piriform cortex, the piriform cortex and the olfactory tubercle, the piriform cortex and the entorhinal cortex.

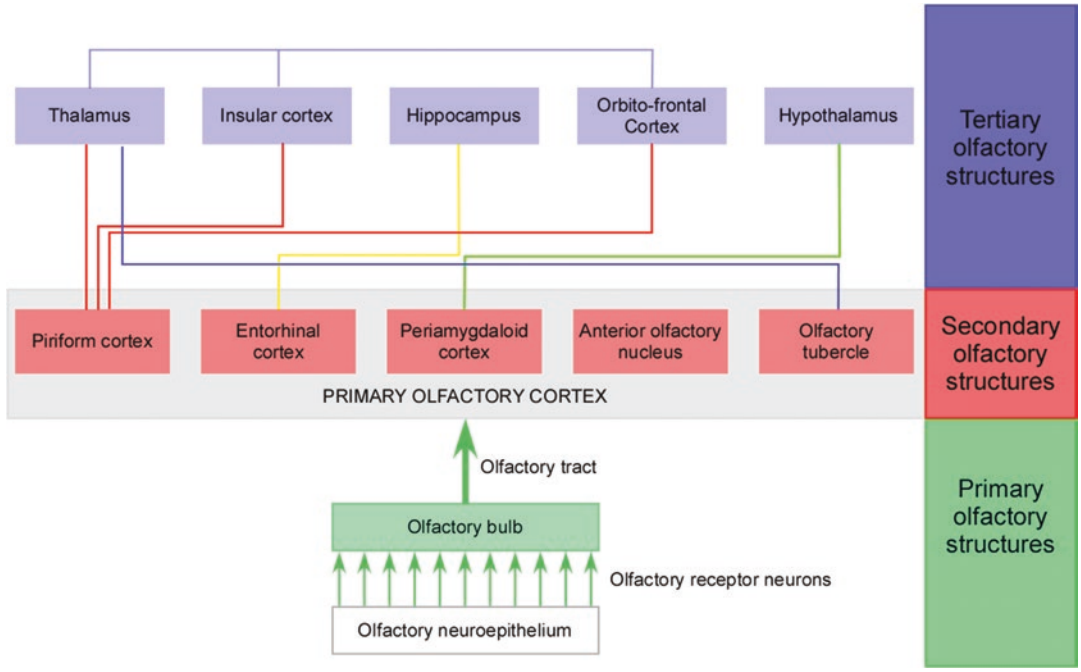

Fig. 30.3 Schematic diagram of major olfactory pathways

30.2.2.4 The Tertiary Olfactory Structures

The tertiary olfactory structures are the thalamus, the hypothalamus, the amygdala, the hippocampus, the orbitofrontal cortex, and the insular cortex.

The thalamus receives information from the piriform cortex and the olfactory tubercle. The hypothalamus, the orbitofrontal cortex, and the insular cortex also receive afferent input from the piriform cortex, while hippocampus is connected to entorhinal cortex. We should also note that there are also some interactions between these tertiary olfactory structures. In this way, the thalamus connects to the orbitofrontal cortex and the insular cortex. Therefore, the orbitofrontal cortex and the insular cortex receive direct input from the piriform cortex and indirect input via the thalamus.

30.2.2.5 Centrifugal Information

Most secondary and tertiary structures have numerous centrifugal fibers leading to the olfactory bulb, with GABA and acetylcholine as principal neurotransmitter. The supposed aim of this centrifugal information is to allow the brain to control the incoming flow of olfactory signals.

30.2.2.6 Properties of Olfactory Pathways

The olfactory pathways are distributed to different brain structures that are involved in the determination of our personal and social behavior. For example, the connections with:

1. Hippocampus and limbic system are thought to influence our memory system.
2. Amygdala system could act on emotional, motivational and craving circuits.
3. Hypothalamus, that mediates feeding regulation, could influence our feeding behavior.
4. Orbitofrontal cortex mediates our conscious perception of odors and could influence our preferences [10].

Hence, odor perception may affect our behavior and plays a major role in our interaction with the environment.

The olfactory system present unique properties as compared to other sensory systems. They are (1) the predominance of ipsilaterality of the olfactory projections, (2) the conduction of odor-evoked signals without an obligatory thalamic relay, and (3) the intimate overlap with limbic regions of the brain [11].

1. Odor processing remains principally ipsilateral [7–9] all the way from the nasal periphery to the primary olfactory cortex. This feature is different for other sensory modalities, such as the visual or auditory systems which, early in the processing pathways, supply sensory information in both hemispheres. This may help the cortex better discriminate and make bilateral odor comparisons and perhaps provide differential access to odor memories.
2. The absence of an obligatory thalamic relay is also in contrast with other sensory modalities in which an incoming signal undergoes thalamic modulation prior to being delivered to the sensory-specific cortex [11]. The absence of thalamic sensory integration in the olfactory pathways would seem to have an evolutionary explanation [11].
3. The connections between the olfactory system and the limbic system appear to be involved in the emotional and memory background to odorant stimuli, our social behavior, and the formation of novel stimulus-reinforced associations [11].

30.2.3 Orthonasal and Retronasal Olfaction

Paul Rozin noted that smell is unique in having a "dual nature"—meaning that it can sense signals originating outside (orthonasal) or inside (retronasal) the body [12].

Orthonasal olfaction refers to odorants originating outside and sniffed in through the nares to reach the olfactory neuroepithelium. This route is used to smell odors from the environment, such as perfumes, food aromas, smoke, predator smell, social odors, or pheromones. Orthonasal olfac-

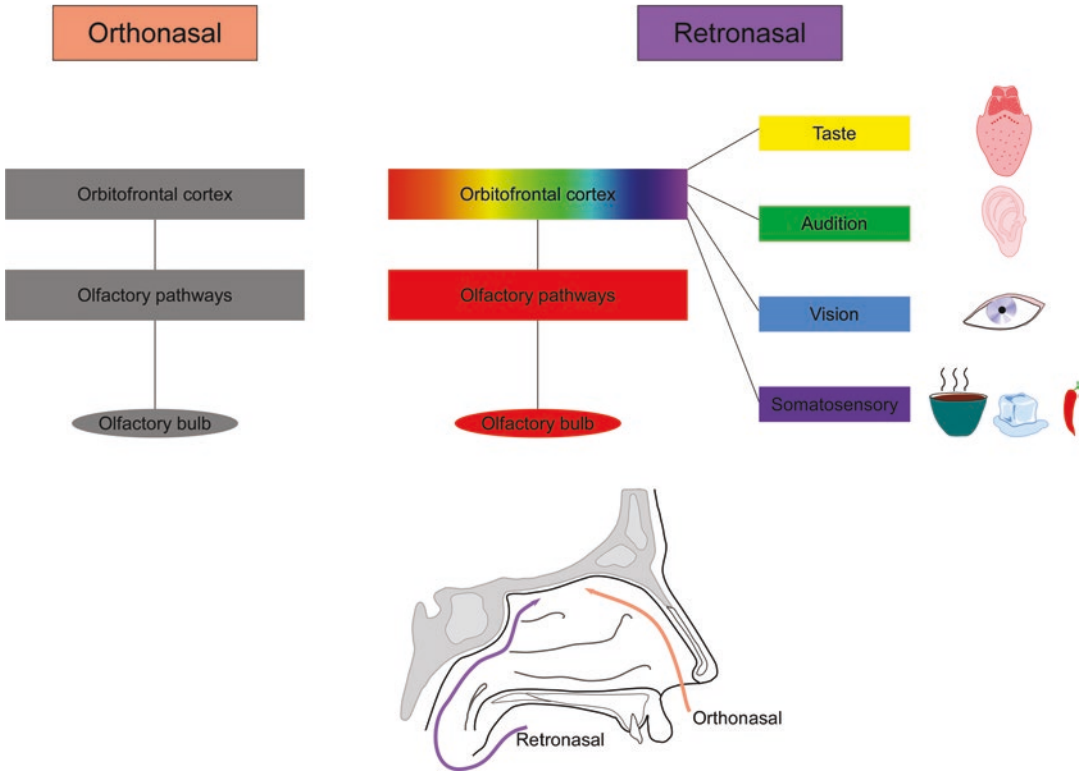

Fig. 30.4 Schematic representation of the central processing of orthonasal and retronasal olfaction. Orthonasal olfaction is processed by the olfactory pathways. On contrast, retronasal olfaction is not only processed by olfactory pathways but is also influenced by other sensory modalities, which are taste, sound, vision and proprioception. These multisensory information are integrated in the orbitofrontal cortex

tion is processed by olfactory pathways and is influenced by the visual pathway.

Retronasal olfaction refers to odorants originating from the back of the mouth and reaching the olfactory neuroepithelium via the nasopharynx. This retronasal stimulation occurs during food ingestion. It is activated only when breathing out through the nose, between mastication and swallowing [10, 13]. The retronasal olfaction, also termed as "flavor," account for an important part of food identification. This explains why a majority of patients suffering from smell disorder also complain of "taste" disorder, although their sense of taste is intact. On contrast to orthonasal olfaction, flavor perception is not only processed by olfactory pathways but is also influenced by almost all sensory modalities, which are taste, touch, sound, and proprioception (for a review see [10]). Indeed, the orbitofrontal cortex receives connections from other sensory neocortical areas (taste, hearing, touch, and vision) [14] (Fig. 30.4). Since it is receiving multisensory input and integrating these different sensory information, the orbitofrontal cortex is an important area to influence our food preferences and choices.

30.2.4 Olfactory and Trigeminal Interactions

The nasal fossa has double innervations from olfactory and trigeminal afferents. Although odorants are defined as volatile compounds having the ability to activate the olfactory system, the vast majority of odorants will actually acti-

vate both the olfactory and trigeminal system. Sensations resulting from the activation of the olfactory system are those of odors, while sensations induced by the stimulation of the trigeminal nerve are somatosensory (tactile, thermic, pain, humidity).

Olfactory and trigeminal systems closely interact with each other, and the stimulation of these two systems leads to important overlap in their activation pattern in the brain [15–19]. The interaction between both systems is complex and takes place both at a peripheral or central level (for a review see [20, 21]). This interaction is difficult to predict, but it has a powerful influence on odor perception both at different concentrations of a single stimulus and between mixtures of chemosensory stimuli. According to the literature, the pattern of interaction seems to depend on stimulus quality, intensity, and relative intensity of olfactory and trigeminal components of the mixture (for a review see [21]). Some reports have investigated the olfactory modulation of trigeminal-mediated sensations in patients with olfactory loss demonstrating that a close interaction and many compensatory mechanisms exist [22].

30.2.5 Variability in Normal Olfactory Function

Among other senses the olfactory function decreases over time and it has been described in numerous previous studies that there is a strong decrease in olfactory function above the age of 55 years [23, 24]. Several mechanisms have been proposed to explain this age-related olfactory dysfunction. At a peripheral level, changes in mucociliary movement, mucus composition, submucosal blood flow, and epithelia thickness might disturb the transport of the odorant to the receptor [25]. At the level of the neuroepithelium it is assumed that the regeneration of olfactory receptor neurons decreases over age [26, 27]. At a central level, brain damages due to chronic ischemia or systemic disturbance might also be proposed as a potential cause of age-related olfactory disorder.

Hummel et al. reported that there is a differential change of olfactory functions with aging. Indeed, olfactory thresholds decrease more strongly with age as compared to odor discrimination and odor identification [23, 28]. Since threshold measurements best reflect the function of the peripheral olfactory system than other olfactory tests [29–31], this finding might indicate that age-related change of olfactory function is at least in part due to damage of the olfactory epithelium [23]. Nevertheless, we should also keep in mind that age-related decrease of olfactory function might also be a consequence of side effects of drugs, onset of neurodegenerative diseases, etc.

A sex-related difference in olfactory function has also been widely reported [23, 32–35], with women outperforming men. Several causes have been proposed to explain this phenomenon, such as hormonal effects and congenital factors. However, the origin of this sex-related difference is still unclear.

Finally, some healthy people might present a specific anosmia. That is a physiological condition where a person of otherwise normal olfactory acuity is unable to detect a specific odorant. Specific anosmias have been described for series of odors [36]. It is admitted that specific anosmia has a genetic basis and the occurrence of specific anosmia indicates that specific receptors are necessary for perceiving specific odors [37–41]. One of the most frequent and well-known specific anosmia is androstenone anosmia. The prevalence of this specific anosmia is still a matter of debate. It is usually admitted that about 30% of the population is unable to detect the odor of the androstenone. But there is a high variability in the prevalence reported in the literature, ranging from 1.8 to 75% [42] (for a review see [42]). This might be at least in part explained by the various stimulation methods, criterion for non-detection, and concentrations that were used in the different studies [42].

30.3 Pathology

Although olfaction is often described as one of the less important sense, smell disorders have severe consequences, including impaired quality of life, daily life problems (cooking, detection of potentially dangerous odors) [43], altered food choices and consumption patterns than can negatively impact health (decreased body weight, overuse of salt inducing blood hypertension, overuse of sugar inducing diabetes mellitus, impaired immunity, etc.), and even depression [44].

The incidence of olfactory dysfunction among the population is still a matter of debate. Authors report an incidence of 1–3% of dysfunction among population [24, 45]. Nevertheless a study by Landis et al. reported higher values of olfactory dysfunction among population without sinonasal complaints, with a rate of 4.7% of anosmia and 16% of hyposmia. The frequency of parosmia and phantosmia was reported with a rate of 2.1% and 0.8%, respectively [46]. Recently, the SARS-CoV-2 pandemic has been found to be frequently associated with olfactory dysfunction, causing an anosmia pandemic across the world.

The evaluation of patients suffering from olfactory disorders requires a precise clinical work-up procedure in order to (1) determine the etiology of the olfactory dysfunction, (2) assess olfactory function and, hence, (3) provide an optional treatment, a prognosis, and appropriate counseling to patients. Assessment of olfactory function is reviewed in Chap. 33.

30.3.1 Classification of Olfactory Disorders

30.3.1.1 Quantitative Olfactory Disorders

Quantitative olfactory disorders are hyposmia, hyperosmia, and anosmia (Table 30.1). Hyposmia refers to a decreased ability to smell. This is a common condition. Indeed, Landis et al. reported that up to 16% of the general population is hyposmic [46].

Table 30.1 Classification of smell disorders

Quantitative smell disorders	Qualitative smell disorders
• Hyposmia • Anosmia – Functional anosmia – Specific anosmia • Hyperosmia	• Parosmia • Phantosmia • Olfactory agnosia

Hyperosmia is a rare condition and refers to enhanced ability to smell. It can happen after exposure to toxic vapors [47] or during migraine [48].

Anosmia refers to the lack of ability to smell. It is assumed that about 5% of the general population exhibit functional anosmia [46]. Functional anosmia refers to a significantly reduced ability to smell although some smell sensations can be present.

30.3.1.2 Qualitative Olfactory Disorders

Qualitative olfactory disorders are parosmia, phantosmia, and olfactory agnosia. Parosmia is sensation that a given odor is different than the typical odor for this substance. Parosmia is typically associated with reduced olfactory sensitivity and is particularly frequent in patients suffering from post-infectious olfactory loss (up to 50%) [49]. It is also associated with post-traumatic olfactory loss or sinonasal-related olfactory disorder. Studies found a prevalence of parosmia in 19% [50], 20% [51], and 28% [49] of patients presenting to « Smell and Taste » clinics, while the prevalence of parosmia in the general population is reported to be 2.1 [46] to 4% [52]. It is typically unpleasant. Euosmia is a rare form of parosmia with a pleasant parosmia to selected odorants [53]. The pathophysiology of parosmia is not clear. There are two hypotheses: the central and the peripheral hypotheses. In periphery, loss of olfactory receptor neurons changes the integrity of the olfactory image, resulting in an incomplete and meaningless picture of the odorant. Centrally, it has been proposed that the integration and interpretation of odors are altered [54].

Phantosmia is the perception of an odor when none is present. It may be reed to a wide range of

pathologies (post-infectious olfactory loss, post-traumatic olfactory loss, rhinosinusitis, neurologic, etc.).

Finally, olfactory agnosia is defined as the inability to recognize odor sensation.

30.3.2 Etiology of Olfactory Disorders

There are several causes of olfactory dysfunction. The most frequent are chronic rhinosinusitis, post-infectious olfactory loss, and post-traumatic olfactory loss. These three etiologies account for up to two-thirds of the patients with olfactory disorder [55, 56]; therefore, we will largely extend on these 3 pathologies. However, several pathologies might also affect olfactory function, such as neurological disease, metabolic diseases, toxics, and tumoral disease of the sinonasal cavities or brain (Table 30.2). It is therefore essential to investigate about the etiology of olfactory dysfunction. An algorithm for the management of olfactory dysfunction is proposed in Fig. 30.5.

30.3.2.1 Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) with or without polyps is the most common cause of olfactory dysfunction, accounting for 14–30% of cases [57–60]. Inversely, olfactory impairment is acknowledged as a key symptom for the diagnosis of CRS [61]. Nevertheless up to one quarter of patients with CRS are unaware of their decreased olfactory abilities, probably because the olfactory dysfunction in CRS develops slowly, and in consequence, only a few patients note this disorder [62].

Olfactory dysfunction in CRS is explained by a combination of conductive olfactory loss (i.e., polyps, edema, nasal discharge, etc.) and neurosensory disturbance due to mucus and neuroepithelial alterations resulting from chronic inflammation [63].

In the context of CRS, olfactory dysfunction is mainly quantitative, appears gradually and fluctuates over time. Patients may also report qualitative dysfunction such as parosmia and

Table 30.2 The different etiologies of olfactory disorders

Rhinologic disease
- Chronic rhinosinusitis (with or without nasal polyps)
- Allergic rhinitis [164–166]
- Atrophic rhinitis [167]
- Post-surgical [167, 168]
- Olfactory cleft syndrome

Post-infectious olfactory loss

COVID-19-related olfactory loss

Post-traumatic olfactory loss

Congenital anosmia

Neurologic disorder
- Alzheimer's disease
- Idiopathic Parkinson's disease, …

Tumor
- Intranasal
  - Esthesioneuroblastoma
  - Adenocarcinoma
- Intracranial
  - Gliomas
  - Olfactory meningiomas

Toxic [169–171]
- Metals (cadmium, manganese, mercury, aluminum)
- Gases (formaldehyde, methyl bromide, styrene, chlorine)
- Solvents (toluene, butyl acetate, benzene)
- REF
- Hairdressing chemicals
- Intranasal zinc

Drug induced (for review, see [172, 173])
- Chemotherapy drugs
- Analgesic (antipyrine)
- Local anesthetics (cocaine HCL, procaine HCL, tetracaine HCL, lidocaine)
- General anesthetics
- Antimicrobial (amoxicillin, aminoglycosides, macrolides, doxycycline, pyrazinamide)
- Antirheumatics (mercury/gold salts, D-penicillamine)
- Antithyroids (propylthiouracil, thiouracil)
- Cardiovascular, hypertensives (angiotensin conversion enzyme inhibitors, nifedipine, amlodipine)
- Gastric medication (cimetidine)
- Intranasal saline solutions (with acetylcholine, menthol, zinc sulfate)
- Opiates
- Sympathomimetics

Metabolic/endocrine (*for a review*, *see* [174])
- Adrenocortical insufficiency
- Cushing's syndrome
- Hypothyroidism
- Pseudohypoparathyroidism
- Hepatic [175] or renal failure [176]

Psychiatric [177]

Idiopathic

Pathologies that are underlined are deeply commented in the text

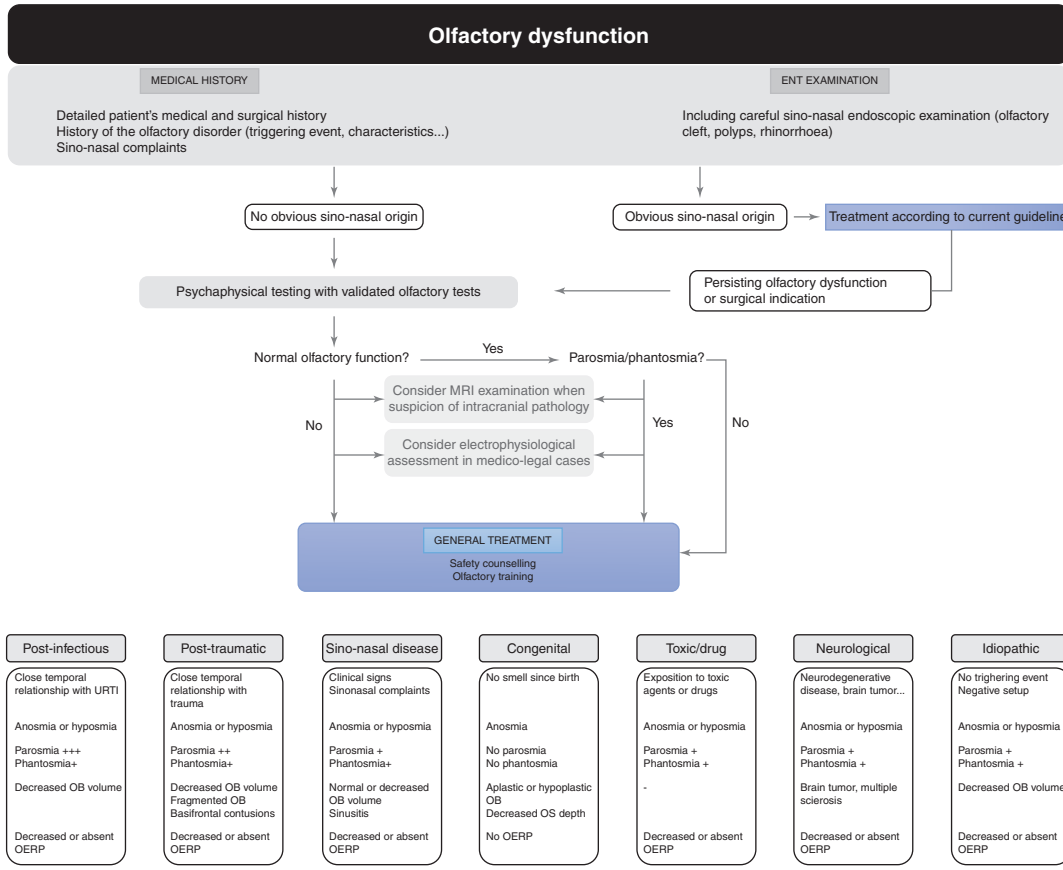

Fig. 30.5 Algorithm for the management of olfactory disorders and summary of the main features of the most frequent olfactory disorders. *OB* olfactory bulb, *OS* olfactory sulcus, *OERP* olfactory event-related potentials

phantosmia. However, these symptoms seem less frequent in sinonasal disease compared to other etiologies (i.e., post-infectious, post-traumatic). Reden et al. [49] reported incidence of parosmia and phantosmia in patients with CRS of 28% and 7%, respectively.

Studies have described that the severity of quantitative olfactory dysfunction is related to the importance of the sinonasal disease, based on endoscopy and CT score [64]. Patients with nasal polyps show a higher incidence of olfactory disturbances and a higher incidence of anosmia than patients with CRS without polyps. This more severe symptomatology may be explained not only by the conductive olfactory loss induced by polyps but also by degenerative changes associated with recurrent infections, scaring, chronic nasal medication, exotoxins, and enhanced secretion of cytokines from *Staphylococcus aureus* infection and neurotoxic cytokines released by a huge eosinophilic population [65–69].

Treatment of CRS should follow current guidelines [61]. Medical treatment notably relies on corticosteroids, either topical or systemic [61]. Corticosteroids are able to improve CRS-related olfactory dysfunction, with usually a higher efficacy of systemic steroids (for a review see [63]). In the last years biological treatments have been developed. Dupilumab is now FDA approved for the treatment of CRS and has favorable olfactory outcome [61, 70]. Surgery can also be proposed to a subset of patients suffering from CRS. Several studies have investigated the effect of surgery on olfactory function and generally showed an improvement of olfactory function [71]. However, there is a large heterogeneity

regarding the methodology and only a few studies used validated psychophysical testing to assess olfaction [71].

30.3.2.2 Post-Infectious Olfactory Loss

Post-infectious olfactory loss is defined as a sudden loss of olfactory function following an upper respiratory tract infection (URTI) and was described for the first time more than 20 years ago [72]. The upper respiratory infection subsides over time and leaves the patient with an olfactory dysfunction that persists over a long period. There is a close connection in time between the URTI and the onset of the olfactory disorder [73]. The exact pathogenic agent is rarely determined but is assumed to be viral, and so this disease is known as "post-viral" or "post-infectious" olfactory loss. The exact incidence of olfactory dysfunction following URTI is not known as many patients with URTI do not report their symptoms, so the exact incidence of common cold in the population is unknown. However, post-infectious olfactory loss is diagnosed in approximately one quarter of the patients in groups presenting to specialized centers, such as smell and taste clinics [44, 74–76]. Recently, a new pathogen, the SARS-CoV-2, is emerged. Besides classical respiratory symptoms initially described, it revealed to create smell disorders in a high rate of patients. COVID-19-related olfactory dysfunction seems to differ from other post-infectious olfactory loss. Therefore, we will give a specific focus to it.

Patients with post-infectious olfactory loss are usually women and the disease typically occurs between the fourth and the sixth decades of life [73, 75, 77]. Onset of the URTI is often sudden and awareness of the olfactory dysfunction is present when major symptoms secondary to the infection subside. Many patients also have endoscopic or radiological evidence of rhinosinusitis. It is therefore mandatory to treat this condition and observe the impact of this treatment on the sensorineural disorder. Patients usually complain of moderate to severe olfactory loss but the degree of olfactory loss is usually less severe than in patients with head trauma [78]. Parosmia and phantosmia are also present and range to 10–50% [49, 72, 79]. Seasonal variation in the incidence of post-infectious olfactory loss has been demonstrated with the highest incidences being in March and May [80]. This is probably due to the seasonal variation of viral particles, such as parainfluenza virus type 3 [75, 81, 82].

Diagnosis should be based on (1) history of an olfactory disorder following an URTI and a close temporal relationship between the two, (2) patency of the olfactory cleft at the endoscopic examination, and (3) absence of any other causes, such as toxic exposure (medication taken to treat the URTI and possibly causing an olfactory disorder themselves), an inflammatory process in the nasal fossa (diagnosed with an endoscopic evaluation), or neurological problems, such as neurodegenerative diseases.

The exact mechanism leading to post-infectious olfactory loss is not yet fully understood. Viral particles may damage the olfactory receptor neuron and provoke immune response that also leads to damages in the olfactory neuroepithelium and damage the central olfactory pathways. Viruses are also capable of penetrating the brain via the fovea ethmoidalis. Many viruses may cause olfactory impairment, examples being the influenza virus, parainfluenza virus, respiratory syncytial virus, coxsackievirus, adenovirus, poliovirus, enterovirus, and herpes virus. The exact determination of the viral agent is not useful in the clinic and viral serology is not mandatory. Experimental intranasal infection with influenza virus A leads to increased apoptosis and increased fibrosis in the olfactory neuroepithelium [83, 84]. This mechanism is thought of as a protective one that limits the access of viral particles to the brain. Histopathological findings relating to the olfactory neuroepithelium of patients with post-infectious olfactory loss have revealed that severely affected patients have reduced numbers of ciliated olfactory receptor cells [85]. Moreover, dendrites of the olfactory receptor neurons usually fail to reach the epithelial surface and therefore have no contact with odorant particles. Attempting to correlate the importance of the olfactory neuroepithelial damage with the extent of the olfactory dysfunction

as well with the chances of recovery generated conflicting results [85, 86]. Overall, post-infectious olfactory loss is probably secondary to a viral attack both at a peripheral level (olfactory neuroepithelium) and at a central level (olfactory bulb) and these two sites interact both in the pathological condition and in the recovery phase.

The spontaneous recovery of olfactory performance is found, due to the plasticity of our olfactory system, in about one-third of the post-infectious olfactory loss patients [87]. Olfactory function may decline (rare), not change, show some improvement, a major improvement, and improve into the absolute normal range or into the range adjusted for age [88]. Several prognosis factors have been described in the literature. Prognosis seems to be more favorable when the psychophysical tests reveal incomplete olfactory loss (i.e., hyposmia vs anosmia) [88–90]. Age and sex also seem to be important in the assessment of the prognosis since women and younger patients tend to recover more frequently than men and older patients [89]. Another prognostic factor is the duration of the disease [88, 90]. Electrophysiological measures are also predictive of recovery since it was demonstrated that the presence of olfactory event-related potentials at the time of diagnosis is linked to a better outcome in patients with post-infectious olfactory loss [91]. With regard to the meaning of qualitative olfactory disorders, reports have been mixed in relation to the likelihood of recovery [49, 90].

At present there is no medical therapy that has been proven effective. Many drugs have been tried in non-randomized and uncontrolled trials: topical or systemic corticosteroids [92], zinc sulfate [93, 94], quinoxaline derivatives [95], alpha lipoic acid [96], and pentoxifylline [97]. Although early promising results with some molecules have been demonstrated, these medications helped patients achieve partial or full recovery in unpredictable ways [87]. Recent systematic reviews about the usefulness of corticosteroids concluded that there is a paucity of high-quality studies demonstrating the efficacy of oral or topical steroids. Notably, topical steroids do not improve olfactory function, while weak evidence supports oral steroids, that could be considered as an option, in some selected patients after careful consideration of the potential side effects [98, 99]. On contrast, olfactory training is acknowledged as the gold-standard treatment of post-infectious olfactory loss [99]. This method consists in smelling four odorants, for 10 min, twice a day, during at least 12 weeks [100]. Finally, adequate counseling of the patient is of importance to help him cope with his deficit in his everyday life (for nutrition, hazard detection, hygiene, etc.).

30.3.2.3 COVID-19-Related Olfactory Dysfunction

Olfactory loss is a common symptom of COVID-19, a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 pandemic was therefore associated to a pandemic of olfactory dysfunction. This raised media and public attention toward the, until there usually neglected, sense of smell.

The reported frequencies of olfactory loss vary a lot across the different studies, probably because of the large heterogeneity in methodological approaches. Meta-analyses have determined that the pool frequency olfactory dysfunction (either based on questionnaire or smell tests) was 56 [101]–61% [102]. Importantly, olfactory dysfunction can be reported as the first symptom of COVID-19 in 20% of cases [103]. Olfactory dysfunction can range from anosmia to hyposmia [104]. Patients usually recover within the first month [104]; however, it is estimated that 5% patients will remain with persistent smell loss at 6 months after the onset [105]. Importantly, olfactory dysfunction does not seem to be associated with other nasal symptoms, such as nasal congestion or rhinorrhea [106]. Parosmia frequently occurs a few months after the acute event and has been reported by 27.5% of patients at 4-month follow-up. It usually resolves over time, but 12.5% of patients still report anosmia at 1 year [107].

Several mechanisms have been proposed to explain COVID-19-related olfactory dysfunction [108]. First, it could result from the release of

proinflammatory mediators at the level of the olfactory cleft. Indeed, high levels of TNF-α and IL-6 have been reported in COVID-19 patients with olfactory dysfunction. These mediators not only could induce edema of the olfactory mucosa and conductive smell loss but could also impair sensory transduction and induce apoptosis [108–110]. Second, ACE2 and TMPRSS2, the entry proteins of SARS-COV-2, have been found in the olfactory supporting cells. Infection of olfactory supporting cells could lead to a disorganization and hence a dysfunction of the olfactory epithelium [111, 112]. Third, although olfactory sensory neurons do not express ACE2 and TMPRSS2, it is possible that these cells are infected through tight junctions with sustentacular cells [108]. Finally, it has been found that IgA produced against SARS-CoV-2 may block odorant receptors carried at the surface of olfactory sensory neurons [113].

Until now, there is no specific treatment for COVID-19-related olfactory dysfunction and olfactory training is recommended considering its effectiveness in other causes of olfactory dysfunction and safety. Moreover, considering the high recovery rate after COVID-19 olfactory dysfunction, it is also important to reassure the patient regarding its probable outcome.

30.3.2.4 Post-traumatic Olfactory Loss

Head trauma is, according to Nordin's literature review published in 2008, the third most common cause of olfactory disorder [114]. The incidence of olfactory disorder following head injury is difficult to estimate because (1) patients admitted to emergency often fail to receive an assessment of their sense of smell due to the potentially life-threatening nature of head trauma and the frequent occurrence of other injuries requiring immediate medical attention, (2) the time and the resources for such an examination are lacking in emergencies, (3) patients are not able to recognize their loss of olfactory function, more especially when there is an associated neurological deficit, (4) there is no medical follow-up if the olfactory disorder has no subjective impact for the patient, and (5) there is a lack of reports about spontaneously resolving olfactory disorder. For these reasons, the reported incidence is probably underestimated and variable depending on recruitment: in patients seen at a Head Injury Clinic, incidence is estimated between 2 and 12% [115, 116] and between 8 and 20% in Smell and Taste Centers [44, 49, 50, 60, 117, 118].

The patients at most risk of post-traumatic olfactory loss are young male adults. This is thought to be related to increased severity of trauma in this population. In both sexes generally, patients aged over 70 are most at risk [115, 119]. The most common type of trauma is a fall in 61% of patients, followed by car accidents in 20% and assault in 13% [115]. Several risk factors for the development of post-traumatic olfactory loss have been described: (1) the severity of the injury with more severe trauma being at higher risk of olfactory dysfunction [115, 120, 121], (2) the impact location and direction with a higher prevalence of post-traumatic olfactory loss when the front of the back of the head is stuck rather than the side [115, 122], and (3) the age of the patient, with a higher risk in the elderly patients [119]. In addition, it is important to note that in a traumatic context, olfaction might also be affected by the treatment of the injury, possibly complicating the etiological diagnosis (i.e., neurosurgical procedures, facial fracture reductions, usage of drugs, such as opioids and antimicrobial agents).

Typically, patients experience a sudden onset of olfactory symptoms [44], occurring some days after the trauma. Head trauma produces, on average a greater degree of olfactory decrement as compared with other etiologies of olfactory dysfunction [44, 119]. Post-traumatic olfactory disorder patients have anosmia ranging from 48 to 78% and hyposmia ranging from 5 to 27.4% [54, 115, 116, 122]. Qualitative disorders are commonly found in patients with head trauma. Parosmia is reported in 14–35% of cases [49, 60, 117] and phantosmia in 10–41% of the patients [49, 50, 117]. The prevalence of parosmia tends to decrease over time.

Three possibly co-existent lesions are likely to cause post-traumatic olfactory loss [116]. First, injuries to the sinonasal tract with obstruction of

the passage to the olfactory cleft can lead to an obstructive post-traumatic olfactory loss. Second, shearing of the olfactory nerves at the cribriform plate might induce an olfactory loss. Notably, olfactory nerves can be injured after: (1) a translational shift of the encephala secondary to postero-anterior coup and contrecoup forces in the case of occipital impact; or (2) fractures is the naso-orbito-ethmoid region involving the cribriform plate. Third, contusions and brain hemorrhage involving olfactory bulbs and/or the olfactory cortex might also produce an olfactory disorder.

The prognosis seems to be reserved: some improvement may be expected in about one-third of the patients, although complete recovery is only achieved in 10–15% [44, 49, 88, 89]. Recovery is most likely to occur within the first 6 months to 1 year after the initial insult [88]. However, late recovery has been described, occurring until 9 years after the trauma [123–125].

No medical treatment has yet been proven to be effective. Olfactory training is currently recommended as gold-standard treatment [100, 126] and appropriate counseling is also mandatory.

30.3.2.5 Congenital Anosmia

Congenital anosmia is defined as the absence of olfactory sensation since birth or early childhood. This condition can be divided in (1) syndromic anosmias (e.g., Kallmann's syndrome [127] and Klinefelter's syndrome [128, 129], congenital insensitivity to pain [130, 131], and ciliary dysfunction [132, 133]) or (2) anosmias without evidence of other defects (isolated anosmia since birth or early childhood), which seems to be more frequent than syndromic anosmia [134–137]. Although 5% of the general population is anosmic [46], congenital anosmia remains a rare cause of olfactory disorder and isolated congenital anosmia account for about 1% of anosmias.

Diagnosis of congenital anosmia is based on anamnesis (patients have no recollection of ever being able to smell), psychophysical and electrophysiological assessment of olfactory function, and imagery. Magnetic resonance imaging is the imaging modality of choice for the assessment of olfactory apparatus in cases of suspected congenital anosmia. Indeed, we know from the literature that in isolated anosmia and in Kallmann's syndrome, the olfactory bulb and olfactory tract can be aplastic or hypoplastic [138–140]. The depth of the olfactory sulcus is also a useful indicator of congenital anosmia since we know that the depth of the olfactory sulcus at the level of the "plane of the posterior tangent through the eyeballs" reflects the presence of olfactory bulbs and tracts [140] and clearly indicates isolated anosmia if it is smaller than 8 mm [141].

When diagnosing a congenital anosmia, it should be discussed to realize a genetic and endocrinological evaluation. Also, since this disease cannot be treated, it is mandatory to give the patient or his/her parents the best information about this disease and to give counseling about everyday life (i.e., gas and smoke alarms, particular attention when cooking, hygiene, etc.).

30.3.2.6 Neurological Disorders

It is well known that some neurodegenerative diseases, such as idiopathic Parkinson's disease and Alzheimer's disease are associated with early olfactory dysfunction [142]. Because of the high prevalence of these neurodegenerative diseases in elderly subjects, the early diagnosis of these diseases constitutes a major public health issue for our aging societies. At present, the early differential diagnosis between idiopathic Parkinson's disease and Parkinsonism associated, for example, to multiple system atrophy, Lewy body disease, or corticobasal degeneration remains difficult, such as the differential diagnosis of mild cognitive impairment that may be the early expression of Alzheimer's disease, but also other forms of neurodegenerative diseases, and late-life depression. Many studies have suggested that the evaluation of the olfactory function can contribute significantly to the early diagnosis of these pathologies.

In idiopathic Parkinson's disease (IPD), olfactory dysfunction was first described by Ansari and Johnson in 1975 [143]. Olfactory disorders are often considered as an early and reliable sign of idiopathic Parkinson's disease (IPD), since

they are present in more than 90% of all IPD patients [144, 145]. In accordance with the staging of Braak [146] it has been hypothesized that the early development of olfactory dysfunction is due to the early involvement of olfactory regions in the course of the disease. Several recent studies have shown that people suffering from idiopathic hyposmia or anosmia have an increased risk of developing IPD [147, 148], and that chemosensory event-related potentials are delayed or absent in IPD patients [149]. While IPD is associated with marked olfactory dysfunction leading to anosmia, other causes of Parkinsonism are not associated with strong olfactory dysfunction. For example, olfactory disorders would be moderate in multiple system atrophy, and absent in Parkinson's disease and in vascular Parkinsonism [150].

Olfactory disorders can also constitute one of the first signs of Alzheimer's disease (AD) [151]. The time course of histopathological changes in AD also indicates that olfactory dysfunction should precede cognitive dysfunction. Indeed, it has been shown that the formation of neurofibrillary tangles occurs first in the entorhinal cortex, while cognitive symptoms appear only once neuropathological changes have spread to the hippocampus and temporal neocortex [151]. Olfactory discrimination of AD patients is significantly lower than olfactory discrimination of patients suffering from mild cognitive impairment, which itself is lower than that of age-matched control subjects [152]. In addition, a recent clinical study has shown that the olfactory bulb and olfactory tract volume is decreased in AD patients, and that this atrophy is already present at an early stage of the disease [153]. Since early diagnosis of AD remains problematic, assessment of olfactory function should be useful for the early differential diagnosis of AD. This should be further investigated.

30.3.2.7 Olfactory Cleft Disease

Olfactory cleft disease is defined as an olfactory dysfunction due to a pathologic process limited to the olfactory cleft that can be visualized on clinical or radiological examination. Only few authors have reported this entity [154–156]. Biacabe et al. showed that olfactory disability was the major symptom of olfactory cleft disease and they identified three possible pathologic processes inducing olfactory cleft disease – malformative, inflammatory, and inflammatory associated with anatomical deformities of olfactory cleft boundaries – and hence suggest that computed tomography scanning is useful for the diagnosis of this disease. Finally, they showed that medical therapy was effective in lowering olfactory thresholds in 25% of the cases. Nevertheless, until now, indications of functional endoscopic surgery remain to be defined after failure of medical therapy.

30.3.2.8 Miscellaneous

Several other pathologies that might affect the olfactory function, such as tumors, toxics, drugs, and endocrine disorders, have been described. They are reported in Table 30.1.

30.3.2.9 Idiopathic Olfactory Loss

For a large number of patients, no obvious etiology to the olfactory disorder can be found. These people are thus considered as suffering from idiopathic olfactory loss. The reported prevalence of idiopathic olfactory loss in the literature range from about 20% [44, 49] to one-third [117] of patients suffering from olfactory disorder. These patients not only complain of quantitative olfactory disorder but may also complain of qualitative olfactory dysfunction [49, 157].

Previous work has indicated that idiopathic olfactory loss may be related to sinonasal disease. In fact in a study of 55 patients, almost 1/3 of patients with idiopathic olfactory loss responded to systemic treatment with corticosteroids [92], possibly indicating the presence of inflammation-related dysfunction. Hence, systemic steroid trial could be considered in patients suffering from idiopathic olfactory loss, after careful consideration of possible side effects. Olfactory training seems to be effective and should thus be proposed to patients suffering from idiopathic olfactory loss [126].

Finally, it is important to keep in mind that some patients with idiopathic olfactory loss may develop idiopathic Parkinson's disease or Alzheimer's

disease [158]. A recent retrospective study from Haehener et al. on a cohort of 474 patients found that 9.9% of patients with idiopathic smell loss developed Parkinson's disease after an 8-year mean follow-up. This rate increased to 28.6% for patients with combined smell and taste loss [159].

30.3.2.10 Olfaction and Quality of Life

We must note that olfactory dysfunction severely impairs the quality of life of patients, including detection of hazardous events, eating habits and cooking, nutritional intake, and interpersonal relations [43]. Furthermore, it has been demonstrated that patients suffering from olfactory disorders have a higher prevalence of mild to severe depression as compared to the general population [44]. Importantly, the impact on the quality of life is more severe when patients have an associated qualitative olfactory dysfunction [160, 161]. Indeed, parosmia leads to higher rate of mild depression than quantitative olfactory disorders. Finally, since patients reporting an improvement of their olfactory abilities have a better quality of life than patients reporting no improvement [162]; it is essential to investigate about the etiology of olfactory dysfunction in instance to provide an optimal treatment to the patients.

Several studies have also highlighted the link between age-related olfactory loss and nutritional disorders in older people. As reported above, there is a physiological decrease of olfactory function with advancing age. This age-related olfactory disorder negatively impacts the food intake of older people. Indeed, not only older people might have a reduced interest in food and hence reduced food intake, but also they tend to have less varied diet and consequently might develop deficiencies. This is problematic since inadequate diet and malnutrition are associated with a decline in functional status, impaired muscle function, decreased bone mass, immune dysfunction, anemia, reduced cognitive function, poor wound healing, and delay in recovering [163]. This may constitute a major public health issue in our aging population.

30.3.2.11 Counseling of the Patient

Consequences for daily life and coping strategy should be integrated in clinical management of patients, focusing on instructional information about fire alarms, domestic gas, hygiene, etc.

Nutritional recommendations should also be proposed to the patients in order to avoid altered food choices and consumption patterns than can negatively impact health (decreased body weight, overuse of salt inducing blood hypertension, overuse of sugar inducing diabetes mellitus, impaired immunity, etc.).

Finally, as reported above, olfactory training seems to be effective and should thus be recommended to patients [126].

30.4 Conclusion

Describing the olfactory pathways, we have shown that olfactory system has connections with brain areas associated with memory processes, feeding circuits, emotional, motivational, and craving circuits. Hence, it is easy to understand that, although often neglected, the olfactory system plays a preponderant role in our everyday's life and strongly influence consciously or non-consciously on emotions, social behavior, nutrition, memory, etc. Therefore, we can easily understand that olfactory disorders severely impact our quality of life and that patients suffering from olfactory disorders need a particular support. Indeed, physicians taking care of patients suffering from olfactory disorders must pay a particular attention to the quality of life of patients and to the potential negative impact of olfactory dysfunction on the patient's health (nutrition, detection of danger, depression, etc.).

Olfactory dysfunction due to sinonasal disease can be treated either medically or surgically, according to available guidelines. Unfortunately, medical treatments are still missing today for non-sinonasal causes and olfactory training remains the mainstay of the treatment. Besides this, considering the impact of olfactory dysfunction on everyday life, it is mandatory to provide patients complete information about the nature of

their olfactory disorder and their prognosis, as well as advices about occupations, safety at home, and how to make food more palatable and safe to eat.

Nowadays, about 20% of the population is hyposmic. But this number could increase in the future years due to our aging population and COVID-19 pandemic. This might constitute a major public health issue in the future years considering the close relationship between olfactory dysfunction and nutritional disorders in elderly people. Further researches are thus mandatory in order to propose new treatments to recover or to compensate for the olfactory loss.

Take-Home Messages

- Olfaction plays an important role in our daily life and olfactory impairment negatively affects quality of life and well-being.
- Besides physiological age-related decline of olfaction, olfaction can be affected by a wide range of pathologies. Identifying these possible causes is mandatory for the appropriate management and counseling of the patient.
- Sinonasal-related olfactory dysfunction should be treated according to current guidelines available.
- Unfortunately, no medical treatment as yet been proven to significantly impact the outcomes of non-sinonasal olfactory dysfunction.
- Olfactory training remains the gold-standard treatment for olfactory disorders.
- Counseling, psychological, and nutritional support are also mainstay of the treatment.

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