Hyposmia

The impact of impairment of sense of smell is often underestimated in clinical practice and its effect on quality of life may be profound (Philpott and Boak, 2014). Diminished sense of smell is common and may affect up to 5% of the population and up to 20% of those over the age of 60 years (Deems et al, 1991). A survey by the National Institute on Deafness and Other Communication Disorders estimated that more than 2.7 million adults in the United States (1.4% of the population) have chronic olfactory impairment (Hoffman et al, 1998).

There is a significant effect of olfactory dysfunction on quality of life and it is associated with a higher level of disability (Miwa et al, 2001). Unfortunately, there is still limited awareness among the general population of the impact of olfactory dysfunction on those who suffer from it.

Although the cause of olfactory loss is usually benign serious medical conditions including neurodegenerative disorders, e.g. Parkinson's disease, may present with this symptom.

An understanding of the olfactory pathways and systems involved in the sense of smell is imperative to identifying the likely cause of symptoms. This article outlines the common causes of olfactory dysfunction and management of the patient with a smell disorder.

Physiology and classification of olfactory dysfunction

The sense of smell is one part of chemosensory reception that comprises the olfactory, gustatory and trigeminal systems. Interpretation of olfactory signals centrally can be in the form of identification, discrimination, sensitivity, hedonics and odour memory. The odour receptors are located in a 3–5 cm^2 area of sensory olfactory epithelium located in the roof of the nasal cavity (*Figure 1*). This epithelium contains olfactory receptor neurones which have cilia that project into a layer of olfactory mucus (*Figure 2*). Odourants dissolve in the mucus and bind to specialized odourant binding proteins which facilitate the transfer of the odourant to the odourant receptor binding site in the cilia of the olfactory receptor neurone (*Figure 3*).

The mechanism of olfactory stimulation by the odourant is still under debate and theories regarding shape-docking and vibration (electron tunneling) have been suggested.

A key point is that the delivery of odourant to the upper nasal cavity requires a clear airway, good respiratory function and no significant mucosal oedema. Odourants may then stimulate the olfactory endings (lock and key theory) producing appropriate stimuli.

The axons of the olfactory receptor neurones pass through the cribriform plate into the olfactory bulb of the brain. Here they synapse with second order neurones

Figure 1. Olfactory receptor epithelium in roof of nasal cavity.

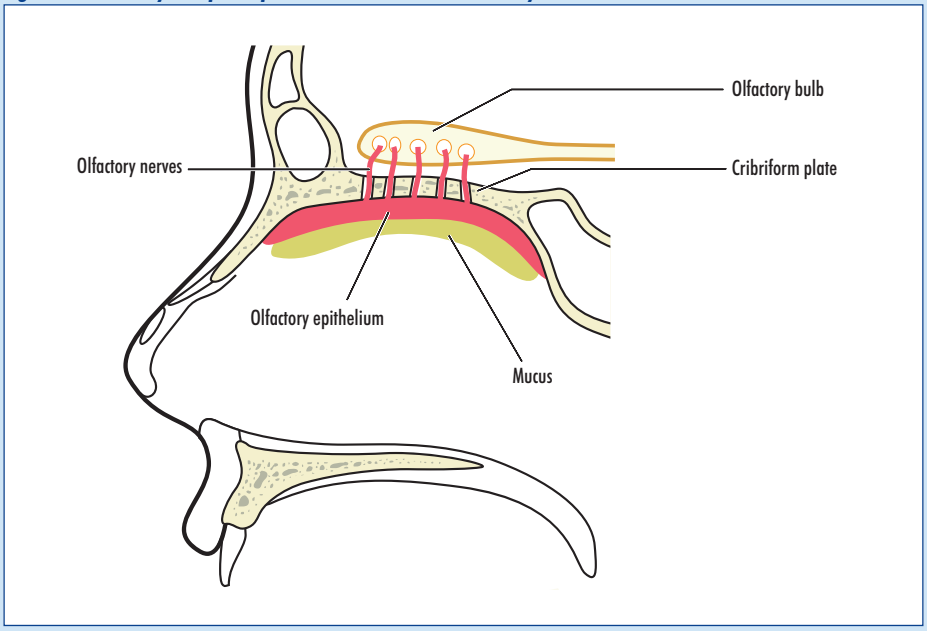
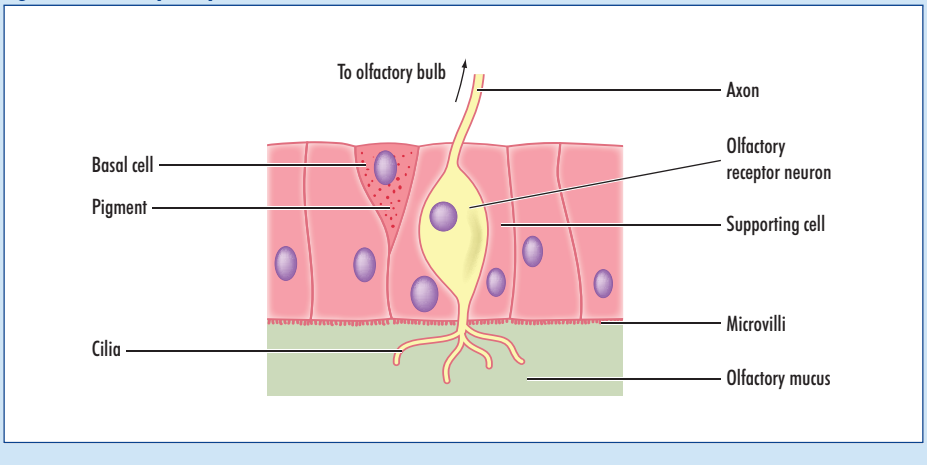


Figure 2. Olfactory receptor neurone.



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in the glomeruli, which then project to higher centres including the thalamus, amygdala and orbitofrontal cortex.

The physiology of smell can be used to understand the various points in the olfactory pathway where problems may occur.

A useful classification involves describing olfactory disorders as conductive (i.e. interference with the transfer of odourant to the olfactory neuroepithelium), sensory (olfactory receptor dysfunction) or neural (relating to central olfactory pathways) (Snow, 1991).

History and examination

The most common causes of olfactory loss will generally be diagnosed with a good history. Taking a focused history should involve asking specifically about any previous head injury, preceding upper respiratory tract infection or chronic sino-nasal inflammation. The key points in the history and examination are covered in the accompanying article 'Assessing the sense of smell' (Syed and Philpott, 2015).

Investigations

Quantitative olfactory testing should be carried out, preferably with a validated test kit. Ideal assessment includes odour threshold, discrimination and identification, but a threshold test is probably the most sensitive indicator of olfactory performance (Hummel et al, 1997). Threshold testing, as achieved with the Sniffin' Sticks, is relatively easy and cheap to perform. The University of Pennsylvania Smell Identification Test is the most widely used odour identification test, and involves presenting the patient with 40 'scratch and sniff' odourant pads with a choice of four answers for each odourant. Threshold olfactory tests involve a dilution series of a stimulus in an odourless diluent, such as light mineral oil. The stimuli are presented via small bottles, or felt-tipped pen-like devices, using a series of ascending or descending concentration trials. These are described in more detail in Syed and Philpott (2015).

Recording of olfactory event-related potentials involves objective electroencephalography assessment of cortical responses to the presentation of an odour. This is predominantly a research technique but has a role in malingering and medico-legal cases, e.g. post trauma.

There are no specific routine blood tests that are indicated in the investigation of olfactory loss when a clear cause is presented in the history, but in cases of suspected idiopathic anosmia, a screen of blood tests for underlying medical conditions may be considered including metabolic disorders and vitamin or mineral deficiencies. Measurement of serum allergen-specific IgE, e.g. radioallergosorbent test, may be indicated in patients with symptoms of allergic rhinitis or in chronic rhinosinusitis.

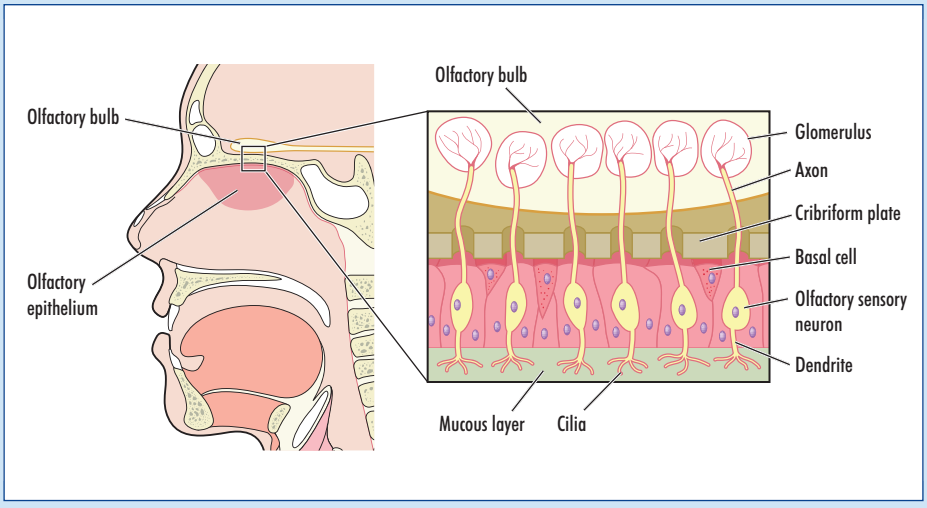
Imaging

High resolution computed tomography of the paranasal sinuses with fine cuts of the skull base in axial and coronal places will identify any bony dehiscence at the cribriform plate or abnormality within the olfactory cleft and provide any supportive information with regard to sino-nasal inflammation. This imaging modality is usually indicated if there are positive conductive factors in the history or on endoscopy.

Magnetic resonance imaging of the brain and olfactory fossa will evaluate soft tissue better and will examine the pathways from the olfactory bulb to the cortical parenchyma. A T2 weighted coronal image gives the best resolution of the olfactory bulbs. The bulb volume is known to correlate well with performance on psychophysical and objective olfactory testing. It is always important that the clinician ordering the imaging reviews the images personally to correlate findings to the patient.

In this way computed tomography imaging is helpful for identifying conductive causes of olfactory loss whereas magnetic resonance imaging is more relevant for sensorineural deficits.

Figure 3. Transmission of stimulus from odourant to olfactory bulb.



Differential diagnosis

Post-viral olfactory loss

Upper respiratory tract infection is the most common cause of olfactory loss. Rhinovirus, coronavirus, parainfluenza virus and Epstein–Barr virus have all been detected in patients with post-viral hyposmia (Suzuki et al, 2007). Olfactory biopsies suggest that there are markedly reduced numbers of olfactory receptors and abnormal receptors in patients with hyposmia. Post-viral olfactory loss in the general population accounts for about 11% of all cases of olfactory loss but about 20% of cases seen in specialist smell and taste clinics (Damm et al, 2004).

Chronic rhinosinusitis

Conductive olfactory disorders are the most common cause of olfactory dysfunction. Chronic inflammation of the nasal airway or sinuses is responsible for about 60% of patients presenting with symptoms of reduced olfaction (Damm et al, 2004). Classical associated symptoms include rhinorrhoea, post-nasal drip, nasal blockage and facial pain or pressure. Problems with olfaction in chronic rhinosinusitis can occur for a number of reasons: physical blockage, e.g polyps, inspis-

sated mucus, e.g. eosinophilic mucin, inflammation of the olfactory neuroepithelium itself, or neuronal injury from bacterial toxins. Treatment with nasal douching, topical corticosteroids and when needed endoscopic surgery can improve olfactory impairment although the degree of improvement will depend on the interventions, previous surgery and patient compliance.

There are other less common conductive causes for disturbed olfaction. There may be anatomical abnormalities, e.g. atresia, adhesions or altered physiology, e.g. altered nasal airflow in a patient with a tracheostomy or post laryngectomy.

Head trauma

Patients presenting with post-traumatic olfactory loss account for about 15–20% of patients in a specialist smell and taste clinic but less than 10% of cases in the general population, and the potential for reversibility may relate to the severity of the initial trauma (Doty et al, 1997; Temmel et al, 2002). High speed acceleration-deceleration injuries may cause shearing of olfactory filaments but most cases result from contre-coup contusions to the cortical parenchyma such as the orbitofrontal cortex. Nasal trauma may also contribute to reduced olfactory acuity by impaired conduction of odourants.

Iatrogenic injury

Iatrogenic trauma from endoscopic sinus surgery or neurosurgery causing direct injury to the olfactory neuroepithelium or neural pathways is a recognized cause of hyposmia. There may also be decreased olfaction from injury to olfactory mucosa on turbinates or synechiae formation between the middle turbinate and nasal septum.

Smoking and toxins

Smoking and a number of environmental and industrial chemicals have been implicated in olfactory dysfunction with the latter causing a toxic rhinitis. Smoking has a cumulative deleterious effect on smell which is reversible. Smoking cessation leads to gradual improvement but this depends upon the amount and duration of previous smoking. The deleterious effect of smoking is increased with a higher pack year smoking history.

Current smokers are nearly twice as likely to evidence an olfactory defect than those that have never smoked (Frye et al, 1990).

Chemical agents that have been reported to affect smell function include cadmium, benzene, paint solvents and aerosolised heavy metals, e.g. nickel or lead (Doty and Hastings, 2001). Most of these agents are thought to act by directly damaging the olfactory neuroepithelium.

Neurodegenerative disease

Anosmia is a well-recognized symptom in patients with Parkinson's disease or Alzheimer's disease. The prevalence of anosmia in patients with Parkinson's disease is 75–97% (Haehner et al, 2009). The onset of olfactory symptoms is believed to occur a few years before the onset of the classical motor symptoms of Parkinson's disease. Smell testing may therefore have a role in the early diagnosis of Parkinson's disease. An University of Pennsylvania Smell Identification Test score of above 31 carries a 91% sensitivity and 88% specificity of correctly diagnosing a male patient suspected of having Parkinson's disease (Doty et al, 1995).

There is a large body of evidence establishing an association between Alzheimer's disease and olfactory impairment (Sun et al, 2012). Patients with mild cognitive impairment and hyposmia (lower University of Pennsylvania Smell Identification Test score) are more likely to develop Alzheimer's disease (Devanand et al, 2000).

Tumours

Neoplastic lesions involving the olfactory bulb and tracts are extremely rare. These may include olfactory groove meningiomas, aesthesioblastoma, frontal lobe gliomas and pituitary tumours. Tumours involving the temporal lobe may also cause smell disturbance in the form of olfactory hallucinations or auras.

Congenital anosmia

Congenital anosmia has an estimated incidence of 1 in 5000–10 000 and when this is an isolated finding it may present late as the affected individual has no concept of odour. There is some evidence that this may exhibit autosomal dominant inheritance relating to a mapping locus on chromosome 18 (Ghadami et al, 2004).

There may be an association with other anomalies, e.g. midline craniofacial defects or deafness. Kallman syndrome refers to the presentation of congenital anosmia as a result of aplasia of the olfactory bulb associated with hypogonadism.

Systemic disease

Other endocrine disorders, e.g. diabetes mellitus and hypothyroidism, may be associated with hyposmia but these are unlikely to be presenting features. Granulomatous and connective tissue diseases with nasal manifestations, e.g. granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) and sarcoidosis, may also lead to olfactory disturbances. Chronic renal and liver failure are also associated with olfactory disturbance including hyposmia. Neurosyphilis may also include anosmia as a presenting sign.

Management

Treatment of olfactory loss should be targeted towards the underlying cause, particularly where the underlying pathology is a conductive problem impairing the transmission of odourant to the olfactory neuroepithelium. A short course of oral corticosteroids may be a particularly useful first measure for patients with a conductive impairment and to address any inflammatory component of sensorineural cases. There are no comparative studies on the effectiveness or type of corticosteroid in the treatment of olfactory dysfunction.

The Dresden Smell and Taste Clinic reports the use of methylprednisolone with a starting daily dose of 40 mg once daily reducing dose by 5 mg every other day for 14 days (Schriever et al, 2012). This was associated with significant improvement in olfactory dysfunction particularly in patients with sino-nasal disease. However, there is evidence that systemic administration of corticosteroids is far superior to the use of local corticosteroids therapy, e.g. nasal sprays, with regard to improvement of olfactory function (Heilmann et al, 2004).

There are few data on the use of vitamins, in particular zinc supplementation, for the treatment of impaired olfaction. Within the peer reviewed literature there is insufficient evidence to support their use

unless a specific deficiency is identified with blood tests (Henkin et al, 1976; Duncan and Seiden, 1995).

The most common reversible cause of olfactory loss is sinonasal disease and medical review by an ear, nose and throat surgeon is recommended. Some patients may need to be reviewed in a tertiary designated smell and taste centre which is more familiar with advanced olfactory and gustatory investigations and treatment options.

Prognosis in post-viral olfactory loss is often predicted by smell test performance on initial assessment and 1 in 3 cases can expect some spontaneous recovery within 3 years of onset (Duncan and Seiden, 1995; Seiden, 2004; Reden et al, 2006). When there is no identifiable pathology to treat, prognosis and therapy are unpredictable. Many patients with idiopathic olfactory loss are over the age of 60 years and the possibility of subsequent neurodegenerative disease should be considered; at present there is no specific way to predict the subsequent onset of such disease but patients can be counselled about symptoms to be vigilant for.

Loss of smell causes significant impairment of quality of life that is unfortunately underestimated by physicians. It is useful to provide information regarding support groups, e.g. Fifth Sense (www.fifthsense.org.uk/), that can provide advice regarding coping strategies. Patients should also be advised about safety hazards as a result of smell impairment. For example, smoke/gas monitors need to be in good working order. The ability to discern when food products have expired in the absence of a clearly marked expiration date is impaired. Although true taste is rarely impaired, many patients perceive a lack of taste (retronasal olfaction) and this may result in poor nutrition which is particularly relevant in the elderly. These patients may need the involvement of a dietician. A combination of olfactory impairment and distortions can affect a significant percentage of patients with many experiencing either weight loss or weight gain (Croy et al, 2014). **BJHM**

Conflict of interest: Mr I Syed: none; Mr C Philpott is a trustee of the Fifth Sense charity.

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USEFUL WEBSITE

www.fifthsense.org.uk – A UK-based charity set up to support people whose lives have been affected by anosmia

KEY POINTS

- Smell dysfunction significantly impairs quality of life and merits thorough examination and investigation.
- The most common causes of olfactory loss are post-viral loss, chronic rhinosinusitis and head injury.
- Smell disorders may be an early sign of neurological diseases, e.g. Alzheimer's disease or Parkinson's disease.
- Prognosis is better in hyposmia than in anosmia in cases of sensorineural loss, but recovery may be seen spontaneously in about a third of cases of post-viral olfactory loss within 3 years.