B-ENT, 2016, **12**, Suppl. 26/2, 39-46

Post-injury smell disorders

Ph. Rombaux[1], C. Huart[1], P. Balungwe[1], C. de Toeuf[1], S. Collet[2], T. Duprez[3]

[1]Department of Otorhinolaryngology, Université Catholique de Louvain, Cliniques Universitaires Saint Luc, Brussels, Belgium, Institute of Neuroscience; [2]Department of Otorhinolaryngology, Cliniques Universitaires Mont Godinne-Dinant, Yvoir, Belgium; [3]Department of Radiology, Unit of Neuroradiology, Universite Catholique de Louvain, Cliniques Universitaires Saint Luc, Brussels, Belgium, Institute of Neuroscience.

Key-words. Olfactory disorders; trauma; pathogenesis; examination; recovery and treatment

Abstract. *Post-injury smell disorders. Problems/objectives:* Head trauma is the third most common aetiology of post-traumatic olfactory loss (PTOL). This literature review aims to report the existing knowledge surrounding this issue, exploring the current understanding of the inducing pathogenesis and the assessment and management standards from the early phases to longer-term considerations.
Methodology: Literature search and appraisal in PubMed on the following themes directly associated with PTOL: olfactory disorders, trauma, pathogenesis, examination, recovery and treatment.
Results: Scientific evidence was mainly available for epidemiology and exploration tools in cases suffering from PTOL. The current research into objective batteries of olfactory tests is promising.
Conclusions: This paper highlights the importance of an adequate assessment of PTOL for an early start in olfactory training

Introduction

Human olfaction is an important component of quality of life and plays an important role in behaviour. Brain trauma is one of the most frequent causes of olfactory disorder; the olfactory bulb, located at the anterior part of the brain above the cribriform plate of the ethmoid bone, is particularly vulnerable to head trauma. Moreover, a variety of brain areas implicated in olfaction may be affected by head trauma. Post-traumatic loss of olfaction is sudden, usually severe and has an important negative impact on quality of life of patients. Adequate management and support are therefore essential.

The olfactory system

Chemosensory perception involves orthonasal and retronasal perception of olfactory stimuli, but also includes taste, somatosensory and visual integration of stimuli. These stimuli may originate from the external world (such as perfumes or odours in the air) or from the internal world (such as from food intake or beverages).

The olfactory neuroepithelium is located at the upper part of the nasal fossa and contains the first olfactory receptor neurons. In humans, it is recognized that approximately 400 genes code for olfactory receptors.[1,2] The sensory information is then concentrated in the olfactory bulb, which contains paired ovoid neural structures located at the anterior and inferior part of the brain just above the cribriform plate. The sensory information is modulated in the olfactory bulb with efferent inhibitory control before being transferred to the primary olfactory cortex, which is located in the antero-medial temporal lobe (for a review, see Huart et al. 2013).[3] Connections between chemosensory perception and other cognitive functions are present in this area and involve the piriform cortex, the amygdala and the hippocampus. The olfactory pathways then project to the secondary olfactory cortex, which is mainly located in the orbitofrontal cortex, and spread across the brain to several regions activated by olfactory stimuli in humans.

These olfactory pathways may be injured by head trauma, and impaired chemosensory perception may be recognized in patients after a traumatic event. This is referred to as post-traumatic olfactory disorder or post-injury smell disorder.

It is essential to note that among the regions of the brain relevant to olfaction, morphological dynamics have been observed.[4] Indeed, when volume losses in relevant grey matter[5] or the olfactory bulb[6-7] have been associated with reversible anosmia, the restoration of relevant brain areas such as the olfactory bulb has been accompanied with the improvement of olfactory function.[8,9] This suggests an association of brain lesion pattern with particular clinical pictures of olfactory dysfunction in humans.

Post-traumatic olfactory loss (PTOL) was first described in the medical literature in 1864 by Hughlings Jackson, who described the case of a patient suffering from a definitive anosmia after being knocked from his horse. Head trauma is, according to Nordin's 2008 literature review, the third most common aetiology of PTOL (Fig 1).[10]

The incidence of olfactory disorder (OD) following head injury is difficult to estimate for many reasons. Firstly, the patients may require important resuscitation manoeuvres in the intensive care unit, with olfactory dysfunction consequently being neglected. Secondly, the trauma may induce a cerebral lesion requiring urgent action, such as the drainage of a haemorrhage, subdural haematoma or cerebrospinal fluid. Thirdly, for minor trauma, the period between the trauma and the recognition of the chemosensory dysfunction may be long. Finally, not all patients with brain trauma will develop a chemosensory dysfunction, and this depends on various factors such as the impact, the velocity and the brain area involved. Most of the olfactory dysfunction occurring after a trauma is secondary to an occipital impact. 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 as being between 2% and 12 %[11,12] and in smell and taste centres between 8% and 20%.[10,13-14]

Patients at greatest risk for PTOL are young male adults (this is thought to be related to the more severe trauma experienced), and patients aged more than 70 years old of both genders.[12,15] The most common type of trauma is a fall in 61% of the patients, followed by car accidents in 20% and assault in 13%.[12] Head trauma produces, on average, a greater degree of olfactory reduction when compared with other OD aetiologies.[13,19] Between 48% and 78% of PTOL patients have anosmia, and between 5% and 27.4% have hyposmia.[11,12,16,17] Qualitative disorders are found fairly commonly in patients with head trauma. Parosmia is reported in 14% to 35% of cases[15-17] and phantosmia in 10% to 41% of the patients.[16,17,18] The prevalence of parosmia tends to decrease over time (41% during the two first years following injury; 15% between six and eight years) and is intermittent in half of the cases.[16,17] This is clearly associated with reduced olfactory bulb volumes and additional cerebral damage.[19] A hypothesis proposed by Leopold to explain this complaint includes a partial loss of olfactory receptor neurons, resulting in the inability to form a complete "picture" of the odorant, or the formation of a distorted odour by the integrative or interpretive centres in the brain.[19] For Mueller, it is due to a reduction in the number of neurons in the olfactory bulb secondary to a loss of interneurons in the olfactory bulb, as a result of a decreased lateral inhibition.[8] Thus, this may allow olfactory activation to produce an irregular pattern, which may result in a parosmic odour. Possible causes of phantosmia proposed by Leopold[19] include an abnormal signal from olfactory neurons to the brain, a loss of inhibitory cells to normally functioning olfactory neurons, or an area of hyper-functioning brain cells generating this odour perception. Clinically, it seems possible that a peripheral trigger from a chemosensory or even trigeminal stimulus could signal a central perception of odour.

Physiopathology

Three possible mechanisms may co-exist in patients with post-injury olfactory disorder: (1) sino-nasal obstruction; (2) tearing or shearing of olfactory nerve fibres; and (3) brain damage in areas involved in olfactory perception.[11]

Firstly, predisposing factors for post-injury olfactory disorder include injury to the sino-nasal tract with obstruction of the olfactory cleft and mucosal alterations (haematoma, oedema, or avulsion); displaced fractures of the nasal skeleton or nasal septum; and post-traumatic rhinosinusitis with an increase in mucosal oedema and in mucus quantity and viscosity. A second explanation is the shearing of the olfactory nerves at the level of the cribriform plate, where the axons of the olfactory receptor neurons pass through the foramina. These lesions may occur after an antero-posterior coup and contra-coup of the encephala, generally after an occipital trauma or after a fracture of the naso-orbito-ethmoid complex. The injury to the olfactory nerve fibres is generally bilateral and complete. It results in a retrograde degeneration of the sensorial receptors in the olfactory neuroepithelium and an absence of olfactory input to the olfactory bulb; this is responsible for sensorineural impairment leading to the chemosensory dysfunction. This leads to a reduction of the olfactory bulb volume, which can be seen some weeks after the trauma and for a long period of time. Damage to olfactory bulbs and tract can occur without any intracranial lesions.

A third mechanism is the presence of lesions, such as contusions and/or haemorrhages in the central olfactory pathways, involving the orbitofrontal cortex, the frontal lobe (gyrus rectus) or the antero-inferior part of the temporal lobe, where higher-order olfactory neurons project bilaterally. Injury to the anterior piriform cortex and amygdala may lead to odour memory disorders.

It has been noted that the risk of developing chemosensory dysfunction after a brain trauma is related to the importance of the trauma (the risk being higher if the trauma is severe),[12,20,21] the direction of the impact during the trauma (an occipital impact is noted in 46% of PTOL cases followed by a parietal impact in 18%, temporal in 16%, multiple in 13%, and frontal in 7%),[12,20] and the age of the patient (the older patient, the higher the chances of developing a chemosensory dysfunction).[18]

Pre-hospital management

If the patient presents with facial fracture, adequate management is required. Besides this, there is no specific treatment that needs to be undertaken during the pre-hospital period.

Assessment and management at the hospital

Of course, the management of the patient must be focused on the management of life-threatening head trauma and the frequent occurrence of other injuries requiring immediate medical attention. During the acute phase of the peri-traumatic event, a major point of attention must be the detection of cerebrospinal fluid leaking from the nasal fossa. In case of severe head trauma or suspected CSF leak, a CT scan will be performed to evaluate the lesions, particularly at the level of the cranial base. If the CSF leak is confirmed (by B2 transferrine dosage or glucose dosage), a broad antibiotic therapy will usually be given. During this phase, there is no validated treatment for restoring and/or protecting olfaction.

Specific otorhinolaryngological evaluation

After the readaptive period, or after several weeks after the trauma, the patient will visit the general practitioner for the olfactory complaint. This period of time between the traumatic event and the first evaluation may vary from some weeks to several years. This is an important aspect in relation to recovery, since the longer this period, the lower the chance of recovering olfaction after a trauma. The GP will probably send the patient to a specialized centre for smell and taste problems, where a complete work-up will be done. Usually, the patient will be seen by an ENT specialist who will perform a complete nasal and sinus examination through rhinoscopy, pharyngoscopy and endoscopy. The nasal endoscopy (flexible or rigid) will focus on the olfactory cleft with special attention to specific diseases that could restrict odours from reaching the olfactory neuroepithelium, and also to sequella of the trauma such as septal deviation, synechia and scar tissue in certain areas. The endoscopic evaluation will also allow any CSF leak to be ruled out. At present, the use of 4K endoscopy, 3D endoscopy or narrow band imaging (NBI) endoscopy has not been validated in the diagnosis of post-traumatic olfactory dysfunction. Detailed and structured medical histories of the patient (medical, surgical and drug history) and of the olfactory disorder (relationship with the trauma, presence of parosmia or phantosmia) are also required.[22]

Complementary evaluation

Subsequent to the clinical examination, patients undergo a complete work-up procedure including assessment of olfaction using psychophysical (and electrophysiological) olfactory testing and evaluation of the brain morphology, with a particular focus on areas relevant to olfaction, using anatomical magnetic resonance imaging.

Psychophysical assessment of olfactory function

Assessment of olfactory function must be performed using tests specifically validated for assessing olfactory function. Several tests have been described in the literature, such as the UPSIT (or its variants)[23] and the Sniffin' Sticks test.[24,25] In Europe, the most commonly used is probably the Sniffin' Sticks test battery ("Sniffin' Sticks", Burghart, Wedel, Germany). In its extended version, this test encompasses three subtests: odour thresholds, odour discrimination and odour identification tests.[29] This test is based on felt-tip pens that contain liquid odours instead of dye. The pen's cap is removed by the experimenter for approximately 3 s, and the pen's tip is placed 1-2 cm in front of the nostrils. First, the olfactory threshold (T) is assessed using n-butanol presented by means of a reversed staircase procedure, using stepwise dilutions in a row of 16 felt tip pens. Subjects are blindfolded. In each trial, three pens are presented in a randomized order, with two pens containing only the solvent and the third containing the odorant at a certain dilution. The task for the subject is to identify the odour-containing pen (three-alternative forced choice; 3-AFC).[29]

Secondly, odour discrimination (D) is assessed by asking the subject to perform a 3-AFC using 16 triplets of odorants. While blindfolded, three pens are presented to the subject, two containing the same odorant and one containing a different odorant. Subjects were asked to identify the different odorant (normal score > 10 correct detections for both sexes).

Third, odour identification (I) is assessed by asking the subject to identify 16 individual odours. For each pen, subjects are asked to perform a four-alternative forced-choice procedure, based on a list of four verbal descriptors.

The scores for threshold, discrimination and identification performances are added together to obtain a composite TDI score (**T**hreshold **D**iscrimination **I**dentification), reflecting global olfactory performance.[26] Established standard criteria for olfactory diagnosis are indicated by TDI ≤ 30.5, with the separation of hyposmia (30.5 ≥ TDI > 15.5) from functional anosmia (hereafter termed 'anosmia') at TDI ≤ 15.5.[27]

Electrophysiological assessment of olfactory function

The recording of ERPs following stimulation of sensory afferents (e.g., visual evoked potentials elicited by an alternating checkerboard) is a technique that is widely used for the functional assessment of sensory systems in clinical diagnostic medicine. Indeed, brief sensory stimuli elicit transient changes in the on-going electroencephalographic activity.

Using such an approach the EEG responses to chemosensory stimulation have been characterized as a negative wave peaking approximately 320-500 ms after stimulus onset (N1), followed by a late positive wave peaking approximately 450-800 ms after stimulus onset (termed P2 and/or P3) (for a review, see Rombaux et al. 2012[28]). All of these responses exhibit the largest amplitudes over the midline recording sites. While a centro-parietal maximum for the N1 amplitude is commonly observed for olfactory responses, a more central maximum is observed for trigeminal stimuli (see Rombaux et al. 2012[33])

Imagery of olfactory pathways

Magnetic resonance imaging (MRI) is the imaging modality of choice for evaluating the olfactory apparatus since this allows for the examination of the olfactory bulb, olfactory tract, olfactory sulcus and central olfactory projection areas.

The olfactory bulb is often considered the most important relay station in odour processing, and the volume of the olfactory bulb, as assessed with MRI-based volumetric analyses, appears to be connected with the functional state of the olfactory system. It has been established that there is a good correlation between the olfactory bulb and the olfactory function, not only in adults but also in children.[29,30] Therefore, an assessment of the volume of the olfactory bulb is useful in the clinical evaluation of patients suffering from olfactory disorders. Several studies have shown that the volume of the olfactory bulb is decreased or fragmented in patients with post-traumatic olfactory loss (Figures 1 and 2).[7,31-32] In post-traumatic olfactory loss, central olfactory projection areas can also reveal abnormalities, such as contusions in basifrontal and temporal areas (Figures 1 and 3).[33] Moreover, olfactory bulb volume has been shown to have a prognostic value for recovery.[34]

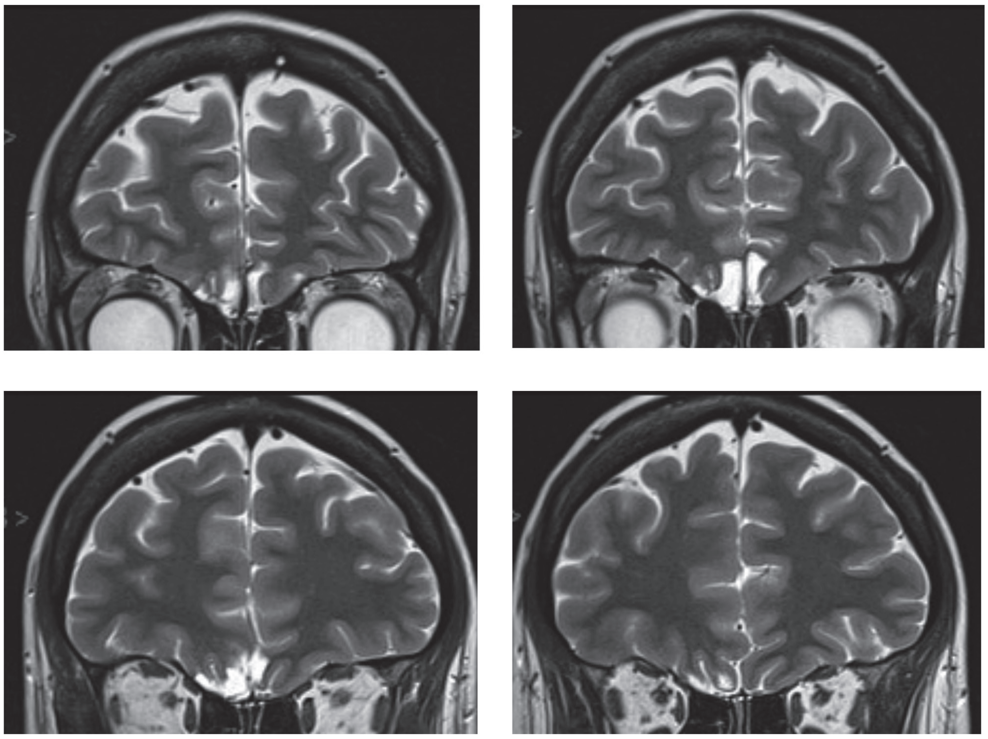

Figure 1

T2-weighted MRI of the brain in the coronal plane. The olfactory bulbs are fragmented (white arrows) and the presence of basifrontal contusions should be noted (asterisk)

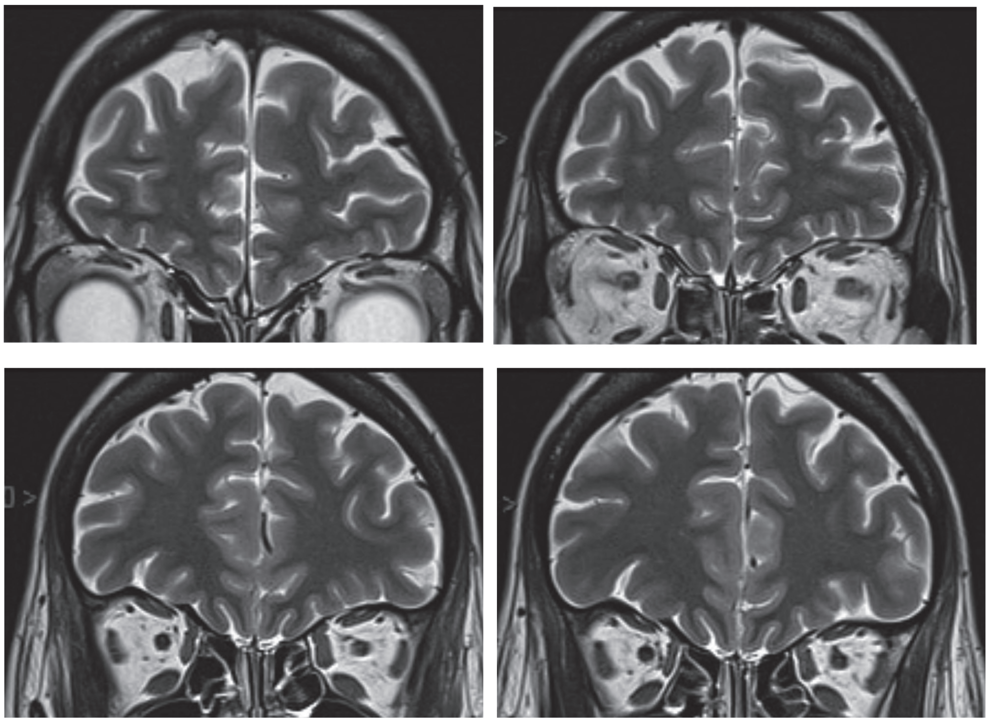

Figure 2

T2-weighted MRI of the brain in the coronal plane. Hypotrophy of the olfactory bulbs consequent to head trauma

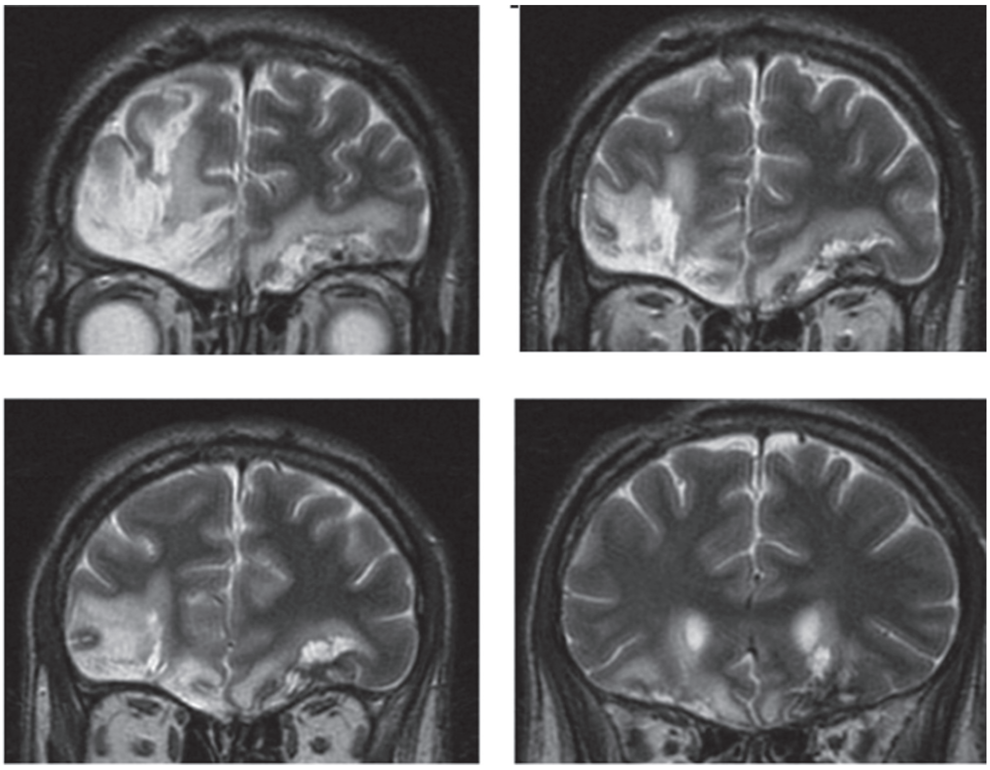

Figure 3

T2-weighted MRI of the brain in the coronal plane. This patient presents severe lesions of the encephala; the olfactory bulbs are not identifiable

Although MRI is the imaging modality of choice, a CT scan can also be useful in the assessment of patients with PTOL, primarily to exclude a sino-nasal cause (such as rhinosinusitis or septal fracture with occlusion of the olfactory cleft), and to evaluate the integrity of the skull base when CSF leak is suspected.

Medico-legal aspects

Olfactory disorders can raise medico-legal problems when the olfactory deficit occurs after a work accident, a traffic accident or an assault.

In the context of medico-legal expertise, it is mandatory to properly evaluate olfactory function, based on the work-up procedure described in the previous section. It is important to note that psychophysical testing relies on the response of the subject, and hence is susceptible to bias from subject response. This is particularly problematic in a medico-legal context. In contrast, olfactory event-related potentials require only minimal cooperation from patients and are thus relatively objective. Consequently, olfactory event-related potentials should be performed in medico-legal situations. Based on the results of psychophysical, electrophysiological and MRI evaluation, it is possible to evaluate the degree of functional disability in terms of anosmia or hyposmia, as well as the prognosis for recovery or the risk of developing a long-term disability. Olfactory dysfunction is clearly associated with increased hazards in everyday life (such as impairment of smoke or gas detection and consumption of food), a decreased quality of life and even depression. This must be taken into account and the patient must be informed. Finally, the impact of olfactory dysfunction will also depend on the patient's occupation; a chef, for example, will be unemployable if there is even the smallest reduction in olfactory function and the potential for legitimate financial compensation is high.

Invalidity varies in function of the country: the "Barème Officiel Belge des Invalidités" or "Belgisch Officieel Barema der Invaliditeiten" (BOBI) estimates that loss of smell represents an impairment of 5% to 15% of the whole person depending on the degree of disability (art 693); however, in the American Medical Association Impairment Rating System, a total bilateral loss of smell is assessed as representing a 3% impairment of the whole person.

Recovery and treatment

The olfactory neurons are able to regenerate throughout a patient's lifetime. It has been noted that following head trauma, the receptor cells attempt to send axons centrally and to re-establish functional connections with the olfactory bulb.[35] Both the speed and the extent of the growth of the disrupted axons depend on the degree of injury. In post-traumatic conditions, however, reinnervation by the regenerating axons often fails due to fibrosis and scar tissue in the area of the cribriform plate and olfactory bulb. Consequently, axons are unable to penetrate and make contact with the olfactory bulb. This supports the usual absence of recovery of the PTOL seen in this scenario. Indeed, 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% to 15%.[13,17,36,37] Recovery is most likely to occur within the first 6 months to 1 year after the initial insult.[41] However, late recovery has been described, occurring up to 9 years after the trauma.[38-39]

No medical treatment has yet been proven to be effective; however, olfactory training seems to be effective in the case of post-traumatic olfactory loss.[40]

Conclusion

PTOL is a common cause of olfactory disorder. It is important to perform a complete clinical work-up of these patients in order to evaluate the degree of olfactory dysfunction, confirm the diagnosis of PTOL and determine a prognosis for recovery of the patient. Particular attention should be paid to patients in a medico-legal context, in order to detect potential malingerers. If psychophysical tests are semi-objective and may be biased by a patient's response, the recording of event-related potentials and the MRI of the olfactory structure allow a relatively objective assessment of olfactory function/structures and are thus particularly important in a medico-legal context.

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Ph. Rombaux, MD, PhD
Dept of Otorhinolaryngology
Cliniques Universitaires Saint Luc
Av Hippocrate, 10
1200 Brussels
Belgium
E-mail: Philippe.rombaux@uclouvain.be