Management of olfactory dysfunction

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An evidence-based update on olfactory dysfunction: who to image, how to test and what works – OT, CRS surgery, biologics and PRP.

Olfactory dysfunction (OD) is highly prevalent, affecting more than 20% of the adult population with a clear age-related decline [1]. The impact that OD can have on a patient's quality of life, social relationships and mental health is profound, although often underestimated by healthcare providers. OD may take the form not only of an impairment in the ability to perceive a smell (quantitative disorders) but also in the distortion in perception of an odorant (qualitative). The presence of parosmia especially has been shown to have a detrimental impact on patients' quality of life and mental health.

An easy shorthand to consider the causes of OD has often been a binary classification of 'conductive' or 'sensorineural', but this probably oversimplifies inflammatory conditions such as chronic rhinosinusitis (CRS) which cause not only obstruction of the olfactory cleft but also in dysfunction of the olfactory neuroepithelium. Other common causes include post-viral olfactory dysfunction (PVOD), notably after SARS-CoV-2 infection, post-traumatic injury, iatrogenic factors, congenital anomalies and systemic conditions such as neurodegenerative and metabolic disorders.

Assessment

The clinical approach, assessment and management of OD has been summarised in the Position paper on olfactory dysfunction: 2023 (Figure 1) [2]. Assessment includes a detailed history, examination and smell testing in defining the nature of OD and severity, along with its impact on quality of life. Endoscopy should focus on the olfactory cleft. Subjective rating of sense of smell by the patient likely underestimates the prevalence and severity of OD and can be supplemented by validated psychophysical tests, such as UPSIT tests or Sniffin' Sticks, which test identification, discrimination and /or threshold levels. CT imaging is typically utilised in sinonasal inflammatory disease, while MRI is more useful in the setting of a normal endoscopy. When onset follows a clear history of onset after viral infection, imaging may not be required, but should be considered if there are any additional neurological symptoms or phantosmia in order to exclude an intracranial lesion such as an olfactory groove meningioma.

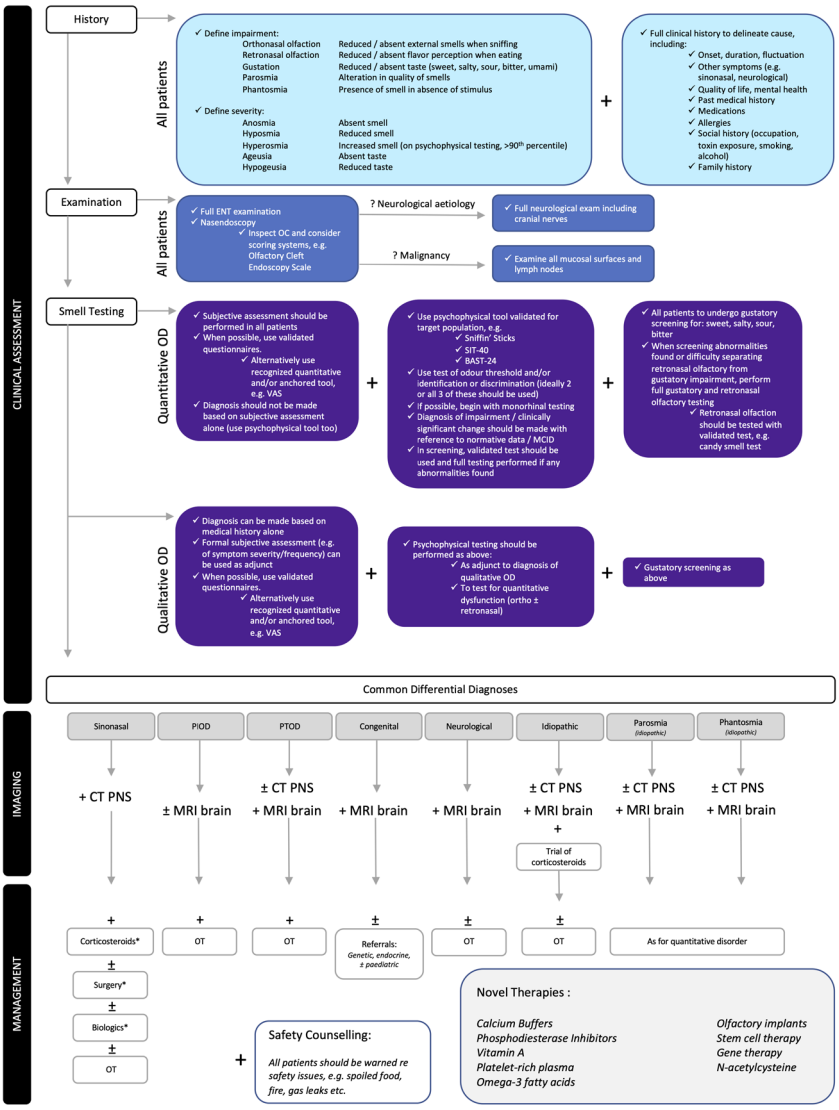

Figure 1: Flowchart with a suggested approach to the assessment, imaging and management of OD. Reproduced with permission from the Position paper on olfactory dysfunction: 2023 [2].

Management of olfactory dysfunction – all aetiologies

Supportive care

As well as discussion of safety issues, such as food hygiene and smoke alarm use, many patients will benefit from formal talking therapies to address the grief and loss that is associated with OD. Patients may also benefit from access to patient support and advocacy groups, with practical advice on maintaining interpersonal relationships and nutrition. Appropriate patient resources can be obtained from the UK-based groups AbScent (https://abscent-network.mn.co) and SmellTaste, formerly Fifth Sense (https://www.smelltaste.org.uk). Information on groups worldwide can

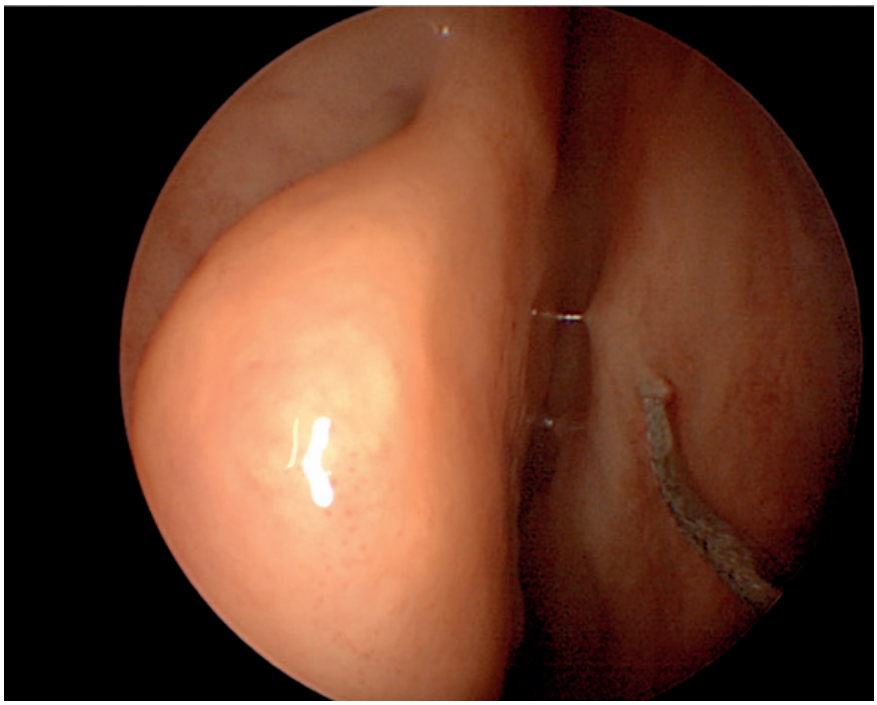

Figure 2: Endoscopic view of PRP injection into the right olfactory cleft.

be accessed at https://gcchemosensr.org/patient-orgs/

Olfactory training

Olfactory training (OT) is a well-established treatment modality, first proposed in a non-randomised trial 2009 by Hummel et al [3]. There is evidence that suggests OT can improve symptoms associated with quantitative and qualitative dysfunction, and it forms the first-line treatment in all non-inflammatory causes of OD. A meta-analysis of 36 included studies across different aetiologies of OD demonstrated a positive effect, with duration of training and younger age of participant being associated with a larger effect size. Classically, OT involves patients using four odorants and smelling each odorant for 10 seconds, twice daily for three months. Modifications to this original protocol involve extending treatment, alternating odorants and increasing odorant concentration.

Management of OD in inflammatory sinonasal disease

Olfactory dysfunction is one of the most common symptoms reported by patients with CRS, and has been shown to associate with a type 2 endotype. Intranasal corticosteroids and saline rinses are used as first-line treatment but poor compliance and restricted access to the olfactory cleft may limit effectiveness. Systemic steroids often achieve rapid improvements, but these can be short-lived. Unfortunately there is a cumulative risk of side effects from repeated courses of systemic steroids, but the response to a single course of prednisolone may help predict benefit from surgery or biologic treatment. Endoscopic sinus surgery to remove nasal polyps and improve access to postoperative topical steroids has been shown to achieve significant improvements in subjective and psychophysical tests of sense of smell, although it can be difficult to maintain. Enhanced postoperative delivery of topical steroids using steroid rinses, steroid-eluting stents or exhalation delivery devices may prolong benefit of surgery.

Biologics have led to a paradigm shift in the management of OD associated with inflammatory sinus disease. Three biologics are currently licensed for use in the management of CRS with nasal polyps. Of these, dupilumab is notable for its speed of onset, with some patients reporting improvements within days of their first treatment, and significant improvements in olfactory function. A meta-analysis comparing biologics with surgery demonstrates similar effectiveness between surgery and biologics at six months, but at 12 months, dupilumab achieves greater improvements than all other options [4].

There is significant geographic variability in reimbursement and, hence, access to these treatments across the world.

Management of post-viral OD

Meta-analyses based on self-report suggest that more than 95% suffering with OD after SARS-CoV-2 infection recover within six months. Psychophysical testing suggests higher levels of persistent OD but with continued spontaneous recovery documented up to at least three years. Patients should be reassured and encouraged to undertake olfactory training.

Despite the opportunity to study interventions in large numbers of patients following the pandemic, there remains uncertainty with regards to the benefits of many interventions that have been proposed for the treatment of PVOD.

There are conflicting studies evaluating the benefits of both topical and systemic corticosteroids in post-viral loss. Thus, the decision to prescribe must be weighed carefully, particularly when considering the known adverse effects of systemic corticosteroids.

Sodium citrate, calcium chelators, topical Retinoic acid (vitamin A), topical insulin, forskolin, cerebrolysin, gabapentin and alpha-lipoic acid have all been evaluated in clinical studies, but currently there is insufficient evidence to make a recommendation for use, and further studies are required.

Palmitoylethanolamide and luteolin (PEA-LUT) are thought to reduce neuroinflammation by modulating and reducing reactive oxygen species. A systemic review and meta-analysis of clinical studies testing PEA-LUT for persistent post-SARS-CoV-2 OD suggested a statistically significant improvement in patients treated with PEA-LUT and OT versus patients treated with OT alone. However this meta-analysis was limited due to the small study sample size leading to underpowered analysis. A pilot study investigated the use of oral omega-3 supplements alongside OT versus OT alone for patients with confirmed PVOD. The study showed a pronounced improvement in odour threshold testing comparing the oral omega-3 supplement group versus the control group.

Taking the limited evidence of benefit into consideration but the low risk of harm, PEA-LUT and / or Omega-3 remain a potential treatment option alongside OT.

Platelet-rich plasma

Platelet-rich plasma (PRP), obtained by centrifuging autologous blood, is a concentrate rich in platelets and pro-regenerative factors. The injection of PRP directly into the olfactory cleft has been investigated to stimulate olfactory recovery.

Yan et al conducted a pilot study to establish safety and then followed with a follow-up multicentre RCT to compare treatment with three PRP injections or sterile saline injections into their olfactory clefts over a four-week period in patients with post-COVID anosmia (Figure 2) [5]. At 12 months there was improvement in both subjective and psychophysical assessment;

notably 88% of the PRP group achieved clinically significant improvements compared with only 31% of the placebo group. A systematic review by Bischoff et al examined PRP evidence in post-viral OD and found a statistically significant improvement, although it highlighted heterogeneity between the studies [6]. Recent publications also suggest potential benefit in traumatic brain injury. Larger studies with long-term follow-up are required, but PRP is a promising treatment option for patients with persistent PVOD.

Conclusion

Further information on the management of olfactory function can be found in the 2022 International Consensus Statement in Allergy and Rhinology: Olfaction [7], and The European Position paper on olfactory dysfunction: 2023 [1]. The significant increase in published research in this field means that these guidelines are already outdated. However, despite the rapidly evolving literature, and with the exception of inflammatory sinonasal disease, there remains a paucity of effective treatments to address this common condition.

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Claire Hopkins will present on this topic at the 20th ENT Masterclass® in January.