Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Anosmia: Brighton Collaboration case definition and guidelines for data collection, analysis, and presentation of immunization safety data

Yi-Chun Carol Liu [a,*], Flor M. Munoz [b], Hector S Izurieta [c], Arina A Tamborska [d,e,f], Tom Solomon [d], Barbara J Law [g], Nipun Chhabra [h,i,j]

[a] Department of Surgery, Division of Pediatric Otolaryngology, Baylor College of Medicine, and Texas Children's Hospital, Houston, TX, USA
[b] Department of Pediatrics, Division of Infectious Diseases, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA
[c] Office of Vaccine Research and Review (OVRR), CBER, U.S. Food and Drug Administration, Silver Spring, MD, USA
[d] National Institute for Health Research Health Protection Research Unit in Emerging and Zoonotic Infections, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Merseyside, United Kingdom
[e] Department of Neurology, The Walton Centre NHS Foundation Trust, Liverpool, United Kingdom
[f] Clinical Infection Microbiology and Immunology, Institute for Infection, Veterinary and Ecological Sciences, University of Liverpool, United Kingdom
[g] Brighton Collaboration, Decatur, GA, USA
[h] Department of Otolaryngology, Case Western Reserve University, Cleveland, OH, USA
[i] VA Northeast Ohio Healthcare System, Cleveland, OH, USA
[j] University Hospitals Ear, Nose & Throat Institute, Cleveland, OH, USA

ARTICLE INFO

Article history:
Received 30 October 2022
Accepted 14 November 2022
Available online xxxx

Keywords:
Anosmia
Adverse event
Immunization
Guidelines
Case definition

ABSTRACT

This is a Brighton Collaboration case definition of anosmia to be used in the evaluation of adverse events following immunization, and for epidemiologic studies for the assessment of background incidence or hypothesis testing. The case definition was developed by a group of experts convened by the Coalition for Epidemic Preparedness Innovations (CEPI) in the context of active development of SARS-CoV-2 vaccines. The case definition format of the Brighton Collaboration was followed to develop a consensus definition and defined levels of certainty, after an exhaustive review of the literature and expert consultation. The document underwent peer review by the Brighton Collaboration Network and by two expert reviewers prior to submission.

1. Introduction

1.1. Need for developing case definition and guidelines for data collection, analysis, and presentation of anosmia as an adverse event

Interest in anosmia, or loss of sense of smell, has increased during the SARS-CoV-2 pandemic since it emerged as a common symptom of coronavirus disease 2019 (COVID-19). In May 2020, it was identified as an adverse event of special interest (AESI) relevant to the development and use of COVID-19 vaccines by the Safety Platform for Emergency vACcines (SPEAC) project. SPEAC is a Brighton Collaboration project funded by the Coalition for Epidemic Preparedness and Innovation (CEPI) with the goal of harmonizing the safety assessment of all CEPI-funded vaccines.

The association of anosmia with SARS-CoV-2 infection may have arisen as a direct result of viral replication or an immunopathogenic host response to infection, or a combination of both. As such, a theoretical risk that anosmia could occur following immunization with one or more COVID-19 vaccine platforms was considered to exist. The Brighton Collaboration Anosmia Working Group has developed a case definition for anosmia as there is no universally accepted definition of anosmia relevant to immunization. A common case definition is essential to ensure data comparability across trials or surveillance systems that would facilitate data interpretation and promote the scientific understanding of the event.

1.2. Definitions and general description of anosmia

Normosmia is the normal sense of smell. Chemosensory dysfunction encompasses smell, taste, and chemesthesis disorders [1]. The loss of the senses of smell (anosmia) and taste (ageusia) are the most common chemosensory dysfunction, and the reduced

* Corresponding author at: Baylor College of Medicine, Houston, TX, United States.
E-mail address: Yi-Chun.Liu@bcm.edu (Y.-C.C Liu).

https://doi.org/10.1016/j.vaccine.2022.11.022
0264-410X/

ability to smell (hyposmia) or taste (hypogeusia) are also common. This case definition will focus on the loss of olfactory function (anosmia).

Abnormalities of olfaction or dysosmia have various presentations (Table 1). According to the American Academy of Otolaryngology-Head and Neck Surgery, anosmia is the complete cessation of smell function [2]. Hyposmia describes the diminished smell function and is sometimes referred to as microsmia. Parosmia is a smell distortion with abhorrent odor perception with an odorant stimulus. Phantosmia is similar to parosmia, but smell distortion occurs without a stimulus.

In the 2016 review of the U.S. National Health and Nutrition Examination Survey (NHANES) 2011–2012 that examined 3603 adults (age 40 + years) for chemosensory alterations, 23 % self-reported smell alterations, with phantosmia, or olfactory hallucination being reported by 6 % [3]. The prevalence of chemosensory alteration rates increased progressively with age. Impaired quality of life has been reported for individuals with severe chronic hyposmia or anosmia [4]. Olfaction is a significant component of flavor perception, and olfactory dysfunction can significantly impair food flavor awareness leading to lower quality of life [5]. Changes in experiences with eating and drinking can lead to depression, with the affected individuals no longer looking forward to meals [6]. In addition to the effect on taste, olfactory impairment can also lead to the inability to detect the environmental odor, such as smoke and leaking gas, which can be a safety concern [7]. Lastly, certain professionals rely on smell as part of their jobs, such as chefs and firefighters [8].

2. Anosmia

2.1. Epidemiology of anosmia

Olfactory dysfunction is common in adults, and the prevalence increases with age [3]. In a study of 1281 adults in NHANES, 12.4 % reported olfactory dysfunction, including 3.2 % with anosmia or severe hyposmia [7]. The age-specific prevalence was 4.2 % for those between 40 and 49 years, 12.7 % for those between 60 and 69 years, and 39.4 % for those aged $\geq$ 80 years. No other population-based study results or studies reporting data for children are available for other countries [9].

2.2. Pathophysiology of anosmia

The pathophysiology of anosmia depends on its etiology, with causative agents resulting in disruption at different levels of the olfactory pathway. In conductive anosmia, obstruction of the nasal airflow prohibits odorants from reaching the receptors of the olfactory dendrites, which are in the olfactory epithelium in the posterior nasal cavity [10] (Fig. 1). In sensorineural anosmia, signal propagation disruption occurs along the olfactory pathway, which connects the olfactory epithelium with the central nervous system (Fig. 1). The dendrites of the olfactory neurons become activated by odorants via G-protein coupled receptors; each neuron expresses

Table 1
Definitions of normosmia and types of olfactory dysfunction.

	Definition
Normosmia	Normal smell
Anosmia	Complete loss of ability to smell
Hyposmia/ micronosmia	Reduced ability to smell
Parosmia/cachosmia	Distorted odor perception (triggered by a stimulus)
Phantosmia	Olfactory hallucination (occurs without a stimulus)
Hyperosmia	Increased olfactory sensation
Olfactory agnosia	Unable to identify odor

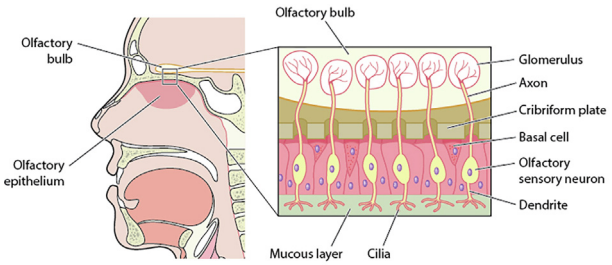

Fig. 1. Detail of the olfactory bulb showing the nerve cells between the bulb and the olfactory epithelium (Shutterstock.com).

only one of the 350 receptor types known in humans [11]. The signal is then transmitted via olfactory axons, which form axonal bundles (also known as filia olfactoria), and then it traverses the cribriform plate, giving origin to the first order synapse located at the olfactory bulb [12]. Although neurons expressing the same receptor type are scattered in the nasal epithelia, their axons converge at the olfactory bulb level, synapsing with the second order neurons at the same positions. From there, the signal travels primarily to ipsilateral foci in the central nervous system, including the olfactory cortex, the thalamus, and the amygdala. Neuronal disruption at any level of this signaling pathway, be it secondary to neurodegeneration, trauma or infections, results in anosmia. Further, some primarily conductive disorders, such as chronic rhinosinusitis, may damage the olfactory epithelium, leading to mixed conductive and sensorineural olfactory loss [12].

2.3. Etiology of anosmia

Conductive and sensorineural causes of anosmia are outlined in Table 2. Conductive anosmia results from sinonasal diseases, such

Table 2
Summary of possible etiologies of anosmia [10]. The percentage contribution to all anosmia cases is given for the most common causes. Where no percentage is given, the contribution is < 5 %.

Conductive etiologies	Sinonasal disease (14 – 30%) • Rhinitis • Rhinosinusitis • Polyp disease • Nasal stenosis • Traumatic nasal obstruction • Nasal tumors Congenital Narrowed olfactory cleft
Sensorineural etiologies	Chronic sinonasal disease (via damage to the olfactory epithelium) Upper respiratory tract infection (19 - 36%) Head trauma (9 – 18%) Toxins • Solvent abuse • Zinc toxicity (cold remedies and nasal decongestants) • Other chemical agents such as benzene, formaldehyde, or sulfuric acid • Medications* Neurological disorders • Neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, frontotemporal dementia • Multiple sclerosis • Cerebral infraction • Space occupying lesions Congenital • Isolated congenital anosmia • Part of a syndrome, e.g., Kallman syndrome Idiopathic (18 – 28%)

* Multiple medications have been associated with anosmia (often manifesting as a secondary taste dysfunction). Commonly used examples include antibiotics (penicillins, tetracyclines), calcium channel blockers (diltiazem, nifedipine), statins, opiates, antidepressants (amitriptyline, paroxetine), phenytoin and furosemide.

as rhinitis, rhinosinusitis, polyps, and tumors. Upper respiratory tract infections (URTIs), trauma, and sinonasal disease are the leading causes of anosmia among adults, accounting for up to two-thirds of all cases [13,14]. The cause of the anosmia is not identified in about 20 % of cases, although age-related olfactory loss may contribute. Rarer, non-conductive causes include congenital, toxic, and neurological [15]. Anosmia was significantly more common in individuals with congenital and post-traumatic etiologies, and hyposmia was more frequent in individuals with post-infectious etiologies in a study of 496 individuals with non-conductive olfactory dysfunction [15]. Clinical history is useful for distinguishing the most common causes of anosmia.

2.3.1. Nasal and paranasal sinus disease

Nasal and paranasal sinus diseases such as chronic rhinosinusitis with or without nasal polyps, allergic rhinitis, and post-viral upper respiratory infections are the most commonly identified causes in patients with olfactory dysfunction [13,16]. The mucosal inflammation and the associated nasal obstruction interfere with olfaction.

Congestion associated with edema, infection, and inflammation in sinonasal disease can directly obstruct the nasal airflow, preventing odorants from reaching the olfactory receptors. However, some patients with chronic rhinosinusitis continue to experience anosmia even when nasal endoscopy or CT imaging reveals no obstruction to their olfactory cleft [17]. This observation is explained by secondary damage to the olfactory epithelium from inflammation. Mouse models show that cytokine release by the sustentacular cells of the olfactory epithelium results in the death of the olfactory neurons, leading to impaired olfactory function [18]. However, the function and histological appearances were recovered when inflammation was suppressed for a sustained time.

2.3.2. Upper-respiratory tract infection and SARS-CoV-2-associated anosmia

Viral upper respiratory tract infections (URTIs) have long been recognized as the leading cause of anosmia, with agents such as rhinovirus, influenza virus, parainfluenza virus, respiratory syncytial virus, coxsackievirus, adenovirus, and other viruses known to cause olfactory impairment [19]. URTIs can cause short-term and prolonged olfactory dysfunction or loss. This prolonged olfactory dysfunction has been reported in 6 % to 13 % of patients after the resolution of an acute URTI [20]. It is thought that viral URTIs cause damage to the peripheral olfactory reception and central olfactory pathways [21,20]. Post-infectious olfactory dysfunction generally improves with time, although some levels of dysfunction may persist [22].

Direct damage to olfactory epithelium and neurons or damage secondary to the immune response is thought to be the main mechanism. However, recognition of anosmia as a primary symptom of SARS-CoV-2 infection has advanced our understanding of mechanisms underpinning this symptom. Although rhinitis and rhinorrhea are important factors in URTI-associated anosmia, many individuals with SARS-CoV-2 infection and anosmia experience no other symptoms [23]. As such, the conductive deficit is unlikely to be the leading mechanism of SARS-CoV-2-induced smell loss, and injury to non-neuronal cells in the olfactory epithelium is thought to be the primary underlying process [24]. SARS-CoV-2 invades human cells via ACE2 receptor in conjunction with transmembrane serine protease 2, which is expressed in the olfactory support cells, such as sustentacular cells and Bowman cells, but not in the olfactory neurons [25]. Dysfunction of the olfactory neurons, rather than damage and death, is consistent with the rapid recovery of smell in SARS-CoV-2-induced anosmia, which is on average two weeks, a delay that is incompatible with neuronal regeneration. The return of olfactory function within such as short time span can be explained by the regeneration of non-neuronal cells from stem cells [24]. Damage to the olfactory epithelium cells can also be aggravated by immune response and secretion of pro-inflammatory cytokines, just as in chronic rhinitis. This can lead to neuronal death, explaining the longer recovery time in rarer cases. Lastly, the direct impact of SARS-CoV-2 on central olfactory centers may also play a role, e.g., via infiltration of the olfactory bulb or viral encephalitis, but this process is unlikely to be the driving factor in the majority of cases [26].

2.3.3. Environmental toxin exposure

Exposure of the olfactory receptors to environmental toxins can cause olfactory dysfunction [27]. Potential toxin exposures include occupational exposure such as ammonia, benzene, formaldehyde, etc. Tobacco smoking may cause olfactory dysfunction, but the olfactory function can improve following smoking cessation [28].

2.3.4. Head trauma

Hyposmia and anosmia are the more frequent presentations among the various olfactory dysfunctions following head trauma. Anosmia occurs in 7 % of all patients with head trauma. The incidence increases with the severity of the head injury and can be as high as 60 % with associated skull fracture and spinal fluid leakage [29]. The mechanism of injury from trauma includes damage that causes mechanical obstruction, disruption of the olfactory axons in the cribriform plate, injury to the olfactory bulb or olfactory cortex[30–33]. Three key mechanisms explain olfactory dysfunction post-head trauma. First, anosmia can be conductive, due to facial and nasal injury obstructing the transit of odorants to olfactory receptors. Next, acceleration and deacceleration forces result in the shearing of olfactory axons traversing the cribriform plate [34]. Lastly, there is also injury to the central olfactory pathway, with contusion of the subfrontal and temporal lobes and encephalomalacia of the olfactory bulb and tracts identified on magnetic resonance imaging [35]. About 80 % of post-head trauma anosmia will manifest in the first five days [29]. The prognosis of post-head trauma anosmia is worse with more severe smell loss when the time interval between trauma and the onset of symptoms is short. In a 23-year follow-up study including 106 patients with post-traumatic smell loss, 11 % of those with anosmia and 27 % with hyposmia regained normal age-adjusted function [36].

2.3.5. Neurological disorders

Anosmia is an early feature of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease and Lewy body dementia [37]. In Alzheimer's disease, there is beta-amyloid and tau deposition in the olfactory bulbs, tracts, and olfactory cortex of the medial temporal lobe. Olfactory dysfunction in patients with mild cognitive impairment predicts the time to onset of Alzheimer's disease [38,34]. Similarly, over 95 % of patients with idiopathic Parkinson's disease suffer from olfactory loss, which may precede motor symptoms by years and helps to differentiate this diagnosis from Parkinson plus syndrome [39]. Beyond neurodegenerative pathologies, the burden of demyelinating plaques in the olfactory centers has also been shown to correlate with olfactory deficits in patients with multiple sclerosis [40]. CNS ischemia, including infarct, hemorrhage, and edema with compression, can also cause damage to the olfactory cortex [37,41].

Kallmann syndrome is a genetic condition with idiopathic hypogonadotropic hypogonadism and anosmia [42]. The condition is associated with impaired embryonic migration of GnRH cells to the hypothalamus and olfactory bulb. Other structural brain diseases include idiopathic intracranial hypertension (pseudotumor cerebri), multiple sclerosis, and both malignant and benign brain tumors [43–45].

2.3.6. Endocrine disorders

Diabetes mellitus, both types I and II, may be associated with olfactory dysfunction. In more than 3000 adults aged ≥ 40 years who participated in the 2013–2014 NHANES study, olfactory dysfunction was reported more frequently in patients with diabetes compared with those without diabetes and more frequently in patients with diabetes on more aggressive treatments including insulin treatment [46].

Hypothyroidism was reported to be associated with hyposmia due to diminished olfactory cortical responses to odor stimuli [47]. Thyroid treatment has been shown to improve olfactory function.

2.3.7. Age-related olfactory loss (presbyosmia)

Age-related deterioration of olfactory function, known as presbyosmia, is common in populations above the age of sixty-five, although the mechanisms responsible for this change are not completely understood [48]. It has been suggested that reduced mucus production in the olfactory mucosa, sclerosis of the cribriform plate with compression of the olfactory axons, and neurodegenerative processes may all contribute [34]. Reduced stem cell populations and the decline in pro-regenerative regulatory factors, such as neuropeptide Y, may also be responsible for impaired replacement and, consequently, the loss of olfactory neuroepithelium [17].

2.3.8. Medications

Medications can cause chemosensory dysfunction, but generally have a greater impact on taste than on olfaction. Medications that can cause olfactory dysfunction include beta-blockers, calcium channel blockers, ACE inhibitors, and intranasal zinc preparations [27].

2.4. Anosmia following immunization

We searched PubMed on 3 March 2022 using the terms 'vaccine adverse event anosmia/ageusia', and 'vaccine safety anosmia/ageusia'. The search resulted in the identification of one relevant publication [49]. This report results from a worldwide study that analyzed neurological adverse events following immunization (AEFIs) with 15 COVID-19 vaccines reported to the WHO pharmacovigilance database between 15 December 2020 and 24 January 2021 (VigiBase). The relevant events were identified in the database using System Organ Classes definitions. A total of 19,529 neurological system AEFI reports were identified. The analysis found disproportionality for the terms anosmia and ageusia, among others.[49].

After additional searching, four other publications relevant to the investigation of anosmia or ageusia as vaccine adverse events were identified. One publication reported data from the U.S. Vaccine Adverse Event Reporting System (VAERS) collected between 1 January 2021 and 14 June 2021. The reporting rate for anosmia was 1.81 per million vaccine doses administered of any COVID-19 vaccine, with 1.35 per million doses administered of Moderna (mRNA-1273), 1.88 per million doses administered for Pfizer-BioNTech (BNT162b2), and 6.98 per million doses administered for Johnson&Johnson-Janssen (Ad26.COV2-S) [49,50].

In a nationwide study of AEFIs following administration of COVID-19 vaccines in South Korea on 36.3 million individuals who had received Pfizer-BioNTech (18.2 million doses), AstraZeneca (14.7 million doses), Moderna (2 million doses) and Johnson&Johnson-Janssen (1.1 million doses) [51], a total of 26 anosmia events were reported: 18 after AstraZeneca; 6 following Pfizer-BioNTech; and 2 following Johnson&Johnson-Janssen. The anosmia incidence rate was approximately-one per million vaccinees, with the highest rate following Johnson&Johnson-Janssen. The incidence rate of anosmia was higher following the AstraZeneca vaccine than the Pfizer-BioNTech vaccine, which were the two most commonly used vaccines [51].

In 2021 patients who presented with post-COVID-19-vaccine smell or taste disorders in five European hospitals European hospitals were reviewed [53]. Six cases of post-COVID-19 vaccination olfactory and gustatory disorders were identified in patients with negative COVID-19 nasal swabs, following the first injection of the AstraZeneca vaccine or the second injection of Pfizer-BioNTech vaccine. None of the patients reported mid- or long-term olfactory or gustatory dysfunction.

In 2014, 4554 consecutive patients presenting to the Smell and Taste Center at the University of Pennsylvania with complaints of chemosensory dysfunction were evaluated [52]. The chemosensory (olfactory) dysfunction for nine patients (0.19 %) was attributed to a prior influenza vaccination.

In summary, although reporting rates and disproportionality analyses of adverse events following immunization from three large surveillance studies have shown that anosmia and ageusia can be reported following COVID-19 immunization rarely, they have the limitations of studies using data from passive surveillance systems, and also the possibility that symptoms could be due to a simultaneous wild virus infection. However, the possibility of a post-vaccine inflammatory reaction in the olfactory neuroepithelium, based on findings in six patients in one elegant but small study, deserves further investigation [53]. The evidence from this literature review assessing a potential association with vaccines other than COVID-19 vaccines is based on one study [52].

3. Diagnosis of anosmia

3.1. History and physical examination

The initial history and physical examination are the most important step in a thorough diagnostic workup for anosmia. Most commonly, patients will present with a reduced sense of smell or altered taste perception. Taste is intimately related to flavor, which may not be readily apparent to the patient until they are asked directed questions about the differentiation between taste perceptions such as salty, sour, sweet, or bitter. A thorough history will often elucidate the timing of onset of the smell disturbance, as well as qualitative factors or symptoms that may be associated with a reduction in smell. Viral-related olfactory loss is usually associated with cold or flu-like symptoms and persists after the resolution of upper respiratory or associated symptoms [12]. Patients with chronic rhinosinusitis with or without nasal polyps often present with fluctuating smell loss or hyposmia, compared with true anosmia [12]. Nasal obstructive symptoms are also more common with nasal or sinus neoplasms, chronic rhinosinusitis, and allergic rhinitis [12]. History of head trauma or traumatic brain injury must be verified during the initial intake, as well as neurologic symptoms or a family history of neurologic disorders.

The next step is a physical exam focusing on the head and neck, nasal and sinus cavities, cranial nerves, and mental status. Additional neurologic workup or more comprehensive mental status assessment may be performed if there is suspicion of neurologic disease, a non-otolaryngologic cause, or associated neurologic symptoms [12]. Nasal endoscopy to assess the olfactory clefts for lesions or masses and evaluate for sinonasal diseases or polyps should be performed in all patients presenting with olfactory loss. This has been shown to be superior to anterior rhinoscopy for diagnostic purposes [54].

3.2. Imaging techniques

Many imaging techniques have been used to study olfactory pathways and assist in the etiological diagnosis of olfactory loss. These include magnetic resonance imaging (MRI) with or without a functional component (fMRI), computed tomography (CT), single-photon emission computerized tomography (SPECT), and positron emission tomography (PET) imaging [55]. Imaging should be considered within the contextual history of the patient's symptoms and history. Imaging is indicated when there is suspicion of intracranial or sinonasal neoplasms, neurologic, central, or congenital causes and traumatic head injuries. CT is the preferred modality for sinonasal disorders, but MRI is useful for neurologic conditions or traumatic brain injuries. PET, SPECT, and fMRI imaging modalities are not recommended in the routine diagnostic workup for anosmia, but may provide valuable information in the research setting or when more functional loss of the olfactory system and associated neurologic pathways is suspected.

3.3. Olfactory tests

Olfactory testing, using a standardized test, is required to quantify the degree of smell loss. This is important not only to categorize the deficit, but also to counsel patients, follow their progression over time, or determine the need for further testing or possible interventions. Olfactory testing also differentiates between true anosmia or severe hyposmia and malingerers or normosmic patients that may suffer from other types of dysosmia. Several standardized tests are commercially available. These tests have been validated for reproducibility. Most tests rely on measuring detection thresholds or the ability to identify specific odorants [12]. The University of Pennsylvania Smell Identification Test is a commonly-used, reproducible smell identification test, including 40 odorants in a scratch-and-sniff format [56]. This test identifies different levels of olfactory perception, including microsmia and anosmia. There are numerous other smell testing methods available (Table 3) [57,55]. These tests may measure threshold, discrimination, and/or identification, or some combination thereof. The perception of odors at low concentration is known as odor threshold; the nonverbal distinction of different smells is odor discrimination; and the ability to name or associate an odor is odor identification [58]. Odor identification tests may be culturally specific, so they should be validated for the target population [57]. Regardless of the method used, olfactory testing provides valuable information and is a critical step in both the workup and accurate diagnosis of anosmia.

Table 3
Examples of olfactory testing [55,57].

Alcohol Sniff Test
Barcelona Smell Test (BAST-24)
Connecticut Chemosensory Clinical Research Center Test
Cross-Cultural Smell Identification Test
Essential Oil Smell Test (AROMA)
Jet Stream Olfactometer
Odourized Marker Test
Olfactory Perception Threshold Test
Open Essence
Pocket Smell Test
Quick Smell Identification Test (Q-SIT)
San Diego Odor Identification Test
Scandinavian Odor Identification Test
Smell Diskettes Test
Smell Threshold Test
Snap & Sniff Olfactory Test System
'Sniffin Sticks'
T & T Olfactometer
University of Pennsylvania Smell Identification Test (UPSIT)

4. Treatment of anosmia

Management of anosmia and olfactory dysfunction depends on the underlying cause, when identifiable or amenable to treatment [12]. Obstructive, conductive, or inflammatory causes, such as chronic rhinosinusitis, tumors, or nasal polyps can be addressed through established treatment or surgery. However, the best treatment for sensorineural causes remains unknown. There are several investigational trials and ongoing research into the treatment of anosmia and olfactory dysfunction. Numerous treatment modalities have been evaluated, such as oral steroids, vitamin supplementation, olfactory bulb removal, and olfactory or smell training. Of these, olfactory training remains a commonly accepted and very safe method. This is recommended for patients with olfactory dysfunction, especially with post-infectious, posttraumatic, or idiopathic causes [57]. Olfactory training involves repeated daily exposure to a range of odorants and while the underlying mechanism is unknown, it is hypothesized to result in regenerative capacity of olfactory neurons [57,59]. Smell training kits, composed of essential oils, are widely available, and can even include household spices or edible items. The therapeutic benefits of smell training may be enhanced with situational cues and exposures to familiar odors in an applicable environment, such as the patient's favorite restaurant. These exposures can serve as emotional cues and help trigger memories associated with certain smells. Additionally, treatment should include discussion of the etiology when identifiable as well as counseling of the risks and environmental hazards associated with anosmia [12].

5. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for anosmia as an adverse event following immunization

Following the process described in the Brighton Collaboration Website https://brightoncollaboration.us/about/the-brighton-method/, the Brighton Collaboration Anosmia Working Group was formed in 2021 and included members of clinical, academic, vaccine safety and public health background.

6. Guidelines for data collection, analysis and presentation

The case definition is accompanied by guidelines, which are structured according to the steps of conducting a clinical trial, i.e., data collection, analysis and presentation (see Appendix A. Supplementary material). The case definition and the guidelines were developed to improve case ascertainment and data comparability in research (epidemiological, observational or interventional) and are not intended to guide or establish criteria for the management of ill infants, children, or adults.

7. Anosmia case definition

Anosmia is a clinical syndrome characterized by the complete loss of the sense of smell.

7.1. Formulating a case definition that reflects diagnostic certainty

The Brighton Collaboration case definition has been formulated such that the Level 1 definition is highly specific for anosmia. Since high specificity usually results in a loss of sensitivity, two additional diagnostic levels have been included in the definition, offering a stepwise increase of sensitivity from Level 1 down to Level 3, while retaining an acceptable level of specificity at all levels. In this way, all possible cases of anosmia should be captured. It needs to be re-emphasized that the grading of definition levels refers to

diagnostic certainty only and does not indicate the clinical severity of an event.

The Working Group determined an order of presenting symptoms and testing indicating diagnostic certainty for the diagnosis of anosmia as shown in Table 4 and the algorithm in Fig. 2.

7.2. Rationale for selected decisions about the case definition of anosmia as an adverse event of special interest following immunization

The Level 1 classification can be reached for an individual reporting a loss of smell after appropriate testing by an expert. The Working Group determined that expertise in conducting a proper evaluation and utilization of available standardized tools for the diagnosis of anosmia are necessary to establish a Level 1 diagnosis. Level 2 classification can be reached for an individual reporting a loss of smell after evaluation by a non-specialist professional, using various tests. Finally, a Level 3 of diagnostic certainty based on a self-report of loss of smell is considered acceptable. Where there is uncertainty about the diagnosis or insufficient information regarding a report of alteration of the sense of smell, the event should be classified as Level 4 until either confirmed and assigned to levels 1 to 3, or ruled out and classified as Level 5, i.e., not a case of anosmia.

7.3. Rationale for individual criteria or decisions made related to the case definition

7.3.1. Diagnostic testing

In addition to a self-report of a change in the ability to smell, specific olfactory testing should be performed to establish the diagnosis of anosmia. As described in Table 1 there are various manifestations in the alterations of the sense of smell, with anosmia being defined as a complete loss of the sense of smell. Given

Table 4
Anosmia case definition and levels of diagnostic certainty.

Level of certainty 1 (definitive case)
Report of loss of sense of smell
AND
Confirmation by a standardized orthonasal olfactory test[a]
AND
Assessment by a specialist medical professional (e.g., otorhinolaryngologist or neurologist)

Level of certainty 2 (probable case)
Report of loss of sense of smell
AND
Confirmation by an office-based non-standardized test[b]
OR
Assessment by a non-specialist medical professional

Level of certainty 3 (possible case)
Report of loss of sense of smell
AND
No objective evaluation by a medical professional[c]

Notes:
[a] standardized tests are commercially available and have been validated as reproducible tests; include information on the assessment test(s) and identification results, but discrimination or threshold test are not required to meet Level 1.
[b] non-commercial, non-validated test e.g., alcohol swab, other office-based assessment.
[c] e.g. coffee smell, or other home-based assessment.

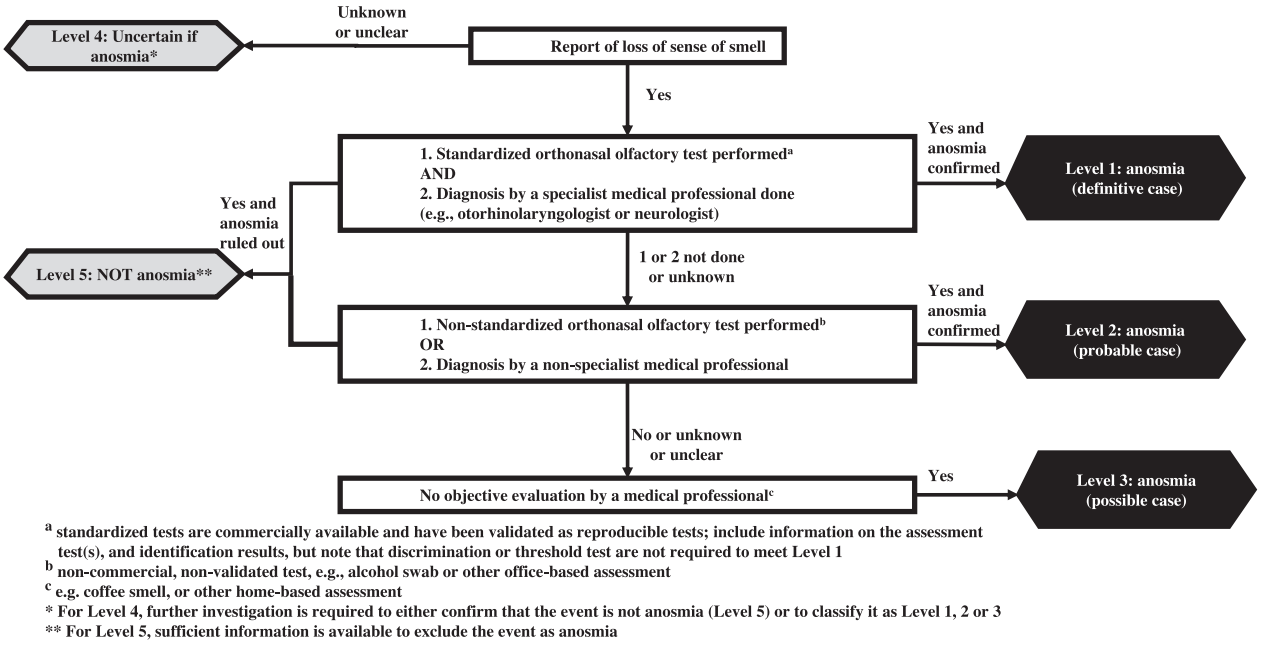

Fig. 2. Algorithm for the Brighton Collaboration case definition and levels of diagnostic certainty for anosmia.

the complexity of diagnostic and testing possibilities and the need to understand the various available diagnostic olfactory tests available, a high level of certainty requires the use of standardized tests performed by an expert (Table 3). Non-standardized assessment of anosmia may include the inability to smell common everyday odors as evaluated by non-validated, non-reproducible home or office ad hoc assessments, for example the inability to smell coffee or alcohol.

7.3.2. Pathology, radiology, and laboratory findings

The Working Group established that specific pathology, radiology and laboratory testing is not necessary to establish a diagnosis of anosmia as described in the case definition. However, these tests may be useful to evaluate a case of anosmia to determine etiology, as described in **section 3.2**.

7.3.3. Influence of treatment on fulfilment of case definition

Given the lack of an established or known response to treatment for anosmia, the Working Group decided against using 'treatment' or 'treatment response' towards the fulfillment of the anosmia case definition.

7.3.4. Timing post immunization

We postulate that a definition designed to be a suitable tool for testing relationships requires ascertainment of the outcome (e.g., anosmia) independent from the exposure (e.g., immunization). Further, anosmia often occurs outside the controlled setting of a clinical trial. In some settings it may be impossible to obtain a clear timeline of the event, therefore, to avoid selection bias, a restrictive time interval from immunization to onset of anosmia should not be an integral part of such a definition. Instead, where feasible, details of this interval should be assessed and reported as described in the data collection guidelines. (Appendix A).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

The authors are grateful for the support and helpful comments provided by the experts consulted as part of the process. The authors are also grateful to Margaret Haugh, MediCom Consult, Villeurbanne, France for medical writing and editorial services.

Disclaimer

The findings, opinions and conclusions contained in this consensus document are those of the individual members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporation). Specifically, the findings in this paper are those of the authors and do not necessarily represent the views of their respective institutions.

Funding

This work was supported by the Coalition for Epidemic Preparedness Innovations (CEPI) under a service order entitled Safety Platform for Emergency vACcines (SPEAC) Project with the Brighton Collaboration, a program of the Task Force for Global Health, Decatur, GA.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.11.022.

References

[1] Parma V, Ohla K, Veldhuizen MG, Niv MY, Kelly CE, Bakke AJ, et al. More than smell—COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. Chem Senses 2020;45(7):609–22.

[2] American Academy of Ototlaryngology-Head and Neck Surgery. Hyposmia and anosmia. 2022. Last accessed 28 June 2022; Available from: https://www.enthealth.org/conditions/hyposmia-and-anosmia/.
[3] Rawal S, Hoffman HJ, Bainbridge KE, Huedo-Medina TB, Duffy VB. Prevalence and risk factors of self-reported smell and taste alterations: results from the 2011–2012 US National Health and Nutrition Examination Survey (NHANES). Chem Senses 2016;41:69–76. https://doi.org/10.1093/chemse/bjv057.
[4] Neuland C, Bitter T, Marschner H, Gudziol H, Guntinas-Lichius O. Health-related and specific olfaction-related quality of life in patients with chronic functional anosmia or severe hyposmia. Laryngoscope 2011;121:867–72. https://doi.org/10.1002/lary.21387.
[5] Stevenson RJ, Mahmut MK, Horstmann A, Hummel T. The aetiology of olfactory dysfunction and its relationship to diet quality. Brain Sci 2020;10(11):769.
[6] Kohli P, Soler ZM, Nguyen SA, Muus JS, Schlosser RJ. The association between olfaction and depression: a systematic review. Chem Senses 2016;41:479–86. https://doi.org/10.1093/chemse/bjw061.
[7] Hoffman HJ, Rawal S, Li CM, Duffy VB. New chemosensory component in the U. S. National Health and Nutrition Examination Survey (NHANES): first-year results for measured olfactory dysfunction. Rev Endocr Metab Disord 2016;17:221–40. https://doi.org/10.1007/s11154-016-9364-1.
[8] Costanzo RM, Miwa T. Posttraumatic olfactory loss. Adv Otorhinolaryngol 2006;63:99–107. https://doi.org/10.1159/000093753.
[9] Enriquez K, Lehrer E, Mullol J. The optimal evaluation and management of patients with a gradual onset of olfactory loss. Curr Opin Otolaryngol Head Neck Surg 2014;22:34–41. https://doi.org/10.1097/moo.0000000000000013.
[10] Holbrook EH, Leopold DA. An updated review of clinical olfaction. Curr Opin Otolaryngol Head Neck Surg 2006;14:23–8. https://doi.org/10.1097/01.moo.0000193174.77321.39.
[11] Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 1991;65:175–87. https://doi.org/10.1016/0092-8674(91)90418-x.
[12] Holbrook EH, Leopold DA. Anosmia: diagnosis and management. Curr Opin Otolaryngol Head Neck Surg 2003;11:54–60. https://doi.org/10.1097/00020840-200302000-00012.
[13] Mott AE, Leopold DA. Disorders in taste and smell. Med Clin North Am 1991;75:1321–53. https://doi.org/10.1016/S0025-7125(16)30391-1.
[14] Temmel AF, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. Arch Otolaryngol Head Neck Surg 2002;128:635–41. https://doi.org/10.1001/archotol.128.6.635.
[15] Fonteyn S, Huart C, Deggouj N, Collet S, Eloy P, Rombaux P. Non-sinonasal-related olfactory dysfunction: A cohort of 496 patients. Eur Ann Otorhinolaryngol Head Neck Dis 2014;131:87–91. https://doi.org/10.1016/j.anorl.2013.03.006.
[16] Malaty J, Malaty IA. Smell and taste disorders in primary care. Am Fam Physician 2013;88:852–9.
[17] Goncalves S, Goldstein BJ. Pathophysiology of olfactory disorders and potential treatment strategies. Curr Otorhinolaryngol Rep 2016;4:115–21. https://doi.org/10.1007/s40136-016-0113-5.
[18] Lane AP, Turner J, May L, Reed R. A genetic model of chronic rhinosinusitis-associated olfactory inflammation reveals reversible functional impairment and dramatic neuroepithelial reorganization. J Neurosci 2010;30:2324–9. https://doi.org/10.1523/jneurosci.4507-09.2010.
[19] Welge-Lüssen A, Wolfensberger M. Olfactory disorders following upper respiratory tract infections. Adv Otorhinolaryngol 2006;63:125–32. https://doi.org/10.1159/000093758.
[20] Konstantinidis I, Haehner A, Frasnelli J, Reden J, Quante G, Damm M, et al. Post-infectious olfactory dysfunction exhibits a seasonal pattern. Rhinology 2006;44:135–9.
[21] Doty RL. A review of olfactory dysfunctions in man. Am J Otolaryngol 1979;1:57–79. https://doi.org/10.1016/s0196-0709(79)80010-1.
[22] Lee DY, Lee WH, Wee JH, Kim JW. Prognosis of postviral olfactory loss: follow-up study for longer than one year. Am J Rhinol Allergy 2014;28:419–22. https://doi.org/10.2500/ajra.2014.28.4102.
[23] Hopkins C, Surda P, Kumar N. Presentation of new onset anosmia during the COVID-19 pandemic. Rhinology 2020;58:295–8. https://doi.org/10.4193/Rhin20.116.
[24] Las Casas Lima MHd, Cavalcante ALB, Leão SC. Pathophysiological relationship between COVID-19 and olfactory dysfunction: A systematic review. Braz J Otorhinolaryngol 2022;88(5):794–802.
[25] Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 2020;6(31). https://doi.org/10.1126/sciadv.abc5801.
[26] Butowt R, von Bartheld CS. Anosmia in COVID-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. Neuroscientist 2021;27:582–603. https://doi.org/10.1177/1073858420956905.
[27] Guarneros M, López-Rivera C, Gonsebatt ME, Alcaraz-Zubeldia M, Hummel T, Schriever VA, et al. Metal-containing particulate matter and associated reduced olfactory identification ability in children from an area of high atmospheric exposure in Mexico City. Chem Senses 2020;45(1):45–58.
[28] Siegel JK, Wroblewski KE, McClintock MK, Pinto JM. Olfactory dysfunction persists after smoking cessation and signals increased cardiovascular risk. Int Forum Allergy Rhinol 2019;9:977–85. https://doi.org/10.1002/alr.22357.
[29] Doty RL, Yousem DM, Pham LT, Kreshak AA, Geckle R, Lee WW. Olfactory dysfunction in patients with head trauma. Arch Neurol 1997;54:1131–40. https://doi.org/10.1001/archneur.1997.00550210061014.
[30] Feiz-Erfan I, Han PP, Spetzler RF, Horn EM, Klopfenstein JD, Kim LJ, et al. Preserving olfactory function in anterior craniofacial surgery through cribriform plate osteotomy applied in selected patients. Neurosurgery 2005;57(suppl_1):86–93.
[31] Howell J, Costanzo RM, Reiter ER. Head trauma and olfactory function. World J Otorhinolaryngol Head Neck Surg 2018;4:39–45. https://doi.org/10.1016/j.wjorl.2018.02.001.
[32] Lecuyer Giguère F, Frasnelli A, De Guise É, Frasnelli J. Olfactory, cognitive and affective dysfunction assessed 24 hours and one year after a mild Traumatic Brain Injury (mTBI). Brain Inj 2019;33:1184–93. https://doi.org/10.1080/02699052.2019.1631486.
[33] Rombaux P, Mouraux A, Bertrand B, Nicolas G, Duprez T, Hummel T. Retronasal and orthonasal olfactory function in relation to olfactory bulb volume in patients with posttraumatic loss of smell. Laryngoscope 2006;116:901–5. https://doi.org/10.1097/01.mlg.0000217533.60311.e7.
[34] Devere R. Smell and taste in clinical neurology: Five new things. Neurol Clin Pract 2012;2:208–14. https://doi.org/10.1212/CPJ.0b013e31826af199.
[35] Yousem DM, Geckle RJ, Bilker WB, Kroger H, Doty RL. Posttraumatic smell loss: relationship of psychophysical tests and volumes of the olfactory bulbs and tracts and the temporal lobes. Acad Radiol 1999;6:264–72. https://doi.org/10.1016/s1076-6332(99)80449-8.
[36] London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. Ann Neurol 2008;63:159–66. https://doi.org/10.1002/ana.21293.
[37] Marin C, Vilas D, Langdon C, Alobid I, López-Chacón M, Haehner A, et al. Olfactory dysfunction in neurodegenerative diseases. Curr Allergy Asthma Rep 2018;18(8). https://doi.org/10.1007/s11882-018-0796-4.
[38] Devanand DP, Michaels-Marston KS, Liu X, Pelton GH, Padilla M, Marder K, et al. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. Am J Psychiatry 2000;157(9):1399–405.
[39] Haehner A, Hummel T, Reichmann H. Olfactory loss in Parkinson's disease. Parkinsons Dis 2011;2011:450939.
[40] Doty RL, Li C, Mannon LJ, Yousem DM. Olfactory dysfunction in multiple sclerosis. Relation to plaque load in inferior frontal and temporal lobes. Ann N Y Acad Sci 1998;855:781–6. https://doi.org/10.1111/j.1749-6632.1998.tb10658.x.
[41] Greebe P, Rinkel GJ, Algra A. Anosmia after perimesencephalic nonaneurysmal hemorrhage. Stroke 2009;40:2885–6. https://doi.org/10.1161/strokeaha.109.557579.
[42] Stamou MI, Georgopoulos NA. Kallmann syndrome: phenotype and genotype of hypogonadotropic hypogonadism. Metabolism 2018;86:124–34. https://doi.org/10.1016/j.metabol.2017.10.012.
[43] Bakay L. Olfactory meningiomas. The missed diagnosis. JAMA 1984;251:53–5.
[44] Kunte H, Schmidt F, Kronenberg G, Hoffmann J, Schmidt C, Harms L, et al. Olfactory dysfunction in patients with idiopathic intracranial hypertension. Neurology 2013;81(4):379–82.
[45] Uecker FC, Olze H, Kunte H, Gerz C, Göktas Ö, Harms L, et al. Longitudinal testing of olfactory and gustatory function in patients with multiple sclerosis. PLoS One 2017;12(1):e0170492.
[46] Chan JYK, García-Esquinas E, Ko OH, Tong MCF, Lin SY. The association between diabetes and olfactory function in adults. Chem Senses 2017;43:59–64. https://doi.org/10.1093/chemse/bjx070.
[47] McConnell RJ, Menendez CE, Smith FR, Henkin RI, Rivlin RS. Defects of taste and smell in patients with hypothyroidism. Am J Med 1975;59:354–64. https://doi.org/10.1016/0002-9343(75)90394-0.
[48] Mackay-Sim A, Johnston AN, Owen C, Burne TH. Olfactory ability in the healthy population: reassessing presbyosmia. Chem Senses 2006;31:763–71. https://doi.org/10.1093/chemse/bjl019.
[49] Dutta S, Kaur R, Charan J, Bhardwaj P, Ambwani SR, Babu S, et al. Analysis of neurological adverse events reported in VigiBase From COVID-19 vaccines. Cureus 2022;14:e21376.
[50] Frontera JA, Tamborska AA, Doheim MF, Garcia-Azorin D, Gezegen H, Guekht A, et al. Neurological events reported after COVID-19 vaccines: an analysis of VAERS. Ann Neurol 2022;91:756–71. https://doi.org/10.1002/ana.26339.
[51] Lee DS, Kim JW, Lee KL, Jung YJ, Kang HW. Adverse events following COVID-19 vaccination in South Korea between February 28 and August 21, 2021: A nationwide observational study. Int J Infect Dis 2022;118:173–82. https://doi.org/10.1016/j.ijid.2022.03.007.
[52] Doty RL, Berman AH, Izhar M, Hamilton HB, Villano D, Vazquez BE, et al. Influenza vaccinations and chemosensory function. Am J Rhinol Allergy 2014;28(1):50–3.
[53] Lechien JR, Diallo AO, Dachy B, Le Bon SD, Maniaci A, Vaira LA, et al. COVID-19: Post-vaccine smell and taste disorders: report of 6 cases 1455613211033125. Ear Nose Throat J 2021. https://doi.org/10.1177/01455613211033125.
[54] Seiden AM, Duncan HJ. The diagnosis of a conductive olfactory loss. Laryngoscope 2001;111:9–14. https://doi.org/10.1097/00005537-200101000-00002.

[55] Saltagi AK, Saltagi MZ, Nag AK, Wu AW, Higgins TS, Knisely A, et al. Diagnosis of anosmia and hyposmia: a systematic review. Allergy Rhinol (Providence) 2021;12. https://doi.org/10.1177/21526567211026568. 215265672110265.

[56] Doty RL, Shaman P, Kimmelman CP, Dann MS. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. Laryngoscope 1984;94:176–8. https://doi.org/10.1288/00005537-198402000-00004.

[57] Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, et al. Position paper on olfactory dysfunction. Rhinol Suppl 2017;54(26):1–30.

[58] Lötsch J, Reichmann H, Hummel T. Different odor tests contribute differently to the evaluation of olfactory loss. Chem Senses 2008;33:17–21. https://doi.org/10.1093/chemse/bjm058.

[59] Wang L, Chen L, Jacob T. Evidence for peripheral plasticity in human odour response. J Physiol 2004;554:236–44. https://doi.org/10.1113/jphysiol.2003.054726.