Olfactory disorder after COVID-19 vaccination

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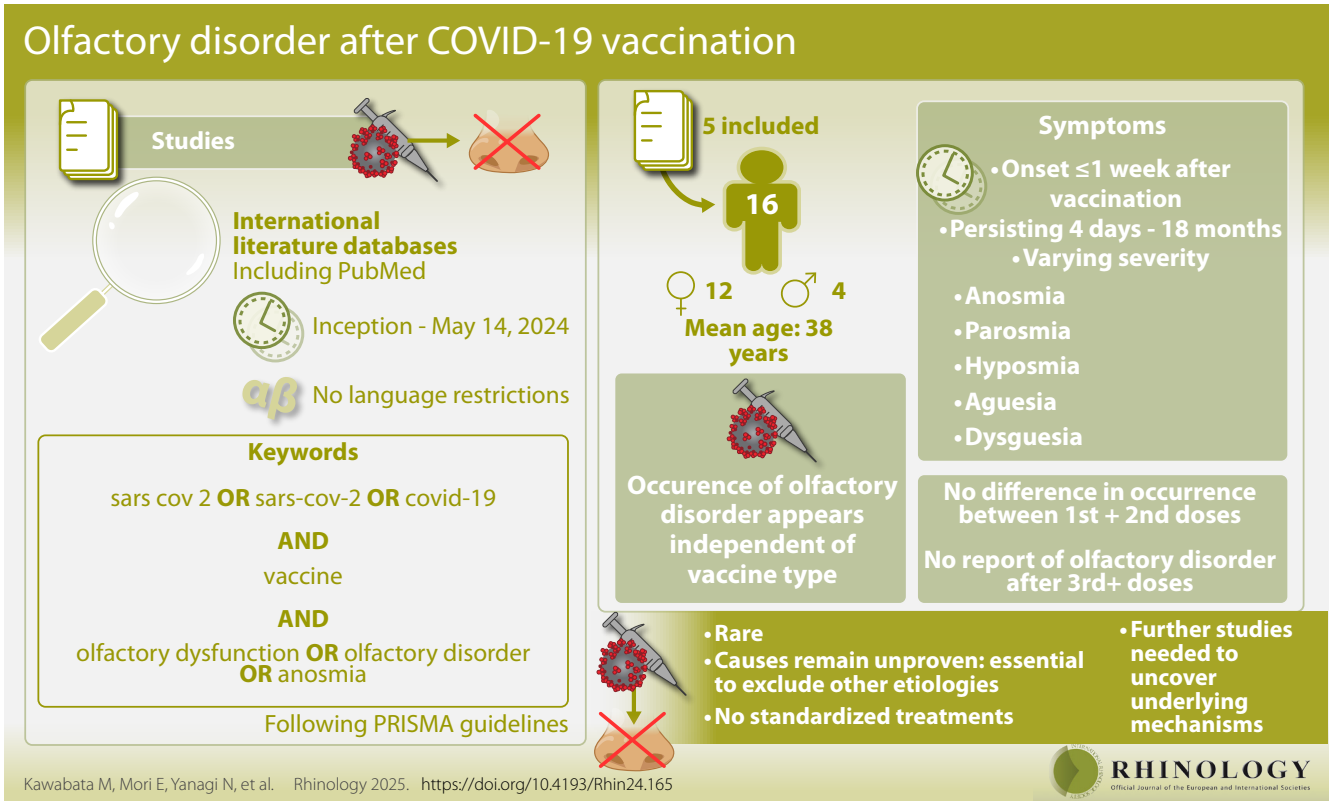

Abstract

This systematic review examines 16 reported cases of olfactory disorders occurring after COVID-19 vaccination. Symptoms such as anosmia, parosmia, hyposmia, ageusia, and dysgeusia appeared within one week of vaccination. Among the 16 patients (12 women, 4 men; mean age 38 years), 9 received the Pfizer mRNA vaccine, 6 received the AstraZeneca viral vector vaccine, and 1 received the Moderna mRNA vaccine. Symptoms persisted from 4 days to 18 months, with varying degrees of severity. Diagnoses were made using Sniffin' Sticks tests and T&T olfactometry, mosty revealing mild hyposmia. Treatment included vitamin B12, multivitamins, olfactory training, Kampo formula, and, in some cases, corticosteroids. The hypothesized mechanism involves inflammatory responses triggered by spike protein interaction with the α7 nicotinic acetylcholine receptor on macrophages. Given the lack of definitive diagnostic methods, careful clinical evaluation is essential to rule out other causes such as subclinical COVID-19 infection. While olfactory disorders have been reported after vaccination, no direct causal relationship has been established. Further research is needed to clarify underlying mechanisms and contributing factors.

Key words: COVID-19, olfactory disorder, vaccination

Introduction

Since the World Health Organization declared the coronavirus disease 2019 (COVID-19) pandemic in March 2020, the virus (SARS-CoV-2) has profoundly impacted social networks, health systems, and economies worldwide. Countries have implemented measures such as social distancing, mask-wearing, and the unprecedented rapid development and distribution of COVID-19 vaccines to control the pandemic. These vaccines have significantly reduced COVID-19-related morbidity and mortality, and their benefits have been shown to outweigh potential risks across various age groups [1-3].

While post- COVID-19 olfactory disorder is well-documented, olfactory disorder following COVID-19 vaccination is less well understood, with only scattered case reports available. Therefore, this study reviews a total of 16 cases of COVID-19-vaccination-related olfactory disorders, 5 cases from our institution and 11 cases from 5 other reports.

Materials and methods

This systematic review was conducted to comprehensively review studies that evaluated and reported olfactory abnormalities following COVID-19 vaccination. All methods used to conduct this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.

Search strategy

A systematic search was conducted in international literature databases, including PubMed, from its inception to May 14, 2024. No restrictions were placed on the original language of the studies. Key words were searched: (sars cov 2 OR sars-cov-2 OR covid-19) AND vaccine AND (olfactory dysfunction OR olfactory disorder OR anosmia). Keywords were combined by "AND" between groups and "OR" in each group.

Eligibility

Any published study that evaluated olfactory disorder following COVID-19 vaccination was eligible. This included case reports, case series, letters to the editor articles in which cases on this topic were reported, or observational studies that included at least one eligible patient consistent with this criterion; studies reporting olfactory disorder due to COVID-19 infection, or non-COVID-19 vaccines were excluded.

Data extraction

Screening of identified studies was based on abstract and title to exclude irrelevant studies.

Full-text articles initially screened were reviewed for inclusion criteria and data extraction. Age, gender, country, vaccine type, number of vaccinations, history of COVID-19 infection, date of onset, duration of symptoms, symptoms, nasal endoscopy findings, COVID-19 PCR test results, method of diagnosis, treatments, outcomes were extracted.

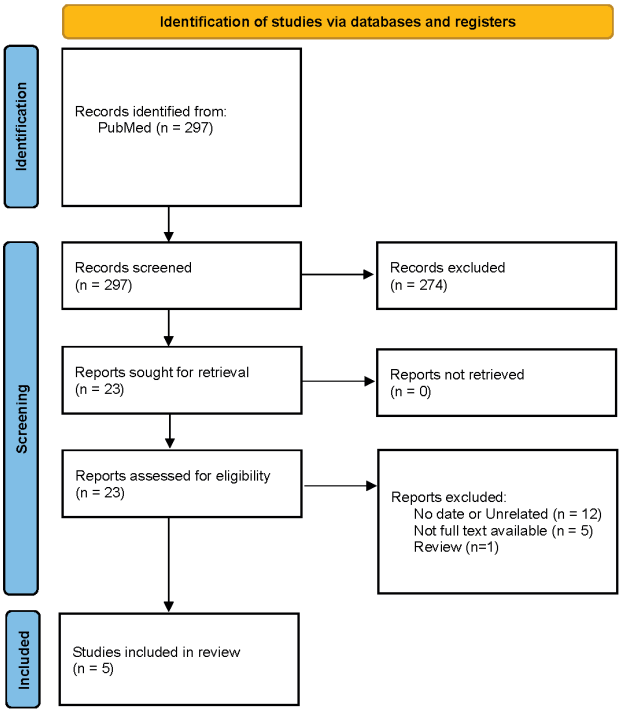

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. The systematic search for this study yielded 297 articles, and an initial screening of titles and abstracts selected a total of 23 articles. The full text of those articles was evaluated and 11 cases from 5 studies were included in this systematic review.

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Ethics approval

This study was approved by the ethics committee of our university (Approval No. 33-159(10774)) and conducted with patient consent.

Results

Summary of the study

The systematic search for this study yielded 297 articles, and an initial screening of titles and abstracts selected a total of 23 articles. The full text of those articles was evaluated and 11 cases from 5 studies were included in this systematic review [4-8] (Figure 1). Five cases of olfactory disorder after COVID-19 vaccination were added this systematic review. In total, 16 cases were included in this study: 12 women and 4 men, with a mean age of 38 years (range: 17-76 years). The characteristics of the included cases are summarized in Table 1.

Table 1. Patients characteristics.

Patient No	Age	Gender	Country	Vaccine manufacturer	Vaccine doses	COVID-19 history	Vaccination to symptom onset	Symptom duration	Symptoms	nasoendoscopy	PCR	Olfactory test	Severity	MRI	Treatment	Outcome
1	30	M	Japan	Pfizer	First	None	5 days	10 months	Parosmia, hyposmia and dysgeusia	narrow	Negative, Day=2	T&T	T&T detection threshold value : 2.6 recognition threshold value : 3.4 Moderate hyposmia	None	Vitamin B12, Tokisyakuyakusan and corticosteroid drop	6 months later, T&T olfactory test showed improvement.
2	17	F	Japan	Moderna	Second	2 months ago	1 day	more than 13 months	Parosmia and dysgeusia	normal	Uncertain	T&T	T&T detection threshold value : 1.6 recognition threshold value : 2.6 Moderate hyposmia	None	Vitamin B12	At the 6-month follow-up, there was no apparent improvement.
3	18	F	Japan	Pfizer	Second	None	8 days	12 months	Parosmia	normal	Negative	T&T	T&T detection threshold value : 1.4 recognition threshold value : 3.4 Moderate hyposmia	None	Vitamin B12 and Tokisyakuyakusan	After 12 months, olfactory impairment improved.
4	41	F	Japan	Pfizer	First	2 months ago	0 days	18 months	Parosmia	Not performed	Uncertain	T&T	T&T detection threshold value : 0.2 recognition threshold value : 1.8 Mild hyposmia	None	Vitamin B12 and Tokisyakuyakusan	18 months later, the sense of smell returned to normal.
5	35	F	Japan	Pfizer	First	None	4 days	17 months	Parosmia, hyposmia	normal	Negative	T&T	T&T detection threshold value : 1.2 recognition threshold value : 1.4 Mild hyposmia	None	Vitamin B12 and Tokisyakuyakusan	17 months later, his sense of smell returned to normal on a T&T olfactory test.
6	25	F	Italy	Astra-Zeneca	First	None	2 days	10 days	Partial loss of smell	Not performed	Negative, Day=1	Sniffin' Sticks	TDI 27 hyposmia	None	None	The Sniffin-Sticks improved became normal 40 days after the onset of symptoms
7	27	F	Italy	Astra-Zeneca	First	None	2 days	9 days	Partial loss of smell	Not performed	Negative, Day=1	Sniffin' Sticks	Not performed	None	None	Improvement of smell 9days after receiving the vaccine and became normosmia after 40days
8	51	F	Italy	Astra-Zeneca	First	None	2 days	7 days	Total loss of smell	normal	Negative	Uncertain	Not performed	None	None	Subsequent progressive smell improvement after 1 week of persisted total loss of smell
9	30	F	France	Pfizer	Second	None	1 day	4 days	Total loss of smell	Not performed	Negative, Day=1, 2	Uncertain	Not performed	None	Uncertain	Progressive olfactory recovery after 4 days
10	44	M	Belgium	Astra-Zeneca	First	None	2 days	7 weeks	Dysgeusia to sweet taste	normal	Negative, Day=1	Sniffin' Sticks Burghart Taste strips	15/16 normal the total loss of salty (0/4)	None	None	Dysgeusia persisted 7weeks
12	38	M	Saudi Arabia	Astra-Zeneca	Second	2 months ago	7 days	10 days	Parosmia	normal	Negative	Sniffin' Sticks	7/16 Hyposmia	None	Oral corticosteroids, nasal spray cortisone, daily oral omega-3, olfactory rehabilitation	Uncertain
13	42	F	Greece	Pfizer	Second	4 months ago	3 days	30 days	Hyposmia	normal	Negative	Sniffin' Sticks	TDI 22 hyposmia	None	Olfactory training	Partial improvement of olfactory testing after 1month
14	39	F	Greece	Pfizer	Second	None	5 days	7 days	Hyposmia	normal	Negative	Sniffin' Sticks	TDI 27 hyposmia	None	None	Symptoms improved within 1wk and became normosmic before starting olfactory training scheme

Table 1 *continued*. Patients characteristics.

Patient No	Age	Gender	Country	Vaccine manufacturer	Vaccine doses	COVID-19 history	Vaccination to symptom onset	Symptom duration	Symptoms	nasoendoscopy	PCR	Olfactory test	Severity	MRI	Treatment	Outcome
15	57	F	USA	Pfizer	Second	Uncertain	Uncertain	Uncertain	Parosmia, hyposmia	Uncertain	Negative	Uncertain	None	On axial T2 and FLAIR images there was T2 signal hyperintensity along the left olfactory bulb and bilateral olfactory tracts suggestive of edema	Uncertain	Uncertain
16	76	M	Italy	Astra-Zeneca	First	None	2 days	Uncertain	Hyposmia, parosmia and dysgeusia	normal	Negative	Sniffin' Sticks	TDI 19.5 : hyposmia	olfactory bulb mild atrophy	Nasal cortisone spray, olfactory training and multivitamin supplementation	hyposmia remained after 3 months

Vaccine type

Of the 16 patients, 9 received Pfizer mRNA vaccine, 6 received AstraZeneca viral vector vaccine, and 1 received Moderna mRNA vaccine. Eight of these patients developed symptoms after the first vaccination, and 8 developed symptoms after the second vaccination.

Extent and duration of symptoms

Most patients developed symptoms within one week after vaccination, though 2 patients had symptoms 8 and 9 days after vaccination. Symptoms included anosmia, parosmia, hyposmia, ageusia, and dysgeusia. In previous reports, the duration of symptoms ranged from 4 to 42 days, whereas in our patients the symptoms persisted for at least 10 months. Although it is difficult to compare olfactory evaluation methods in different countries, two cases of loss of sense of smell, eight cases of hyposmia, and nine cases of dysgeusia have been reported, including our case and those previously reported.

COVID-19 disease history

Of the 16 patients, 10 had no history of COVID-19, 5 had a history of infection, and 1 was unknown.

Diagnosis and treatment

Five patients were evaluated by T&T olfactometry and seven patients were evaluated by Sniffin' Sticks. The T&T olfactometry test uses five odors, each with varying concentrations. A concentration of -2 represents the weakest odor. Each lowest concentration at which the patient detects and identify the odor is recorded as the detection and identification threshold. The identification threshold 1.0 or below indicate normosmia, between 1.1-2.5 indicate mild hyposmia, between 2.6-4.0 indicate moderate hyposmia, between 4.1-5.5 indicate severe hyposmia, and 5.6 or above indicate anosmia. In the Sniffin' Sticks test, patients smell an odor-infused pen and select the closest match from four options. TDI scores under 30.5 indicate hyposmia, and scores below 16.5 indicate anosmia. The median recognition threshold value for T&T in the five cases was 2.6, indicating moderate dysfunction. On the Sniffin' Sticks, four cases showed a median TDI of 24.5, indicating hyposmia. Three of the Sniffin' Sticks examinations also performed the 16-pen Sniffin' Sticks test, with a median of 11.

MRI was performed in 2 of the 16 patients, one of which was T2 signal hyperintensity along the left olfactory bulb and bilateral olfactory tracts suggestive of edema. In the other case, the findings were suggestive of olfactory bulb mild atrophy.

Patients received a variety of treatments as empiric therapy. Nine patients received treatment or olfactory training. Seven patients took vitamin B12. Two patients took multivitamins. Four patients were treated with a combination of Tokishakuyakusan (TSS) and vitamin B12. TSS, a traditional Japanese Kampo herbal

formula, has been widely used in the treatment of patients with gynecological disorders, including climacteric disturbance, menstrual irregularity, dysmenorrhea, and infertility. TSS has also been prescribed for patients with post-infectious olfactory dysfunction and has shown efficacy in Japan [16].

Follow-up olfactory test results showed that 4 out of 5 patients at our institution recovered from olfactory disorder.

In the study by Lechien et al. [4], one patient received oral corticosteroids, vitamin B12 and vitamin B9. They reported that the patient's parosmia improved after 6 weeks, although it did not recover completely. Fantin et al. [8] reported a patient with hyposmia, dysgeusia, and parosmia after receiving the first dose of COVID-19 vaccine. This patient received nasal cortisone spray, olfactory rehabilitation, and multiple vitamin supplements. The patient's hyposmia remained after 3 months. In a study by Konstantinidis et al. [6], olfactory training was suggested for the patient's decreased sense of smell, and partial improvement was seen after 1 month.

Discussion

Main findings

This systematic review indicates that olfactory disorder may occur after COVID-19 vaccination. The review revealed symptoms such as anosmia, ageusia, parosmia, hyposmia, and dysgeusia shortly after vaccination.

Based on the results, olfactory disorder reported after COVID-19 vaccination was more prevalent in women. Other studies have also shown that olfactory disorders are more common in women due to their superior performance in olfactory discrimination and generally more sensitive olfactory function [9, 10].

There was no difference in the occurrence of olfactory abnormalities between the first and second doses of the vaccine, and no reports after the third dose or subsequent doses. A study by Nguyen et al. [11], involving 1,323 participants, demonstrated that the incidence of adverse events following immunization (AEFIs) after a booster vaccination was consistent with that of the first or second vaccination. However, a study by Jieun et al. [12] found that adverse reactions were more frequent after receiving the completed primary series (CPS) compared to the updated bivalent booster (UBB). This could be because as individuals continue with sequential vaccinations, their adaptive immune response becomes more refined and primed, leading to fewer AEFIs after receiving the UBB compared to the CPS [12].

The occurrence of olfactory abnormalities does not appear to depend on the type of vaccine. This lack of variation between mRNA and viral vector vaccines may be due to a common underlying response to vaccination, a hypothetical mechanism that will be discussed below.

Hypothesized pathogenesis

One hypothesized mechanism of olfactory disorder reported after COVID-19 vaccination is the interaction of local spike protein expression with the α7 nicotinic acetylcholine receptor on macrophages. This interaction prompts cholinergic pathways and triggers the release of inflammatory cytokines. Subsequent signaling spreads distally from the vaccination site via neural pathways, triggering an inflammatory response at remote sites such as the olfactory epithelium [13].

Other vaccination-induced olfactory disorders

While most of the reported vaccination-related olfactory disorders have been associated with COVID-19 vaccines, cases following influenza and tick-borne encephalitis (TBE) vaccinations have also been reported.

One study reported 9 (0.19%) of 4554 patients who received influenza vaccination had olfactory disorder. The mechanism of pathogenesis is not yet known [14].

A case of hyposmia following TBE vaccination did not recover after 1 year of follow-up [15].

Immune response and olfactory dysfunction

Studies of autoimmune diseases suggest that immune-mediated mechanisms could contribute to olfactory disorder, as conditions like systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, and multiple sclerosis have shown association with olfactory disorder due to underlying neuroinflammatory processes [17-19]. It is plausible that an aberrant immune response triggered by COVID-19 vaccination may contribute to transient or persistent olfactory disorder.

Gender disparity and perception bias

Women tend to seek treatment for olfactory issues more frequently than men, and studies have shown a higher prevalence of olfactory disorders in women, with ratios ranging from 1.5 to 2:1 [20,21]. In this review, the female-to-male ratio was 3:1, which may reflect selection bias or a true difference in susceptibility. Additionally, the duration of olfactory disorder varied widely among patients, ranging from a few days to over a year. This discrepancy may, in part, be influenced by perception bias - patients who believe their olfactory disorder was caused by vaccination may be more likely to closely monitor their symptoms and report prolonged issues. Conversely, those with shorter symptom durations may recover without seeking medical attention, leading to underreporting. This highlights the need for standardized follow-up assessments to better understand the true course of post-vaccination olfactory disorder.

Diagnostic workup

Psychophysical testing methods such as Sniffin' Sticks and T&T olfactometry are essential for objectively assessing olfactory dysfunction. These methods provide quantifiable data that can be used to verify the presence and severity of symptoms, which

is particularly relevant in medico-legal cases where subjective complaints must be substantiated with clinical evidence. Given the potential implications for occupational health and legal claims, standardized olfactory and taste testing should be considered an essential component of the diagnostic workup.
Additionally, some patients may have had pre-existing mild olfactory disorder that became noticeable only after vaccination. This heightened awareness could be attributed to recall bias, where individuals become more attuned to their sensory function following a medical event such as vaccination. Future studies should account for this possibility by assessing pre-vaccination olfactory function whenever feasible.
The diagnosis of olfactory disorder after vaccination is essentially a diagnosis of exclusion. It is crucial to exclude intracranial and other potential concomitant causes of olfactory disorder. While there is no uniform method for diagnosis, abnormalities on sinus CT scans or improvement in olfactory function following oral steroid use may suggest an inflammatory phenomenon. Repeated RT-PCR and serology tests are important to differentiate vaccine-related effects from undiagnosed COVID-19 infection. MRI should be performed only when clinically indicated such as to exclude intracranial diseases, and not as a routine part of the diagnostic workup for post-vaccination olfactory disorder. Although olfactory disorder after vaccination is rare, healthcare providers should remain aware of this rare complication.

Potential treatment options

The effectiveness of treatments for post-vaccination olfactory disorders remains unclear. Vitamin B12 and multivitamins have been used for their neuroprotective properties, though their efficacy is not well-established. Tokishakuyakusan has been traditionally used in Japan for post-infectious olfactory dysfunction, and some studies suggest it may promote olfactory nerve regeneration [16]. Olfactory training is widely recommended for various forms of olfactory dysfunction and has shown some benefit in post-infectious cases. However, no standardized treatment exists for vaccine-related olfactory disorders, and further research is needed to establish evidence-based therapeutic strategies.

Conclusion

Olfactory disorder has been reported after COVID-19 vaccination, though causality remains unproven. Given the rarity of this phenomenon and the challenges in establishing direct causation, careful exclusion of other etiologies, including subclinical COVID-19 infection, is essential. No standardized treatment exists, although empirical treatments such as vitamin B12, olfactory training and Kampo medicine have been used. Further studies with larger cohorts and controlled methodologies are needed to elucidate the mechanisms underlying these cases.

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Authors' contributions

MK, EM: drafting the work; MK acquisition, analysis and interpretation of data for the work; EM, MT: substantial contributions to the conception or design of the work; EM, MT: revising the manuscript critically for important intellectual content; MK, EM, MT, NY, NO: final approval of the version to be published and agreement to be accountable for all aspects of the work.

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Conflicts of interest

None of the authors declare any conflict of interest.

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