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CLINICAL LETTER

Olfactory dysfunction after coronavirus disease 2019 (COVID-19) vaccination

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Olfactory dysfunction is an official World Health Organization symptom of coronavirus disease 2019 (COVID-19), with a prevalence of 70% to 90% in some studies. Several pathophysiologic mechanisms have been proposed,[1,2] including:

1. obstruction of the olfactory cleft;
2. infection of the sustentacular supporting cells, which express angiotensin-converting enzyme2 (ACE-2);
3. injury to olfactory sensory cells via neuropilin-1 receptor (NRP1); and
4. injury to the olfactory bulb.

Olfactory loss appears to be related mainly to damage to the olfactory neuroepithelium rather than to an obstructed olfactory cleft. Two of the above mentioned mechanisms entail viral spike binding to olfactory epithelium cells (olfactory receptor neurons and sustentacular cells).[2] Viral proteins, mainly spike protein, appear to cause indirect tissue injury without actively replicating the virus. Because the recently developed anti-COVID-19 messenger RNA (mRNA) vaccines encode or bear the spike protein, it is possible that the immune response or the spike protein itself might induce olfactory epithelial damage.

Until now, no official data has been published on olfactory dysfunction after vaccination, although 70 cases of anosmia, 58 cases of parosmia, and six cases of hyposmia are among the 100,809 reported reactions to the drug in the UK listed in the COVID-19 mRNA Pfizer-BioNTech vaccine analysis print.[3] Here, we present two cases of smell impairment after COVID-19 vaccination. Both patients presented with hyposmia after their second dose of the Comirnaty vaccine (Pfizer-BioNTech BNT162b2). They were healthy female subjects, nonsmokers, and had no history of nasal disease or previous nasal surgery.

Patient 1 had been infected with COVID-19 four months earlier without requiring hospitalization. Three weeks after infection, she had experienced hyposmia as measured by the validated Sniffin' Sticks battery test (Burghart GmbH, Wedel, Germany) (threshold-discrimination-identification [TDI] score: 18), but showed significant improvement 1 month after the initial assessment (TDI: 30). Then, 3 days after her second dose of vaccination (4 weeks after the first dose), she complained of decreased olfactory ability (TDI: 22). The patient did not complain of parosmia either during infection or postvaccination. However, she did experience muscle aches and headache in the same postvaccination period.

Patient 2 had no previous COVID-19 infection. She presented with hyposmia (TDI: 27) 5 days after receiving a second dose of the vaccine. No parosmia or other symptoms were reported. All TDI scores for both patients are presented in Table 1.

Both patients had negative real-time polymerase chain reaction (RT-PCR) COVID-19 tests for active infection. In addition, enzyme-linked immunosorbent assay

TABLE 1 Kinetics of olfactory test results and serology test results for both patients

Patient	Sex	Age (years)	COVID-19 infection	Nasal endoscopy	TDI score post infection	TDI score post infection	Vaccine	TDI postvaccination	TDI postvaccination follow-up	Serology 40 days after second vaccination
Patient 1	F	42	Nov 2020	Patent olfactory cleft	TDI: 18 Dec 2020	TDI: 30 Jan 2021	Pfizer (2 doses)	TDI: 22 Feb 2021	TDI: 27 in 30 days with olfactory training	IgM: - N-IgG: 4.4 AU/ml S-IgG: 156.5 AU/ml
Patient 2	F	39	No infection	Patent olfactory cleft			Pfizer (2 doses)	TDI: 27 Feb 2021	TDI: 34 in 7 days	IgM: - N-IgG: - S-IgG: 74 AU/ml

Abbreviations: COVID-19, coronavirus disease 2019; F, female; IgM, immunoglobulin M; N-IgG, nucleocapsid protein–immunoglobulin G; S-IgG, spike protein–immunoglobulin G; TDI, threshold-discrimination-identification score.

(ELISA) serology tests revealed no evidence of recent infection, because immunoglobulin M (IgM) was not detected; patient 1 had positive serology for nucleocapsid protein–immunoglobulin G (N-IgG) and spike protein–immunoglobulin G (S-IgG), and patient 2 was positive for S-IgG only (Table 1). Nasal endoscopy revealed no evidence of nasal inflammation and showed patent olfactory clefts in both cases.

The first patient was advised to start olfactory training with four odors (lemon, rose, eucalyptus, and cloves) and showed partial improvement on olfactory testing (TDI: 27) 1 month later. The second patient improved within a week after the initial assessment and became normosmic before start to follow an olfactory training scheme (TDI: 34). The Comirnaty vaccine elicits cellular immune responses against spike protein. This response appears to be weak after the first dose of the vaccine and stronger after the second one.

Although the mechanism is not understood, the immune response induced by vaccination might explain olfactory dysfunction. Wallitzec-Dworschak et al.[4] suggested that postinfectious olfactory loss might be related to immune-mediated processes, asanti-nuclear antibodies were significantly more frequent in patients with olfactory dysfunction compared to controls. In addition, reduced olfactory function has already been shown in several autoimmune disorders, such as multiple sclerosis, pemphigus vulgaris, psoriasis vulgaris, and Sjögren syndrome.[4]

According to Farsalinos et al.,[5] spike protein interacts locally with the alpha7 nicotinic acetylcholine receptors (nAChRs), deregulating the inflammatory reflex.[6] According to this hypothesis, spike protein, when expressed locally after vaccination, may interact with alpha7 nAChRs in macrophages. The deregulation of the cholinergic pathway might subsequently trigger the release of pro-inflammatory cytokines, while additional signals might be transmitted via neural pathways from the local injection site to a distant one. As a result, the so-called "inflammatory reflex" produces neural signals that can "travel" via the vagus nerve to the brainstem and are then brought to distant tissues via efferent nerves.[6] The existence of such a neuroimmunological interaction regulating cytokine release may explain inflammatory responses in distant sites, such as the olfactory epithelium.

In summary, our observations may initiate a discussion of olfactory dysfunction as a side effect of COVID-19 vaccination.

REFERENCES

1. Moein ST, Hashemian SM, Mansourafshar B, et al. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol*. 2020;10(8):944-950.

2. Hopkins C, Lechien JR, Saussez S. More that ACE2? NRP1 may play a central role in the underlying pathophysiological mechanism of olfactory dysfunction in COVID-19 and its association with enhanced survival. *Med Hypotheses*. 2021;146:110406.
3. COVID-19 mRNA Pfizer- BioNTech Vaccine Analysis Print. 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/982474/Covid-19_mRNA_Pfizer_BioNTech_vaccine_analysis_print2.pdf. Accessed April 30, 2021.
4. Wallitzec-Dworschak U, Zimmermann AM, Poletti S, Hummel T. Antinuclear antibodies in post infectious smell loss - a pilot study. *Rhinol Online*. 2019;2:1-5.
5. Farsalinos K, Eliopoulos E, Leonidas DD, et al. Nicotinic cholinergic system and COVID-19: in silico identification of an interaction between SARS-CoV-2 and nicotinic receptors with potential therapeutic targeting implications. *Int J Mol Sci*. 2020;21(16):5807.
6. Tracey KJ. The inflammatory reflex. *Nature*. 2002;420(6917):853-859.

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