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Relationship Between Anosmia, Interleukin-6, and Disease Course of SARS COVID-19 Infection

ABSTRACT

Background: Olfactory dysfunction became increasingly popular as an early symptom of COVID-19 infection, associated with a positive outcome and milder course of the disease. Initial studies suggest that interleukin-6 directly damages the olfactory bulb, thus playing an important role in the mechanism of anosmia. Higher plasma levels of interleukin-6, on the other hand, are related to the severe course of the disease after COVID-19 infection.

Methods: The present study explores the predictive power and the relationship between anosmia and plasma levels of interleukin-6 in 122 patients who were hospitalized with COVID-19 in the period March to November 2021 in the Hospital Base for Active Treatment of Military Medical Academy, Varna, Bulgaria.

Results: The positive correlation between plasma levels of interleukin-6 and disease severity was confirmed. Also, we observed a significant decrease in interleukin-6 plasma levels during the course of the disease in patients with a favorable outcome. There was no statistically significant difference between plasma levels of interleukin-6 in recovered patients with and without anosmia. We also reported a high percentage of hospitalized and deceased patients with anosmia.

Conclusions: In patients with moderate-to-severe SARS CoV-2 infection, anosmia has not been proven to be a prognostic sign for a positive outcome of the disease. However, our data show that plasma levels of interleukin-6 have good predictive power for the course and outcome of the infection. We found a positive correlation between interleukin-6 and the severity of the disease. Favorable outcome was most often preceded by a rapid drop in interleukin-6 levels.

Keywords: COVID-19, anosmia, interleukin-6

INTRODUCTION

Olfactory dysfunction is not a rare condition. Population distribution shows that 19.1% of adults suffer a form of olfactory dysfunction. This number increases to 80% in patients aged over 75.4 years.[1] Infectious diseases including COVID-19 are among the most common causes of temporary or continuous loss of the sense of smell. Meta-analyses have shown that olfactory or taste dysfunction in COVID-19 infection in the population ranges between 67% and 31% in patients moderate-to-mild symptoms, respectively. In 20% of all cases, the loss of smell and taste is reported to be among the first symptoms to appear within 4 days of infection.[2]

Numerous publications have accumulated in the scientific literature that anosmia and dysgeusia in COVID-19 are favorable prognostic symptoms. The paradox remains unclear that a number of studies have cited interleukin-6 (IL-6)[3,4] as a direct olfactory agent, while its high plasma levels are an unfavorable prognostic factor.

This study aims to determine the relationship between plasma levels of IL-6, the presence of anosmia, and the outcome of the disease in hospitalized patients with moderate-to-severe SARS COVID-19 infection.

MATERIAL AND METHODS

This retrospective study was conducted in the period March-November 2021 in the Hospital Base for Active Treatment of Military Medical Academy, Varna, Bulgaria. A total

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Table 1. Descriptive Statistics for Age, Interleukin-6 Plasma Levels, Anamnesis for Anosmia and Outcome of the Disease

Descriptive statistics	n	Minimum	Maximum	Mean	Standard Deviation	Variance
Age (years)	122	30.00	89.00	60.8852	14.86924	221.094
Interleukin-6 levels (total)	122	1.37	305.02	47.1262	55.57536	3088.620
Interleukin-6 levels (recovered)	96	1.37	305.02	41.439375	54.13608	2930.715
Interleukin-6 levels (deceased)	26	1.69	186.60	70.608	56.54273	3197.08
Sense of smell	122	0.00	1.00	0.7787	0.41684	0.174
Outcome	122	0.00	1.00	0.7705	0.42225	0.178
Valid N (listwise)	122					

of 122 hospitalized patients with severe COVID-19 infection were included. Patients were tested for IL-6 levels in the plasma. The obtained results were compared with the anamnestic data for loss of smell and taste, as well as with the outcome of the disease—recovered and deceased. Statistical analysis was performed using International Business Machine's Statistical Package for Social Sciences program.

The study was approved with protocol number 2399 of July 19, 2022, by the Local Ethics Board of MBAT Varna MMA appointed by annual order RD-1-03 of January 4, 2022. The research is conducted in compliance with the ethical considerations and all principles for medical research involving human subjects according to the WMA Declaration of Helsinki. Our patients sign a package of informed consents regulating various aspects of their stay in the hospital—funding, diagnostic and clinical methodologies, student training, and processing of the results obtained.

RESULTS

As presented in Table 1 a total of 122 patients (77 males and 45 females) were included in the study. Their mean age (±standard deviation (SD)) was 60.89 ± 14.87 years. Of the patients, 96 (78.69%) recovered and were discharged from the hospital, and 26 of the examined patients (21.31%) passed away.

The mean level of IL-6 (±SD) was 47.13 ± 55.58. In the group of recovered patients, the mean IL-6 plasma level was 41.44 ± 54.14. In the group of deceased patients, the mean IL-6 plasma level was 70.61 ± 56.54. The IL-6 control studies during the treatment of recovered patients showed a rapid drop, with a mean value of the first study of 89.8035 and a best control of 12.4560.

Regarding anosmia, 27 of all patients (22.1311%) reported olfactory disorders. A glance at the percentage ratio of disease outcome and preserved/impaired sense of smell shows that there is no supporting data for the hypothesis that anosmia is a positive predictive symptom of SARS COVID-19 infection. Because we have 2 nominal scales, we compared the percentage of survived patients with anosmia to the percentage of deceased patients with anosmia (Table 2). Those 2 were approximately the same. A similar ratio between 2 sets of data is associated with no significant relationship between the 2 phenomena.

Further, we investigated the correlations between IL-6 plasma levels, sense of smell, disease outcome, and age. The results are presented in Table 3. There is a weak negative correlation between IL-6 levels and disease outcomes with a general tendency for higher levels to be associated with a higher risk of a negative outcome. Nevertheless, the relationship is weak, leading to the conclusion that a static measurement of IL-6 levels is not a reliable prognostic measure. In our sample, the highest measured IL-6 result was in the group of recovered patients, but it was followed by a rapid drop in a control testing. As expected, the other significant correlation in our data was between age and disease outcome. Age was proven to be a risk factor and a negative prognostic sign. However, we found no significant correlation between IL-6 levels and anosmia or between anosmia and disease outcome. This result contradicts the hypothesis that anosmia is a positive prognostic sign of COVID-19 infection.

We further investigated the possibility to use IL-6 plasma levels' predictive potential by conducting a receiver operating characteristic analysis. As expected, IL-6 plasma levels turned out to have prognostic power for the disease outcome, but with only moderate strength (Figure 1 and Table 4). An IL-6 value of 17 points to a higher risk of complications and a more severe course of the disease during SARS COVID-19 infection. It is not a definite marker, but such a measure by a simple blood test could be used as guidance for the severity of the disease and the possible treatment options.

Contrary to many publications pointing to IL-6 as a direct olfactory agent, our analysis found no association between IL-6 plasma levels in patients with anosmia (Figure 2 and Table 5).

The results of this study cannot confirm a direct olfactory damage mechanism of plasma IL-6. Of course, there may be no correlation between tissue and serum IL-6 levels.

MAIN PONTS

- No association was found between IL-6 plasma levels and anosmia.
- There is no conclusive data that anosmia is a positive prognostic sign for disease outcome of COVID-19 infection.
- Favorable disease outcome of COVID-19 infection is preceded by a rapid drop of IL-6 levels.

Table 2. Percentage Ratio Between Anosmia Anamnesis and Disease Outcome

Outcome Sense of Smell	96 Survived Patients	26 Deceased Patients
Normosmia	76.5957%	82.1429%
Anosmia	23.4043%	17.8571%
	100%	100%

Table 3. Pearson's Correlation for Age, Interleukin-6 Plasma Levels, Anamnesis for Anosmia and Outcome of the Disease

Correlations		Age	Interleukin-6	Anosmia	Outcome
Age	Pearson's correlation	1	.211*	.176	−.402**
	Significance (2-tailed)		.019	.053	.000
	n	122	122	122	122
Interleukin-6	Pearson's correlation	.211	1	.054	−.228*
	Significance (2-tailed)	.019		.551	.012
	n	122	122	122	122
Anosmia	Pearson's correlation	.176	.054	1	−.056
	Significance (2-tailed)	.053	.551		.539
	N=n	122	122	122	122
Outcome	Pearson's correlation	−.402	−.228	−.056	1
	Significance (2-tailed)	.000	.012	.539	
	n	122	122	122	122
	Significance (2-tailed)	.011	.914	.087	.015
	n	122	122	122	122

*Correlations significant at $P \leq .005$.
**Correlations significant at $P \leq .001$.

DISCUSSION

Angiotensin-converting enzyme 2 (ACE2) receptors are a proven gateway to the COVID-19 virus cell. They can be found in a variety of tissues, including the heart, oral mucosa, kidneys, skeletal muscle, respiratory system, and central nervous system (CNS). This indicates that the COVID-19 virus can cause multisystem disorders in the human body, affecting different organs and tissues at the same time.[5,6] In the human olfactory bulb, ACE2 receptors are abundant in the supporting cells, and a minimal number of the ACE2 receptors are located in the nerve fibers themselves (Figure 3).[7,8] DosSantos et al[9] hypothesized that olfactory stem cells had sufficient expression of ACE2 receptors for viral invasion and that the virus could reach the CNS as they matured. Butowt and Von Bartheld[10] believe that anosmia is caused mainly by the invasion of supporting cells and with a low probability of secretions and swelling of the mucosa or direct infection of olfactory cells and the brain. Subsequently,

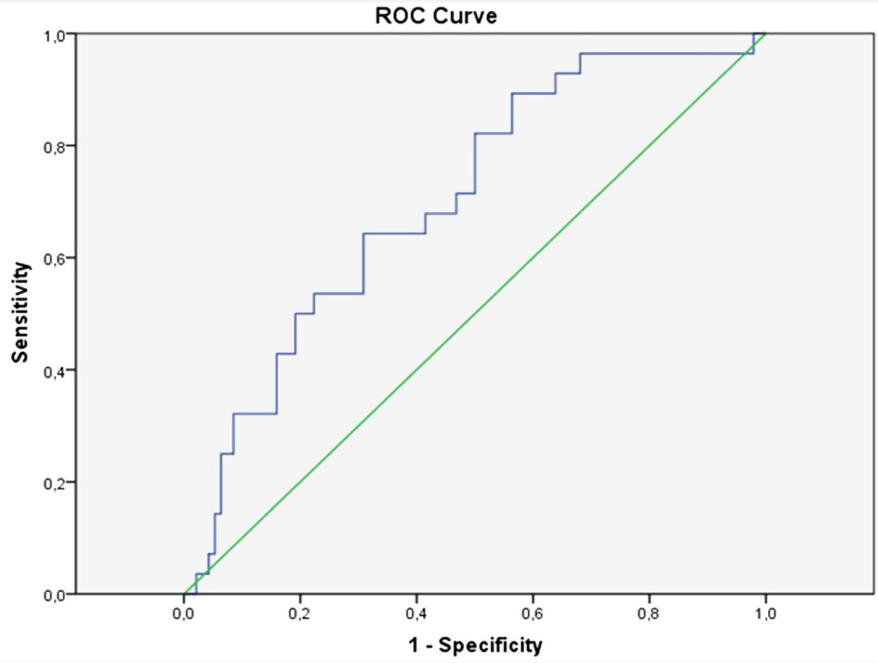

Figure 1. Receiver operating characteristic analysis of interleukin-6 plasma levels as a predictor of disease outcome after SARS COVID-19 infection.

Table 4. Cutoff Points of Interleukin-6 Plasma Levels As a Predictor of Disease Outcome After SARS COVID-19 Infection

Coordinates of the Curve		
Test Result Variable(s):Interleukin		
Positive if Greater Than or Equal Toa	Sensitivity	1 – Specificity
1.4700	1.0000	0.9894
17.1150	0.8214	0.5000
40.6650	0.6429	0.3085
284.8900	0.0000	0.0106

AUC = 0.702; Standard error = 0.054; CI, 0.596-0.808.

migration of immunocompetent cells begins. This process significantly increases the levels of cytokines and tumor necrosis factor-alpha (TNF-α).[5]

The primary protease TMPRSS2 facilitates the invasion of the virus by increasing its expression with the age of the individual,[7] which explains the more severe disease course.

The nasal mucosa is constantly exposed to aggressive factors from our environment—both microorganisms and chemicals. That is why the body constantly replaces all of its cells. A properly functioning sense of smell requires continuous cleansing of destructured cells from macrophages, their activity being modulated by the chemokine fractalkine (CX3CL1) —a ligand secreted by damaged olfactory sensory neuron (OSN), under the influence of disintegrin-like metalloproteinase 10 (ADAM10) and TNF-α-converting enzyme (ADAM17)[11,12] A study by Blomster[13] showed that impairments of this mechanism in mice lead to secondary cell death in the olfactory mucosa and severe olfactory disorders. However, fractalkine is abundantly expressed by many other tissues, including activated endothelium through the proinflammatory cytokines IL-1β and TNF-α, and is an important regulator of many aspects of endothelial function and dysfunction, including thrombosis. Rivas-Fuentes et al[14] hypothesized that blocking ACE2 receptors by SARS-2 viruses leads to the accumulation of fractalkine and overactivity of immunocompetent cells, consequently leading to thrombopathy. The amount of angiotensin II also increases at the expense of its derivative Ang 1-7. The latter reduces vascular inflammation and platelet aggregation in blood vessels.[15] The increased number of immunocompetent cells logically leads to increased levels of inflammatory cytokines IL-6 and TNF-α.

Interleukin-6 plays a key role in the cytokine storm by inducing various acute phase proteins (C-reactive protein, serum amyloid A, α1-antichymotrypsin, haptoglobin, fibrinogen, and complement components) and activates the coagulation cascade with the onset of disseminated intravascular coagulation. Elevated IL-6 levels are significantly associated with severe clinical manifestations.[16] The dynamic change in IL-6 levels is also a predictor of disease outcome.[17]

There are studies that find a correlation between the plasma level of IL-6 and the presence of anosmia,[3,18] as well as studies that do not find such a relation.[19]

Elevated levels of IL-6 have been found in the serum of patients with dysosmia as well as in the olfactory bulb and CNS during various infections with human influenza virus (1918 H1N1 influenza virus, 2009 H1N1 influenza virus, and HPAI H5N1 virus).[3,20,22] Experiments confirm that virus-infected microglial cells and

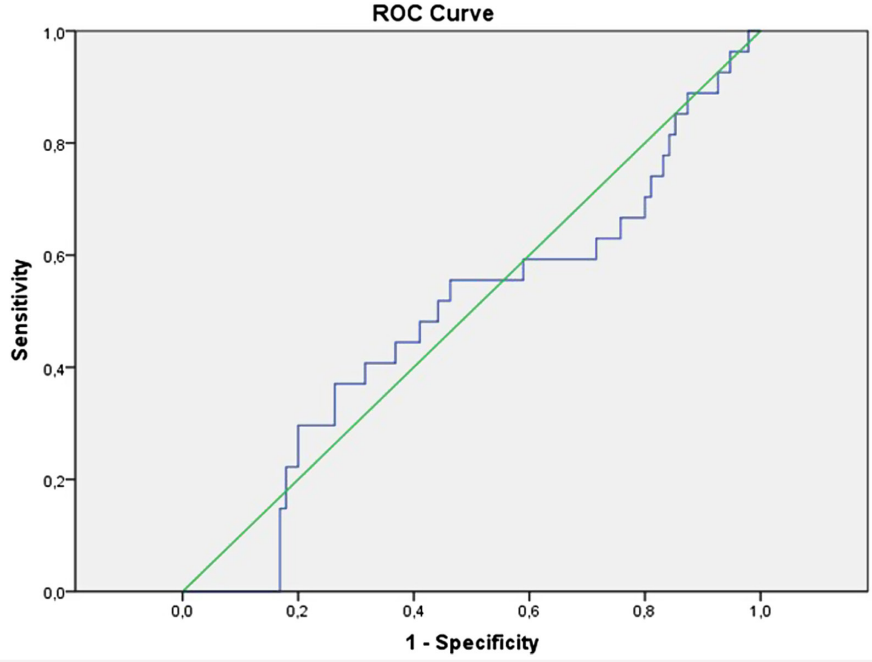

Figure 2. Receiver operating characteristic analysis of interleukin-6 plasma levels in cases of anosmia after SARS COVID-19 infection.

Table 5. Cutoff Points of Interleukin-6 Plasma Levels in Cases of Anosmia After SARS COVID-19

Coordinates of the Curve		
Test Result Variable(s):Interleukin		
Positive if Greater Than or Equal To[a]	Sensitivity	1 – Specificity
1.4700	1.0000	0.9895
3.8750	0.8889	0.8737
8.4000	0.6667	0.7579
27.0850	0.5556	0.4632
40.6650	0.4444	0.3684
284.8900	0.0000	0.0105

AUC = 0.486; Standard error = 0.065; CI, 0.359-0.613; a is 0.065.

astrocytes secrete IL-6[23-25] and primary glial cells cultured in vitro secrete large amounts of inflammatory factors such as IL-6, IL-12, IL-15, and TNF-α after infection. with coronaviruses. This, of course, does not require an urgent increase in serum IL-6 levels.

Genetic predisposition of COVID-19-infected patients has been proven to be a statistically significant factor in self-assessed anosmia and other major symptoms.[26] A sequence in the field of the UGT2A1/UGT2A2 gene (chromosome 4q13.3) has been found to influence the development of anosmia with a frequency of 19%-37% in the US population 27, with ethnic groups originating in Southeast Asia differing greatly from the rest of the population. These groups are genetically heterogeneous with respect to ACE2 receptors.[28-30]

The frequency of anosmia also varies across COVID-19 serotypes. In variant D614G, up to 90% of patients have anosmia.[31] The first data on the omicron strain did not show a loss of taste and smell in a relatively mild course. By comparison, in the 2006 SARS pandemic, with only 80% genetic similarity of the causative agents, only 1 case of anosmia was reported.[32]

Another hypothesis for the occurrence of anosmia is the change in the level of zinc (Zn) in the body, based on the need for the trace element for the action of carbonic anhydrase—an enzyme with an important role in the perception of taste and smell. Zinc deficiency is associated with decreased Th1 cytokines—gamma-interferon and IL-2 and unchanged production of Th2 cytokines (IL-4, IL-6, and IL-10), which causes a shift of Th1/Th2 balance to the predominance of Th2 cytokines.[33] This leads to a direct reduction in the number of ACE2 receptors and is considered to be the body's defense mechanism.[34] Elevated Zn levels are toxic and also impair the perception of aromas.[35,36]

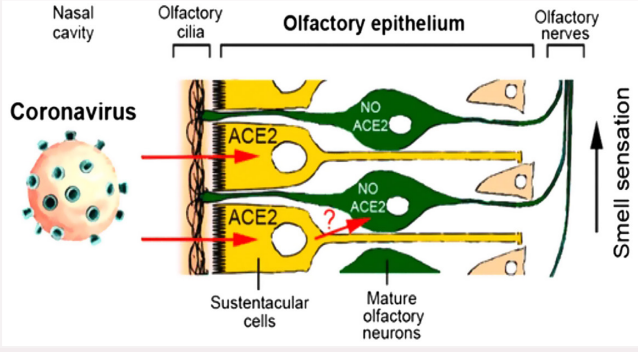

Figure 3. A possible mechanism for SARS-2 invasion in the nasal mucosa.[7]

The question remains, is anosmia in COVID-19 really a positive prognostic sign? A number of studies on severe SARS-2 have shown that anosmia is observed in a large percentage of hospitalized patients.[37] According to Liu,[17] even severely ill patients with anosmia have a survival advantage, but this advantage is lost in intensive care unit and mechanical ventilation. Our results fully support this view. It should not be forgotten that mild cases are mainly among young people who have a preserved sense of smell. With other mild symptoms, anosmia will be the leading symptom for such patients. On the contrary, adult patients with severe course and a previously impaired sense of smell will not pay much attention to such a symptom. There are not enough studies on late anosmia and their impact.

According to the results exported earlier, the present study cannot confirm a mechanism of direct olfactory damage by IL-6 in patients with COVID-19 infection. Of course, there is no mandatory correlation between tissue and plasma IL-6 levels. The increase in IL-6 tissue levels is possible after a secondary invasion of the damaged areas by immunocompetent cells. Related studies may reveal different mechanisms of damage or stages of the same process.

In our study, we confirmed that increased plasma levels of IL-6 are related to a higher risk of complications and negative outcomes. However, we found no relationship between IL-6 plasma levels and anosmia. In addition, we did not find a correlation between anosmia and disease outcome. We could not confirm the hypothesis that anosmia is a positive prognostic sign for SARS COVID-19 infection. It might be due to the fact that in our sample only moderate to severely ill patients were included.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Board of MBAT Varna MMA (approval No: 2399 from July 19, 2022).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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REFERENCES

1. Brämerson A, Johansson L, Ek L, Nordin S, Bende M. Prevalence of olfactory dysfunction: the Skövde population-based study. *Laryngoscope*. 2004;114(4):733-737. [CrossRef]

2. Borsetto D, Hopkins C, Philips V, et al. Self-reported alteration of sense of smell or taste in patients with COVID-19: a systematic review and meta-analysis on 3563 patients. *Rhinology*. 2020;58(5): 430-436. [CrossRef]
3. Henkin RI, Schmidt L, Velicu I. Interleukin 6 in hyposmia. *JAMA Otolaryngol Head Neck Surg*. 2013;139(7):728-734. [CrossRef]
4. Cazzolla AP, Lovero R, Lo Muzio L, et al. Taste and smell disorders in COVID-19 patients: role of interleukin-6. *ACS Chem Neurosci*. 2020; 11(17):2774-2781. [CrossRef]
5. Torabi A, Mohammadbagheri E, Akbari Dilmaghani NA, et al. Proinflammatory cytokines in the olfactory mucosa result in COVID-19 induced anosmia. *ACS Chem Neurosci*. 2020;11(13): 1909-1913. [CrossRef]
6. Aragão MFVV, Leal MC, Cartaxo Filho OQ, Fonseca TM, Valença MM. Anosmia in COVID-19 associated with injury to the olfactory bulbs evident on MRI. *AJNR Am J Neuroradiol*. 2020;41(9):1703-1706. [CrossRef]
7. Bilinska K, Jakubowska P, Von Bartheld CS, Butowt R. Expression of the SARS-CoV-2 entry proteins, ACE2 and TMPRSS2, in cells of the olfactory epithelium: identification of cell types and trends with age. *ACS Chem Neurosci*. 2020;11(11):1555-1562. [CrossRef]
8. Sayin I, Yazici ZM. Taste and smell impairment in SARS-CoV-2 recovers early and spontaneously: experimental data strongly linked to clinical data. *ACS Chem Neurosci*. 2020;11(14):2031-2033. [CrossRef]
9. DosSantos MF, Devalle S, Aran V, et al. Neuromechanisms of SARS-CoV-2: a review. *Front Neuroanat*. 2020;14:37. [CrossRef]
10. Butowt R, von Bartheld CS. Anosmia in COVID-19: underlying mechanisms and assessment of an olfactory route to brain infection. *Neuroscientist*. 2021;27(6):582-603. [CrossRef]
11. Hundhausen C, Misztela D, Berkhout TA, et al. The disintegrin-like metalloproteinase ADAM10 is involved in constitutive cleavage of CX3CL1 (fractalkine) and regulates CX3CL1-mediated cell-cell adhesion. *Blood*. 2003;102(4) :1186-1195. [CrossRef]
12. Tsou CL, Haskell CA, Charo IF. Tumor necrosis factor-alpha-convert ing enzyme mediates the inducible cleavage of fractalkine. *J Biol Chem*. 2001;276(48):44622-44626. [CrossRef]
13. Blomster L. *Role of Fractalkine/CX3CL1 Signalling in the Regenerating Olfactory Epithelium*. Examination Project, University of Kalmar; 2008. http://lnu.diva-portal.org/smash/get/diva2:126673/FULLTEXT01
14. Rivas-Fuentes S, Valdés VJ, Espinosa B, Gorocica-Rosete P, Salgado-Aguayo A, Could S-C. Could SARS-CoV-2 blocking of ACE2 in endothelial cells result in upregulation of CX3CL1, promoting thrombosis in COVID-19 patients? *Med Hypo*. 2021;151:110570. [CrossRef]
15. Fraga-Silva RA, Sorg BS, Wankhede M, et al. ACE2 activation promotes antithrombotic activity. *Mol Med*. 2010;16(5-6):210-215. [CrossRef]
16. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*. 2014;6(10):a016295. [CrossRef]
17. Liu Z, Li J, Chen D, et al. Dynamic interleukin-6 level changes as a prognostic indicator in patients With COVID-19. *Front Pharmacol*. 2020;11:1093. [CrossRef]
18. Sanli DET, Altundag A, Kandemirli SG, et al. Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia. *Am J Otolaryngol*. 2021 ;42(1):102796. [CrossRef]
19. Vaira LA, Deiana G, Lechien JR, et al. Correlations Between olfactory psychophysical scores and SARS-CoV-2 viral load in COVID-19 patients. *Laryngoscope*. 2021;131(10):2312-2318. [CrossRef]
20. Mori I. 1918 H1N1 Influenza virus infection—induced proinflammatory cytokines in the olfactory bulb could trigger lethargic disease. *J Infect Dis*. 2018;218(10):1686-1687. [CrossRef]
21. de Wit E, Siegers JY, Cronin JM. 1918 H1N1 influenza virus replicates and induces proinflammatory cytokine responses in extrarespiratory tissues of ferrets. *J Infect Dis*. 2018;217(8):1237-1246. [CrossRef]
22. De Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med*. 2006;12(10):1203-1207. [CrossRef]
23. Hanisch UK. Microglia as a source and target of cytokines. *Glia*. 2002;40(2):140-155. [CrossRef]
24. Frei K, Malipiero UV, Leist TP, Zinkernagel RM, Schwab ME, Fontana A. On the cellular source and function of interleukin 6 produced in the central nervous system in viral diseases. *Eur J Immunol*. 1989;19(4):689-694. [CrossRef]
25. Righi M, Mori L, De Libero G, et al. Monokine production by microglial cell clones. *Eur J Immunol*. 1989;19(8):1443-1448. [CrossRef]
26. Williams FMK, Freidin MB, Mangino M, et al. Self- reported symptoms of Covid-19 including symptoms most predictive of SARS-CoV2 infection, are heritable. *Twin Res Hum Genet*. 2020;23(6):316-321. [CrossRef]
27. Shelton JF, Shastri AJ, Fletez-Brant K, 23andMe COVID-19 Team, Aslibekyan S, Auton A. The UGT2A1/UGT2A2 locus is associated with COVID-19-related loss of smell or taste. *Nat Genet*. 2022 Feb; 54(2):121-124. [CrossRef]
28. Benetti E, Tita R, Spiga O, et al. ACE2 gene variants may underlie interindividual variability and susceptibility to COVID-19 in the Italian population. *Eur J Hum Genet*. 2020;28(11):1602-1614. [CrossRef]
29. Cao Y, Li L, Feng Z, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov*. 2020;6:11. [CrossRef]
30. Strafella C, Caputo V, Termine A, et al. Analysis of ACE2 genetic variability among populations highlights a possible link with COVID19-related neurological complications. *Genes (Basel)*. 2020;11(7):741. [CrossRef]
31. von Bartheld CS, Hagen MM, Butowt R. The D614G virus mutation enhances anosmia in COVID-19 patients: evidence from a systematic review and meta-analysis of studies from South Asia. *ACS Chem Neurosci*. 2021;12(19):3535-3549. [CrossRef]
32. Hwang CS. Olfactory neuropathy in severe acute respiratory syndrome: report of a case. *Acta Neurol Taiwan*. 2006;15(1):26-28.
33. Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. *J Infect Dis*. 2000;182(suppl 1):S62-S68. [CrossRef]
34. Equils O, Lekaj K, Fattani S, Wu A, Liu G. Proposed mechanism for anosmia during COVID-19: the role of local zinc distribution. *J Transl Sci*. 2020;7(1):1-2. [CrossRef]
35. Komai M, Goto T, Suzuki H, Takeda T, Furukawa Y. Zinc deficiency and taste dysfunction; contribution of carbonic anhydrase, a zinc-metalloenzyme, to normal taste sensation. *BioFactors*. 2000;12(1-4):65-70. [CrossRef]
36. Hsieh H, Vignesh KS, Deepe GS, Choubey D, Shertzer HG, Genter MB. Mechanistic studies of the toxicity of zinc gluconate in the olfactory neuronal cell line Odora. *Toxicol In Vitro*. 2016;35:24-30. [CrossRef]
37. Gusmãoa PAOA, Roveda JRC, Leite ASM, Leite AS, Marinho CC. Changes in olfaction and taste in patients hospitalized for COVID-19 and their relationship to patient evolution during hospitalization. *Braz J Otorhinolaryngol*. 2021;8694(21):00193-00192. [CrossRef]