

COVID-19 anosmia and gustatory symptoms as a prognosis factor: a subanalysis of the HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID-19) Registry

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Abstract

Olfactory and gustatory dysfunctions (OGD) are a frequent symptom of Coronavirus disease 2019 (COVID-19). It has been proposed that the neuroinvasive potential of the novel SARS-CoV-2 could be due to olfactory bulb invasion, conversely studies suggest it could be a good prognostic factor. The aim of the current study was to investigate the prognosis value of OGD in COVID-19.

These symptoms were recorded on admission from a cohort study of 5868 patients with confirmed or highly suspected COVID-19 infection included in the multicenter international HOPE Registry (NCT04334291).

There was statistical relation in multivariate analysis for OGD in gender, more frequent in female 12.41% vs 8.67% in male, related to age, more frequent under 65 years, presence of hypertension, dyslipidemia, diabetes, smoke, renal insufficiency, lung, heart, cancer and neurological disease. We did not find statistical differences in pregnant ($p=0.505$), patient suffering cognitive ($p=0.484$), liver ($p=0.1$) or immune disease ($p=0.32$). There was inverse relation (protective) between OGD and prone positioning (0.005) and death (<0.0001), but no with ICU (0.165) or mechanical ventilation (0.292). On univariable logistic regression OGD was found to be inversely related to death in COVID-19 patients. The Odds Ratio was 0.26 (0.15-0.44) ($p<0.001$) and Z was -5.05.

The presence of anosmia is fundamental in the diagnosis of SARS-CoV-2 infection, but also could be important when classifying patients and in therapeutic decisions. Even more knowing that it is an early symptom of the disease. Knowing that other situations as being Afro-American or Latino-American, Hypertension, renal insufficiency, or increase of C-reactive protein (CRP) imply a worse prognosis we can make a clinical score to estimate the vital prognosis of the patient.

The exact pathogenesis of SARS-CoV-2 that causes olfactory and gustative disorders remains unknown but seems related to the prognosis. This point is fundamental, insomuch as could be a plausible way to find a treatment.

Introduction

Coronavirus disease 2019 (COVID-19) is a multiorgan manifestation caused by a betacoronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Most of patients are asymptomatic or experience mild disease. Depending on the series, between 5-10% progresses to more severe disease (2). Anosmia is a frequent symptom of SARS-CoV-2 infection and could be more frequent in the youngest (3). Besides is more frequent in SARS-CoV-2 infection than in other viral infections as influenza (3). Anosmia and ageusia have recently been hinted as significant early symptoms in COVID-19 and could be an isolated symptom with all the epidemiological implications that it entails (4, 5). For example, recommend the isolation of patients, as has been suggested by various scientific societies (3, 4).

The pathophysiology of anosmia could be related to patient's prognosis. Although the exact pathogenesis of anosmia in COVID-19 remain unclear, should be related to involvement of nasal epithelium or the olfactory nerves (4). Moreover, it could be related to the neuroinvasive capacity of the SARS-CoV-2 and explain some of the recent MRI and autopsy findings (6-8). On the other hand, some studies suggest that could be a marker of early detection and recognition of infected patients (9, 10). Hypothesis as the early activations of the immunity as a protector factor could explain anosmia as a good prognosis factor.

The current study aimed to investigate if olfactory and gustatory dysfunction (OGD) in COVID-19 is a good prognosis symptom and analyze the biological plausibility.

Patients And Methods

Study design and population

Olfactive disorder was recorded on admission from a cohort study of 5868 patients with confirmed or highly suspected COVID-19 infection included in the multicenter international HOPE Registry (<https://www.hopeprojectmd.com>), The OGD was self-reported. Registry NCT04334291 on ClinicalTrials.gov. The HOPE-Registry was established through an international consortium. Detailed information about participating countries and hospitals, protocol and definitions are reported on the website of the Registry. In this interim analysis hospital data and patients were included until the second of April 2020. All Patients discharged (deceased or alive) from any hospital center with a confirmed diagnosis or a COVID-19 high suspicion were included in the HOPE Registry. The local ethics committee approved this study and was consistent with the guidelines of Helsinki. A list of participating hospitals, investigators, collaborators and the protocol is available in the appendix.

Outcome definition

We assessed the risk of death of patients with OGD on admission of 5868 patients with COVID-19. Patients were stratified into two groups: if absence of olfactive dysfunction, anosmia and hyposmia and dysgeusia.

Characteristics of olfactory alterations, defined as anosmia (complete absence of olfaction), hyposmia (reduced olfaction, with at least 2 types of smell preserved), dysosmia (reduced olfaction with presence of unpleasant smells), and other (including difficult to define sensations) and gustatory alterations, defined as defined as ageusia (complete absence of taste), hypogeusia (reduced taste,), dysgeusia (reduced and unpleasant taste), and other

Primary endpoint was defined as all-cause in-hospital death. Secondary outcomes were in-hospital complications such respiratory insufficiency, acute kidney injury , pneumonia, sepsis and embolic events.

All patients were asked about OGD in admission. Unconscious or confused patients or those who were not able to complete the study protocol were excluded

Statistical analysis

Data are presented as mean \pm standard deviation for continuous variables with a normal distribution, median (interquartile range) for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. Student's-t test and the Mann-Whitney U-test was used to compare continuous variables with normal and non-normal distributions, needed. The Chi-squared test or Fisher's exact test was used to compare categorical variables. Univariate analysis was performed for qualitative variables and reported as odds ratios (OR) with 95% CI. Given the multiplicity of variables, only factors with $p < 0.01$ on univariate analysis (dyslipidemia, diabetes mellitus, smoking, chronic kidney failure, heart disease, lung disease, cerebrovascular disease, connective disease, cancer, immunosuppression condition) were entered into the Cox multivariate regression analysis to define independent risk factors for the main outcome. Possible collinearity and interactions were evaluated with the introduction of multiplicative terms calculating the tolerance and the variance inflation factor. The relationship between olfactory disorders and the predicted probability of death was graphically represented after modeling this association using fractional polynomials. All tests were two-sided, and a P value less than 0.05 was considered statistically significant. Statistical analysis was performed with the IBM SPSS 20.0 software package and STATA software, version 15.

Study protocol

The HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19) is an international "real-world" all-comers retrospective cohort registry from all patients discharged (deceased or alive) after hospital admission for SARS-CoV-2 infection. It was performed as an initiative without conflict of interest, with voluntary participation and no financial remuneration. The study was approved by Ethics Research Committee from the Hospital Clínico San Carlos (Madrid, Spain) (20/241-E) and the Spanish Agency for Medicines and Health Products classification (EPA-0D). It was also performed according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. The study was registered 157 online at ClinicalTrials.gov (NCT04334291). Written informed consent was not requested due to the anonymized nature of the study and the situation of alarm in health resources due to the pandemic. The only exclusion criteria was the patient's refusal to participate. The list of participating hospitals and investigators, as well as study protocol and the Research Ethics Committee approval are available online (<https://hopeprojectmd.com>). Each participant center filled in an online anonymized database, available on the same website. All the authors reviewed the manuscript and vouch for the accuracy and completeness of the data provided

Results

Clinical characteristics

From 5868 patients there were 469 that were not included because of lack of clinical data. Mean age was 64.27±16.93. 59,2% (2906) were male. 84.5% (4152) were Caucasian, 11.5% (563) Latino-American, 2.7% (133) Asian and 0.6% (29) Afro-American. There were 19 (9,4%) of pregnant patients. There were 5.2% (230) smokers 49.5% (2423) hypertension, 34.1% (1666) with dyslipidemia, 19.4% (952) suffer diabetes, 6.7% (329) renal insufficiency, 13.3% (947) lung disease, 23.6% (1148) heart disease, 8.2% (395) neurological diseases, 2.7% (131) connective tissue disease, 3.9% (189) liver disorder, 13.8% (667) cancer and 7.5% (344) immune disease (table 1). The percentage of anosmia or hyposmia was 6.4% (377), dysgeusia 6.9% (404) and any 8.5% (505) (table 2). Of total of patients, 6.02% (303) were admitted in ICU, 7.2% (346) needed mechanical ventilation, 10.40% (495) required to adopt the prone position and 22.00% (1079) were death (table 2).

There was statistical relation in multivariate analysis for OGD in gender, more frequent in female 12.41% vs 8.67% in male, related with age, more frequent under 65 years, presence of HTA, dyslipidemia, diabetes, smoking, renal insufficiency, lung, heart, cancer and neurological disease. We did not find statistical differences in pregnant ($p=0.505$), patient suffering cognitive ($p=0.484$), liver ($p=0.1$) or immune disease ($p=0.32$) (table 1). There were inverse relation (protective) between OGD and prone positioning (0.005) and death (<0.0001), but no with ICU admission (0.165) or mechanical ventilation (0.292) (table 3)

On multivariate logistic regression OGD was found to be inversely related to death in COVID-19 patients. The Odds Ratio was 0.26 (0.15-0.44) ($p<0.001$) and Z was -5.05 (table 3, fig 1). On the other hand, hypertension, renal insufficiency, autoimmune disease, oxygen saturation below 92% and age over 70 were independent risk factors for death .

Discussion

OGD has become an important symptom in COVID-19. It is a frequent symptom, affecting about 40% of outpatients and also an important infection and infective marker (3,11, 12). Although in our series the prevalence of OGD was 8.5% (504 patients), this could be explained because inpatients use to be younger and have severe disease and it could be possible that anosmia is more frequent in mild disease (10). In fact, in our study this dysfunction was more frequent in younger patients (<52 years 15.80% vs 56-65 y. 15.48% vs 66-76 y. 7.05% vs >76 y. 3.47 $p<0.000$). Our results are in line with other inpatients studies (13). Female were significantly more affected by these dysfunctions (12.41% than male 8.67% $p<0.0001$). This finding is according to previous studies (4, 8, 9). The olfactory and gustative dysfunction was significantly more frequent in Afro-Americans and Latino-American than Caucasian or Asian people ($p<0.0001$). There were only 19 pregnant patients and we do not find any differences among them.

One interesting point is that anosmia was significantly more frequent in smokers (27.85% vs 10.16% $p<0.0001$) and there was no relation with hypertension. These findings could be related to a previous

lesion of nasal mucosa because the tobacco and predisposes to a higher olfactive epithelium lesion or the immune system has a higher reaction because of periodic toxic stimulation.

Patients reporting a loss of smell have fivefold decreased risk of death (OR 0.26 $p > 0.001$) compare with those without this disorder, and it was not related to any other factor. These findings confirm previous studies, and it seems clear that the presence of anosmia would imply a more benign prognosis of the disease (9, 10). Indeed, the olfactory system is a unique neuroimmune interface where interaction between nervous and immune systems (14). It is well known that virus or environmental toxicants can induce inflammatory responses, including infiltration of immune cells and production of cytokines (15, 16). This inflammation can induce olfactive sensitive neurons degenerations and apoptosis as a protective mechanism (17). Because the health of the central nervous system (CNS) is likely to be heavily influence by the immune status of the olfactory system, the reactions should be harmonic, because new olfactory sensory neurons (OSN) may help in the repair of nasal damaged tissue (18). On the other hand, immune cells in the olfactory mucosa regulate the depletion of old OSN and generation of new OSN (19). This situation could explain our results that patients with an immune dysfunction could have less OGD, because could be a lower immune reaction and therefore less epithelial and olfactive cells degeneration.

The pathophysiological point of view is quite interesting. Our group, like others, has already hypothesized about the possible relation between anosmia and CNS viral invasions (4, 20, 21). In fact, the olfactory nerve is a traditional way because is excused to the external world (22, 23). Other viruses like poliovirus or influenza use this route (24). And there is evidence that another coronavirus can reach the CNS direct through the olfactory bulb (25, 26). Nevertheless, it has not been demonstrated the neurotropism of SARS-CoV-2, and the neurological symptoms seems to be more related to the cytokine storm than to direct invasion. Most of the cerebrospinal fluid (CSF) analysis have been negative for SARS-CoV-2 RCP, and our study shows a better prognosis something clearly different from those seen in other viruses like influenza (27). For all those reasons we agree that the anosmia have to be related to the invasion of the olfactive epithelium and the possibility of neuroinvasion have to be relatively low and could be more related with Neuropilin-1 (28, 29). Furthermore, from the biological plausibility the olfactive sensitive neurons that do not express ACE-2 receptor which is fundamental in the SARS-CoV-2 cell invasion (28-30). Indeed, there is an elevated ACE2 expression in the olfactory neuroepithelium (230). Most of MRO studies shown normal olfactory bulb or an inflammation thar could be related to both, cytokine liberation or neuronal invasion (7, 31, 32)

We believe that a prior nasal epithelium invasion by SARS-CoV-2 should activate normal immunological reactions in patients and promoted type 1 IF activating anti-viral immunity and suppression of hyperinflammation (33, 34). This means that infected cells are rapidly cleared, viruses are inactivated by neutralizing antibodies and there is minimal inflammation (34). Avoiding in this way a dysfunctional immune response with excessive infiltration of monocytes, macrophages and T cells, the systemic cytokine storm and the secondary pulmonary and multi-organ damage (34).

The presence of anosmia is essential in the diagnosis of SARS-CoV-2 infection, but also could be important when in categorize patients and also in therapeutic decision-making. Even more, knowing that it is an early symptom of the disease. Knowing that other conditions as being Afro-American or Latino-American, Hypertension, renal insufficiency, or increase of RCP imply a worse prognosis we could develop a clinical score to estimate the vital prognosis for COVID-19 patients .

The exact pathogenesis of SARS-CoV-2 that causes olfactory and gustative disorders remains unknown but for sure is absolutely related to the prognosis. This point is relevant, insomuch as could be a plausible way to find a treatment. For this reason, study the anosmia and dysgeusia mechanism in COVID-19 seems to be fundamental. further prospective studies are needed to confirm our results.

Declarations

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DECLARATIONS OF INTEREST: none

Abbreviation List

CNS	Central nervous system
CSF	Cerebrospinal fluid
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein)
HOPE-COVID-19	Health Outcome Predictive Evaluation for COVID-19
OR	Odds ratios ()
OGD	Olfactory and gustatory dysfunctions
OSN	Olfactory sensory neurons
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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Tables

Table 1. Baseline demographics and clinical findings of COVID-19 individuals with or without olfactive and gustatory dysfunction with hospital admission determined using Multivariate analysis

		N=5399		OGD		P
Gender	Female	2006	40,8%	249	12,41%	0.0001
	Male	2906	59,2%	252	8,67%	
Age	52	1190	24,7%	188	15,80%	0.0001
	53-65	1150	23,8%	178	15,48%	
	66-76	1249	25,9%	88	7,05%	
	>76	1238	25,6%	43	3,47%	
Ethnicity	Afro-American	29	0,6%	17	58,62%	0.0001
	Caucasian	4152	84,5%	331	7,97%	
	Latino-American	563	11,5%	142	25,22%	
	Asian	133	2,7%	7	5,26%	
	Other	35	0,7%	4	11,43%	
Pregnant	NO	4893	99,6%	498	10,18%	0.505
	YES	19	0,4%	3	15,79%	
HTA	NO	2475	50,5%	287	11,60%	0.003
	YES	2423	49,5%	211	8,71%	
Dyslipidemia	NO	3217	65,9%	367	11,41%	0.0001
	YES	1666	34,1%	128	7,68%	
DM	NO	3960	80,6%	436	11,01%	0.0001
	YES	952	19,4%	65	6,83%	
Smoking	Ex	799	18%	63	7,88%	0.0001
	No	3403	76,8%	346	10,17%	
	Yes	230	5,2%	64	27,83%	
Renal insufficiency	NO	4582	93,3%	482	10,52%	0.012
	YES	329	6,7%	19	5,78%	
Lung disease	NO	3965	80,7%	428	10,79%	0.010
	YES	947	19,3%	73	7,71%	
Heart disease	0	3721	76,4%	405	10,88%	0.011
	1	1148	23,6%	92	8,01%	

Neurological disease	NO	4442	91,8%	478	10,76%	0.0001
	YES	395	8,2%	15	3,80%	
Connective tissue disease	NO	4713	97,3%	477	10,12%	0.484
	YES	131	2,7%	16	12,21%	
Liver disease	NO	4645	96,1%	482	10,38%	0.1
	YES	189	3,9%	12	6,35%	
Cancer	NO	4180	86,2%	446	10,67%	0.003
	YES	667	13,8%	44	6,60%	
Immune disease	NO	4229	92.5%	437	10.33%	0.329
	YES	344	7.5%	42	12.21%	

Table 2. Risk estimation in OGD vs no OGD patients

Variable	No OGD	OGD	OR	Interval	P
ICU admission	303 (6.02%)	37 (7.4%)	1.213	0.851-1.729	0.165
Prone positioning	495 (10.40%)	33 (6.70%)	0.626	0.434-0.902	0.005
Mechanical ventilation	346 (7.20%)	39 (8.00%)	1.116	0.79-1.576	0.292
Death	1079 (22.00%)	30 (6.00%)	0.226	0.155-0.329	>0.0001

Table 3. Cox multivariate regression analysis regarding anosmia and other risk factors associated with in-hospital death.

Variable	OR	95% Confidence Interval	P	Z	
Olfactive disorder	0,26	0,15	0,44	<0,001	-5,05
Hypertension	1,61	1,31	1,98	<0,001	4,51
Obesity	1,12	0,91	1,39	0,292	1,05
Renal insufficiency	3,58	2,61	4,89	<0,001	7,96
Autoimmune disease	2,43	1,76	3,34	<0,001	5,44
Sat O2<92%	5,72	4,71	6,95	<0,001	17,57
Increase CRP	1,86	1,20	2,89	0,006	2,77
Age>70 years	4.00	3.23	2.89	<0,001	4,94