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New loss of smell and taste: Uncommon symptoms in COVID-19 patients in Nord Franche-Comte cluster, France

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ABSTRACT

Background: New loss of smell or taste was not included among the common symptoms of COVID-19 until March 2020 when the pandemic started in Western countries. We aim to describe the prevalence and features of anosmia and dysgeusia in COVID-19 patients.
Methods: We retrospectively investigated the clinical features of confirmed cases of COVID-19 in *Nord Franche-Comté* Hospital, Trevenans, France, between March, 1st and March, 14th 2020. We used SARS-CoV-2 real-time RT-PCR in respiratory samples to confirm the cases.
Results: Of the 70 patients enrolled, the mean age was 57.0 years, and 29 patients (41%) were men. Median Charlson comorbidity index was 1.70 (±2.5). Twenty-seven (39%) patients had pneumonia. Fatigue (93% [65]), cough (80%[55]), and fever (77%[54]) were the three main symptoms. Neurologic symptoms were present in more than half of the patients: anosmia (53%[37]) and dysgeusia (48%[34]). The mean duration of anosmia was 7.4 (±5, [1–21]) days, and 51% (36/70) of patients recovered before 28 days of evolution. Only one patient with anosmia had not recovered at the end of the follow-up. Patients with anosmia had pneumonia less often (10/37 vs 17/33, p = 0.036), were hospitalized less often (13/37 vs 20/33, p = 0.033), and needed oxygen therapy less often (6/37 vs 17/33, p = 0.002) than patients without anosmia. There were no statistically significant differences for viral load between patients with anosmia and patients without anosmia (5.5 [2.0–8.6] vs 5.3 [2.1–8.5] log copies/mL respectively, p = 0.670). The fatality of COVID-19 in our study was 6%, with four deaths.
Conclusions: Anosmia and dysgeusia are present in half of COVID-19 patients. The mean duration of anosmia was 7 days, and the outcome seems favorable in less than 28 days.

Introduction

An outbreak of pneumonia began in December 2019 in Wuhan (China) (Zhu et al., 2020). A novel coronavirus was identified as the causal agent (Lu et al., 2020) and was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On the 11th of March 2020, the WHO General Director announced that coronavirus disease 2019 (COVID-19) was the first pandemic caused by a coronavirus (Anon, 2020a).

The clinical description from the COVID-19 outbreak in China reveals that most patients (81%) had minor symptoms, an influenza-like illness (ILI), or mild pneumonia, and 19% had a severe or critical pneumonia (Wu and McGoogan, 2020). Clinical descriptions show that fever, cough, fatigue, and myalgia are usually the main symptoms; the expression of the COVID-19 ILI seems non-specific, no specific symptoms can direct to suspect a case without notion of exposition (Wang et al., 2020a; Huang et al., 2020; Wang et al., 2020b; Wu et al., 2020; Guan et al., 2020; Chen et al., 2020).

A major French cluster of COVID-19 began on March 1st 2020 in Mulhouse city (less than 30 miles from our hospital). After clinical examination of the first patients, we noticed that many cases described a new loss of smell or taste. Information about these two neurologic symptoms with SARS-CoV-2 infection is scarce.

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The concept of anosmia after a viral infection is known as post-infectious/post-viral olfactory loss (POL). Different kinds of viruses can induce a POL, including coronaviruses such as HCoV-229E (Suzuki et al., 2007).

In this study, we aim to describe the prevalence and features of anosmia in COVID-19 patients.

Methods

Less than 30 miles from our hospital (*Nord Franche-Comté* (NFC) Hospital) in Trevenans, a major French cluster of COVID-19 began on March 1st, 2020, in Mulhouse city. We conducted a retrospective observational study between March, 1st and March, 14th 2020,

Table 1
Comparison of the comorbidities, symptoms, and outcome of COVID-19 patients with anosmia and patients without anosmia in *Nord Franche-Comte* Hospital, 2020.

Characteristics			All patients (n = 70)	Patients with anosmia (n = 37)	Patients without anosmia (n = 33)	p-value
Medical history						
Age (Y): mean (SD)			57 (±19)	50 (±16)	64 (±20)	0.001
Sex		Female	41 (59%)	25	16	0.106
		Male	29 (41%)	12	17	0.106
Health care worker			22 (31%)	16	6	0.024
Current smoking			10 (14%)	4	6	0.499
Comorbidities	≥1 comorbidity		36 (52%)	13	23	0.004
	HTA		16 (23%)	5	11	0.016
	Cardiovascular disease[a]		15 (21%)	5	10	0.087
	Diabetes		10 (14%)	2	8	0.038
	Asthma		7 (10%)	6	1	0.009
	COPD[b]		4 (6%)	0	4	0.009
	Malignancy		3 (4%)	1	2	0.599
	Immunosupression[c]		3 (4%)	1	2	0.599
Charlson comorbidity index: mean (SD)			1.70 (±2.5)	0.70 (±1.5)	2.8 (±2.9)	<0.001
Neurologic symptoms (anosmia/dysgeusia)						
Anosmia			37 (53%)	NA	NA	NA
Dysgeusia			34 (48%)	31	3	<0.001
General symptoms						
Number of symptoms (ORL, other): mean (SD)			9.2 (±3.3)	10.7 (±2,4)	7.5 (±3.2)	<0.001
Fever measured >38 °C			54 (77%)	28	26	0.757
Feeling of fever			13 (19%)	8	5	0.487
Highest temperature (T°C): mean (SD)			38.7 (±0.9)	38.5 (±0,8)	39 (±1)	0.042
Fatigue			65 (93%)	34	31	1
Respiratory symptoms						
Cough			56 (80%)	30	26	0.811
Sputum production			20 (29%)	12	8	0.449
Hemoptysis			6 (9%)	3	3	1
Dyspnea			24 (34%)	11	13	0.395
Rhinolaryngological symptoms						
Rhinorrhea			34 (48%)	21	13	0.147
Nasal obstruction			13 (18%)	8	5	0.463
Sore throat			14 (20%)	10	4	0.144
Epistaxis			3 (4%)	3	0	0.242
Tinnitus			7 (10%)	5	2	0.434
Hearing loss			4 (6%)	3	1	0.616
Pain Symptoms						
Myalgia			41 (59%)	26	15	0.035
Arthralgia			38 (54%)	24	14	0.060
Headache	All headaches		51 (73%)	30	21	0.116
	Frontal headache		18 (39%)	14	4	0.027
	Diffuse headache		20 (%)	10	10	1
	Other headache[d]		13 (1%)	6	7	0.760
Ocular symptoms						
Conjunctival hyperemia			3 (4%)	1	2	0.599
Tearing			4 (6%)	2	2	1
Dry eyes			3 (4%)	2	1	1
Blurred vision			3 (4%)	3	0	0.242
Sneezing			13 (18)	7	6	0.937
Gastro-intestinal symptoms						
Nausea			22 (31%)	12	10	1
Vomiting			2 (3%)	0	2	0.219
Diarrhea			28 (40%)	17	11	0.282
Abdominal pain			14 (20%)	10	4	0.144
Physical examination						
Respiratory rate >22/min			15 (21%)	5	10	0.087
Sat 0_2 at admission (%)			93 (±3.4)	95 (±3.7)	92 (±3.1)	0.068

Table 1 (*Continued*)

Characteristics	All patients (n = 70)	Patients with anosmia (n = 37)	Patients without anosmia (n = 33)	p-value
Auscultation with crackling sounds	27 (39%)	10	17	0.036
Viral load				
Viral load in respiratory samples: mean (range)	5.4 [2.1–8.6]	5.5 [2.0–8.6]	5.3 [2.1–8.5]	0.670
Outcome				
Hospitalization	33 (47%)	13	20	0.033
Hospitalization in intensive care unit	7 (10%)	4	3	1
Oxygen therapy	23 (33%)	6	17	0.002
Death	4 (6%)	2	2	1

[a] Defined by: cardiac failure, cardiac arrhythmia, coronary heart disease, stroke, peripheral arterial obstructive disease, and thromboembolic disease.
[b] Chronic obstructive pulmonary disease.
[c] Defined by: transplantation, cirrhosis, long-term steroids therapy, and immunomodulators treatments.
[d] Twelve patients had retro-orbital headache, and one patient had temporal headache.

wherein we enrolled all adult patients (≥18 years) with confirmed COVID-19 who were examined at the infectious diseases consultation or hospitalized in the hospital. Pregnant women, children (<18 years), and patients with dementia (who cannot report functional symptoms) were excluded. We ended the follow-up of the study on March, 24th 2020.

Diagnosis was confirmed by real-time RT-PCR on respiratory samples, mainly nasopharyngeal swabs, sputum, bronchial aspirates, or bronchoalveolar lavage fluids. Briefly, viral RNA was extracted using the NucleoSpin® RNA Virus kit (Macherey-Nagel) according to the manufacturer's instructions and amplified by RT-PCR protocols developed by the Charité (E gene) (Corman et al., 2020) and the Institut Pasteur (RdRp gene) (Bernard Stoecklin et al., 2020) on LightCycler 480 (Roche). Quantified positive controls were kindly provided by the French National Reference Center for Respiratory Viruses, Institut Pasteur, Paris.

Data required for the study were collected from the medical files of patients: age, sex, comorbidities (Charlson score, arterial hypertension, diabetes, cardio-vascular disease–defined by cardiac failure, cardiac arrhythmia, coronary heart disease, stroke, peripheral arterial obstructive disease, and thromboembolic disease–, chronic obstructive pulmonary disease, asthma, malignancy, immunosuppression–defined by transplantation, cirrhosis, long-term steroids, and immunomodulators treatments–), current smoking, and whether or not they were a health care worker. We noted the presence or not of anosmia and/or dysgeusia and the features of anosmia (date of apparition since the onset symptoms, duration of anosmia). Respondents rated smell and taste as "Good" or "Present" (considered as patients without anosmia/dysgeusia) or "Poor" or "Absent" (considered as patients with anosmia/dysgeusia). We checked whether these symptoms existed before infection. Patients were illegible to differentiate dysgeusia with loss of appetite. We also checked that the patients have no co-medications that could cause an alteration of smell or taste. Other signs recorded included fever >38 °C, feeling of fever, highest temperature, fatigue, myalgia, arthralgia, sore throat, headache and its localization (diffuse, frontal, other localization), rhinorrhea, nasal obstruction, epistaxis, dysgeusia, tinnitus and hearing loss, conjunctival hyperemia, tearing, dry eyes, blurred vision, sneezing, cough, sputum production, hemoptysis, dyspnea, respiratory rate >22, sat 0_2 at admission, crackling sounds during auscultation, nausea, vomiting, diarrhea, and abdominal pain. We also recorded the viral load in respiratory samples and the outcome: hospitalization or not, necessity of oxygen therapy, hospitalized in intensive care unit, and death.

A home follow-up is recommended in our national guidelines for patients who were not hospitalized, until they are asymptomatic for more than 48 h (DICOM, 2020). We collected the data from the first contact with the patient at the hospital and during the follow-up. We followed up prospectively each patient until they were asymptomatic. Practically, patients who were not hospitalized were called 7 days (±7 days) after the first symptoms and every week until their recoveries.

In this work, we aim to describe the prevalence and features of anosmia in COVID-19 patients. We divided patients into two groups, patients with anosmia and patients without anosmia, in order to compare the characteristics (comorbidities, clinical features, and outcome) of patients with anosmia *versus* (vs) patients without anosmia.

For the statistical analysis, usual descriptive statistics were used. All variables were assessed using a univariate analysis. Continuous variables were expressed as mean and standard deviation (SD) with ANOVA test. Categorical variables were expressed as numbers, percentages, or mean and compared by $\chi 2$ test or Fisher's exact test between the two groups (patients with anosmia and patients without anosmia). A p-value < 0.05 was considered significant. We used SPSS v24.0 software (IBM, Armonk, NY, USA).

Results

Features of the population and neurologic symptoms

70 patients were included in this study. The mean age was 57.0 (±19) years old, and 29 (41%) were men. The median Charlson comorbidity index was 1.70 (±2.5). Seven symptoms were present in more than half of the patients: fatigue (93%, n = 65), cough (80%, n = 55), fever (77%, n = 54), headache (73%, n = 51), myalgia (59%, n = 41), arthralgia (54%, n = 38), and anosmia (53%, n = 37) (Table 1). Twenty-seven (39%) patients had crackling sounds during auscultation, with a diagnostic of pneumonia. Tinnitus seemed uncommon (10%, n = 7), and hearing loss was scarce (6%, n = 4). The most common neurologic symptom was anosmia (53%, n = 37), followed by dysgeusia (48%, n = 34). The mean duration of anosmia was 7.4 (±5, [1–21]) days. Forty percent (15/37) of all patients had a duration ≥7 days, and 16% (6/37) of all patients had a duration ≥14 days. One patient (1/37) had not recovered at the end of the follow-up (after 28 days). Anosmia began after 4.7 (±1.5, [1–7]) days of symptom evolution. In 31 cases (84%), COVID-19 patients had both anosmia and dysgeusia, and in 21 cases (57%), patients had both anosmia and rhinorrhea; however, patients with anosmia presented a nasal obstruction in only 8 cases (22%).

Comparison between patients with anosmia and patients without anosmia

Patients with anosmia had a lower Charlson comorbidity index than patients without anosmia (0.70 ± 1.5 vs 2.8 ± 2.9, p < 0.001). In the same way, the frequency of HTA, diabetes, and

cardiovascular and pulmonary diseases (except for asthma) was higher in the group of patients without anosmia than in the group of patients with anosmia. Patients with anosmia had asthma more often than patients without anosmia (6/37 vs 1/33, p = 0.009).

Patients with anosmia reported a higher number of symptoms than patients without anosmia (10.7 ± 2.4 vs 7.5 ± 3.2; p < 0.001); they also reported more myalgia (26/37 vs 15/33, p = 0.035) and frontal headache (14/37 vs 4/33, p = 0.027) than patients without anosmia. No significant differences were found between the two groups with regard to other functional symptoms. With regard to physical symptoms, patients with anosmia had pneumonia less often (10/37 vs 17/33, p = 0.036), and the highest measure of body temperature was 0.5 °C lower than patients without anosmia.

Concerning the viral load in respiratory samples, there were no statistically significant differences between patients with anosmia and patients without anosmia (5.5 [2.0–8.6] vs 5.3 [2.1–8.5] log copies/mL respectively, p = 0.670).

With regard to outcome, patients with anosmia were hospitalized less often (13/37 vs 20/33, p = 0.033), and when they were hospitalized, they needed oxygen therapy less often (6/37 vs 17/33, p = 0.002) than patients without anosmia.

Discussion

Our population has a mean age of 57.0 (±19) years, and 59% were women. HTA, diabetes, and cardiovascular and pulmonary diseases had a prevalence ≥10%, as in other studies. The main symptoms of our population were the same as the symptoms described in other studies, except for anosmia and dysgeusia which had never been described in COVID-19 patients from Western countries, to our knowledge (Wang et al., 2020a; Huang et al., 2020; Wang et al., 2020b; Wu et al., 2020; Guan et al., 2020; Chen et al., 2020). Only recently, a study published on April 6 conducted by Lechien et al. reported that 357 patients presented with olfactory dysfunction related to COVID-19 (Lechien et al., 2020). The lack of description of neurologic symptoms in COVID-19, especially in Asia, is probably a consequence of the potential gravity of the disease. The description of anosmia and dysgeusia may seem accessory, especially when clinicians deal with critically ill patients (Yang et al., 2020). Furthermore, details of symptoms are difficult to obtain when patients are critical. Other assumptions to explain these differences between Asia and Europe are the theoretical possibility of a mutation of the SARS-CoV-2 viral genome, and genetic variability between ethnic groups which can explain a polymorphic clinical expression.

With regard to the population, patients with anosmia were younger than patients without anosmia; patients with anosmia had a mean age of 50 years old and were women in 68% of cases. It is interesting to note that in the literature, the same age is described for patients with POL, with a proportion of 70% of women (Harris et al., 2006; Lee et al., 2014). Currently, smoking was not associated with anosmia. In the study by Lechien et al., patients with anosmia had a mean age of 37 [±11.4] years, without cardiovascular comorbidities. However, their population profile were outpatients.

Asthma is significantly associated with anosmia in our study (six out of seven patients with asthma had anosmia), and Lechien et al. also found an association between anosmia and asthma. From the literature, we know that persistent asthma has a cumulative impact on the loss of smell in patients with nasal polyposis (Alobid et al., 2011), and asthma was recently identified as a driving factor for olfactory loss in patients with chronic rhinosinusitis (Schlosser et al., 2020); however, to our knowledge, asthma is not a risk factor of POL. In chronic rhinosinusitis, hyposmia is more related to mucosal inflammation than to nasal obstruction (Gaines, 2010). It is possible that some of our asthma patients had a predisposition for mucosal inflammation due to an allergic rhinosinusitis associated with asthma (we did not collect the medical history of chronic rhinosinusitis).

Pathogenesis of anosmia related to COVID-19 is unknown. In our study, 31 cases (84%) had both anosmia and dysgeusia; however, only 8 cases (22%) with anosmia presented a nasal obstruction. Furthermore, there were no statistically significant differences for nasal obstruction between patients with anosmia and patients without anosmia. This led us to suspect another pathogenesis for anosmia than a nasal congestion with nasal obstruction. In addition, anosmia during a viral rhinitis with nasal obstruction is usually resolved in less than 3 days (Akerlund et al., 1995), while in our study, the mean duration of anosmia was more than 7 days, and half of the patients had anosmia for more than 7 days. For example, in patients with POL, the main suspected mechanism is damage of the olfactory epithelium; we know that MRI of the olfactory bulb showed a reduction of its volume (Rombaux et al., 2006), and biopsy of the olfactory cleft revealed a diminution of the olfactory receptors (Yamagishi et al., 1994). However, central damage during viral infection is also suspected (Kim et al., 2012). Different kind of viruses can induce a POL, including coronaviruses (Chen et al., 2020). However, there is no description of POL induced by one of the three main highly pathogenic coronaviruses for human beings. Our patients with anosmia have a strong association with dysgeusia; dysgeusia is also described with patients with POL (Rawal et al., 2016). Anosmia is significatively associated with frontal headache. The frontal localization of headache could be due to an acute rhinosinusitis with a mucosal inflammation due to SARS-CoV-2. As discussed above, we assume that mucosal inflammation can participate in the pathogenesis of anosmia. However, in anosmia related to COVID-19, a neurotropism of SARS-CoV-2 should be discussed—the assumptions include an invasion of the olfactory receptors or damage of the first cranial nerves in the nasal cavity cell membrane and/or central lesion, as described in POL with other viruses. Furthermore, there is increasing evidence that coronaviruses are not always confined to the respiratory tract but also invade the central nervous system inducing neurological diseases (Anon, 2020b). In addition to smell and taste disorders, patients with COVID-19 may present rhinolaryngological symptoms such as tinnitus and hearing loss. In a recent publication, Kilic et al. concluded that sudden sensorineural hearing loss (SSNHL) may be one of the symptoms of COVID-19 (Kilic et al., 2020) and can also be considered to be a neurologic symptom. Three mechanisms have been implicated in the occurrence of SSNHL associated with viral infections: neuritis caused by viral involvement in the cochlear nerves, cochleitis due to viral involvement in the cochlea and perilymphatic tissues, and the stress response resulting from the cross-reaction of the inner-ear antigens to viral infections (Kilic et al., 2020).

In contrast with functional symptoms, physical symptoms such as pulmonary parenchyma damage and high fever are observed less often in patients with anosmia than patients without anosmia. It seems that patients with anosmia have more painful functional symptoms but less frequently present with pneumonia due to SARS-CoV-2. They are also hospitalized less frequently, and they need oxygen therapy less frequently. Our hypothesis is that anosmia affects younger patients with fewer comorbidities, and thus is accompanied by low risk of severe pulmonary damage.

Patients with anosmia do not have a higher viral load than patients without anosmia. The intensity of viral load in respiratory samples does not explain the presence or absence of anosmia.

Concerning the evolution, only one patient did not recover at the end of the follow-up of the study (after a follow-up of 28 days); eighty-one percent of our patients recovered before 14 days of evolution. In medical literature, the evolution of POL can be long: a

study with 63 patients who had a POL showed that after one year, 80% of patients reported subjective recovery (Lee et al., 2014). In comparison, the evolution of acute anosmia linked to COVID-19 seems often favorable in few days.

A better knowledge of the symptoms of COVID-19 is essential for several reasons. Firstly, to help with detection of a COVID-19 case, anosmia and dysgeusia are uncommon in influenza infection without nasal obstruction (Souty et al., 2019). With a non-specific ILI, the presence of anosmia/dysgeusia can lead to suspect a case of COVID-19, especially when we do not have the notion of exposition in the beginning of an outbreak. On the other hand, to adapt prevention, during an outbreak of SARS-CoV2, consultation for acute anosmia and/or dysgeusia should lead to suspect a case of COVID-19, with the necessary hygiene measures to protect doctors and other patients being implemented. In another recently published study (Zayet et al., 2020) that included 217 outpatients consulting for a suspicion of COVID-19, we concluded that the specificity of anosmia and dysgeusia was respectively of 85% and 84%. The specificity of the combination of anosmia and dysgeusia reached 91% for a positive PCR result (Zayet et al., 2020). The combination of these 2 symptoms had a positive predictive value of 83% for a positive SARS-CoV-2 RT-PCR result (Zayet et al., 2020).

Finally, to adapt treatment, avoid nose cleaning with physiologic serum and contraindicate use of systemic or local corticosteroids. Indeed, during the outbreak of COVID-19, some patients complained of rhinorrhea associated with anosmia and may have used physiologic serum to clean their noses. The existence of a theoretical risk of increased viral dissemination may lead doctors to instruct patients to avoid it, and, in addition, this prescription is probably useless because there is usually no associated nasal obstruction. The lack of data regarding intranasal corticosteroids in COVID-19 and the potential risk of using systemic corticosteroids especially in the first stage of this infection may encourage clinicians to contraindicate corticosteroids in this situation.

One of the limitations of our study is the limited number of patients; a bigger study to confirm and support our results would be of benefit. Another limitation is the recruitment with a bias of selection of health workers. Our politic of detection of possible cases of COVID-19 is larger for health workers with possibly less symptomatic form; this might explain the fact that we have more health workers in the group of patients with anosmia. However, this is interesting and reveals that probably most of the cases of anosmia may be seen by general practitioners.

Conclusion

Anosmia can be considered to be an unknown neurologic symptom in COVID-19. More than half of patients with COVID-19 have anosmia. Eighty-four percent of patients presented both smell and taste disorders. The evolution seems favorable in less than 28 days in COVID-19 patients with anosmia.

Summary of the article's main point

We included 70 patients infected with SARS-CoV-2 in this study. Thirty-seven (53%) patients had anosmia, which was associated with dysgeusia in 81% of cases. The mean duration of anosmia was 7 days with 51% (36/70) recovery before 28 days of evolution. Only one patient with anosmia had not recovered at follow-up.

Conflict of interest

All authors declare no competing interests. We thank all the patients involved in the study.

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None declared.

Ethics approval and consent to participate

Due to the retrospective nature of the study, the Ethics & Scientific Committee of Nord Franche-Comté Hospital (Unité de recherche clinique de l'hopital Nord Franch-comté: Clinical Research Unit) determined that patient consent was required. Informed consent about study participation was officially requested verbally and noted in writing in the patient's medical record, according to national regulations for retrospective study. All patients' data were anonymized prior to the analysis.

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