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ORIGINAL CONTRIBUTION

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Self-reported olfactory and gustatory dysfunction in patients with COVID-19 infection*

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Abstract

Objective: To investigate the incidence, comorbidity and recovery period of smell and taste loss in patients with COVID-19 infection, who were treated as outpatient or admitted to the hospital.

Methods: 103 patients with COVID-19 infection were recruited from a COVID-19 Test Centre (CTC) and hospital wards. Subjects filled in an online self-report survey retrospectively at least six months after recruitment. The following epidemiological and clinical outcomes have been studied: age, gender, comorbidities, general and otolaryngological symptoms and recovery of the olfactory or gustatory loss.

Results: All patients suffered from mild to severe respiratory disease. A high frequency of smell and taste dysfunctions was reported (71.2% and 78.9% respectively). 33% of the patients reported anosmia and 33% reported ageusia. The most frequent symptoms were fever, loss of smell and taste, dyspnoea and headache. The most common comorbidities were hypertension, obesity and diabetes. Males suffered 2.6 times more often from olfactory dysfunction than females. No statistical difference with regard to recovery time were found between man and women. There was a significant difference in the sense of taste scores before COVID-19 infection and during COVID-19 infection. Smell and taste dysfunction was related to clinical course of the infection. There was no difference in recovery of smell and taste recovery between CTC, ward and ICU patients. 87.2% of the patients reported to have recovered from their smell and taste dysfunctions after 4 months. Parosmia after recovery of loss of smell has been reported by 13% of the patients.

Conclusion: After 4 months, 87% of the patients with COVID-19 infection had recovered from their smell and taste loss. The smell dysfunction was related to the clinical course of the disease but it seems that there is no difference in recovery time of smell dysfunction between patients with severe and critical course disease.

Key words: coronavirus, COVID-19, anosmia, smell, hyposmia, dysgeusia, taste, gustatory, olfactory, infection

Introduction

Since spring of 2020, coronavirus SARS-CoV-2 is spreading globally causing a severe acute respiratory syndrome, the COVID-19 infection. It emerged from China and quickly spread to the entire world. More than 55 million people have been infected since the beginning and one and a half million died from the disease. Similarly to infections causes by other kinds of corona viruses, the most common initial symptoms of the COVID-19 infection are cough, fever, fatigue, headache, myalgia, and diarrhoea. Severe illness usually begins approximately 1 week after the onset of symptoms. The great majority of patients infected with SARS-CoV-2 have mild disease and can threated at home. Dyspnea is the most common symptom of severe disease and is often accompanied by hypoxemia. Progressive respiratory failure develops in many patients with severe COVID-19 soon after the onset of dyspnea and hypoxemia. Admission is necessary at this

stage of disease. Patients with severe infection can also develop neurological manifestations such as acute cerebrovascular diseases, skeletal muscle injury and impaired consciousness. A life-threatening condition requiring mechanical ventilation and intensive care support.

The function of smell has an important role in detecting warnings of dangerous hazards in daily life but may also encounter some foot related and social emotional problems. The olfactory function can be diminished in patients with COVID-19 infection and may affect the quality of life of the patients olfactory and gustatory dysfunction have been reported alone [1], or in combination with other symptoms and may appear before other complaints become apparent. Sudden onset of smell and taste loss as a symptom alone has been used for awareness and as a screening tool for this disease.

Smell and taste dysfunction is a common symptom of all kind of viral infections like rhinovirus, (para) influenza virus, Epstein–Barr virus, and some coronaviruses leading to a common cold; due to inflammation of the nasal mucosa there will be swelling and rhinorrhoea, which blocks the passage to the olfactory epithelium in the nose [4]. In contrast, COVID-19 can be presented with smell and taste dysfunction without nasal congestion or any other complains. It is pointed out that mechanisms of COVID-19 related dysfunction of smell and taste compared with other viral infections can be a result of interference of other parts of the central nervous system than the olfactory bulb alone [2]. Prevalence rates of olfactory dysfunction are reported by several studies to range between 47% and 67% [1].

The rapid recovery observed in COVID-19 differs from other post-viral olfactory dysfunction, for which over 80% of the patients reported recovery after one year and longer, suggesting a slow regeneration of the olfactory epithelium and olfactory bulb.

One of the most important questions is the recovery of smell and taste dysfunction. It has been pointed out that most patients with COVID-19 related olfactory loss were treated as out-patient ambulatory and not requiring hospitalization [3], but not much is known about the recovery of smell loss between these groups. The aim of the study was to evaluate the demographic and clinical characteristics and time of recovery of smell and taste dysfunction of patients suffering from COVID-19 infection, who were treated as out-patient or admitted into our hospital.

Materials and methods

The current study was approved by the Central Committee on Research Involving Human Subjects (NL20.076). Patients were invited to participate and the informed consent was obtained.

Subjects and settings

Patients who were suspected by general practitioners to be infected were sent to a COVID-19 test clinic (CTC) and were asked for symptoms including smell and taste loss. This was done by a separate questionnaire used by general practitioners. All the patients of the CTC who reported to have smell and taste dysfunction, as well as the patients with COVID-19 infection who had been hospitalized in the Reinier de Graaf Gasthuis were sent an online self-report survey that included questions about their smell and taste prior, during and after recovery from their COVID-19 infection. Eligible patients had to meet the following inclusion criteria: ≥ 18 years old, confirmed COVID-19 infection and informed consent obtained.

126 patients filled in the survey; 23 had to be excluded: 1 patient was younger than 18, 20 patients were COVID-19 negative, 2 patients didn't fill in the survey correctly. A total of 103 patients were included in the analysis (CTC n= 36, hospital n= 67).

Table 1. Baseline patient characteristics.

Variables	N	%
Age (years, mean)	54.2 ± 14.4	
Sex		
Female	43	41.7
Male	60	58.3
Smokers	6	5.8
Non smokers	97	94.2
Most frequent comorbidities		
High blood pressure	23	22.3
Obesity	14	13.6
Diabetes	13	12.6
Medical course		
CTC	36	35.0
Admitted on ward	50	48.5
Admitted on ICU	17	16.5

Data collection and statistical analyses

The online survey was created with Castor EDC electronic data capture-system (Hoboken, NJ, USA).

The self-reported scores of smell and taste senses were noted using a digital Visual Analogue Scale. By using a digital caliper, patients scored their sense of smell and taste from 0 till 100 (0: no sense of smell/taste at all, 100 normal smell/taste).

Patients were asked to have any of the following comorbidities: diabetes mellitus, high blood pressure, obesity, cardiac or pulmonary diseases, neurological diseases problem (e.g., Parkinson, Alzheimer, dementia), oncological diseases, chronic rhino-sinusitis or allergy, severe head trauma and thyroid disease. Besides loss of smell and taste senses, patients were asked for other symptoms like fever, dry cough, productive cough, dyspnea, rhinorrhea, dysphagia, gastro-intestinal illness, myalgia, headache or other symptoms (IBM SPSS statistical software version

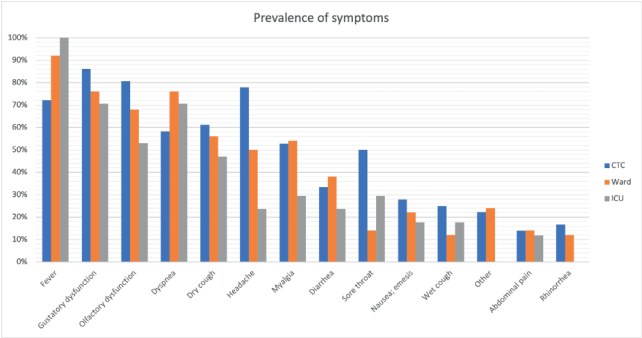

Figure 1. Other symptoms than smell and taste disorders at time of COVID-19 infection.

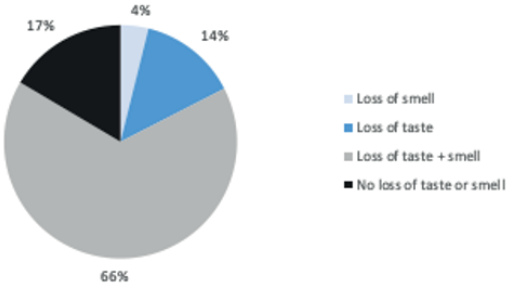

Figure 2. Loss of smell and taste.

25.0 (IBM, Armonk, NY, USA) was used to perform the statistical analyses. Variables were compared using t-tests, crosstabs, chi-square (χ^2) test, ANOVA with post-hoc analysis, and correlation analysis. The level of statistical significance was set at $p < 0.05$, with 95% confidence intervals (CIs).

Results

Demographic and clinical data of the patients are summarised in Table 1.

None of the patients reported smell or taste disorders as the only complain; in all cases there was a combination with another symptom. The most common were fever, dyspnea and headache. The symptoms that were reported by the patients are indicated in Figure 1.

Out of the 103 included patients, 50 (49%) had to be admitted to the COVID-19 ward of the hospital, 17 (17%) were treated at the Intensive Care Unit, and the rest (34%) were sent home to recover after testing.

A total of 72 patients suffered from an olfactory dysfunction and 82 patients of dysfunction of taste. The characteristics are noted in Table 2 and Figure 2.

Based on VAS scores, patients reported a decrease of their sense of smell of 47% during the COVID-19 infection in contrast

Table 2. Smell and taste characteristics.

	N	%
Loss of smell and taste	68	66.0
Loss of smell only	4	3.81
Loss of taste only	14	13.5
No smell or taste complaints	17	16.7
Smell disorder		
Total loss of smell	34	47.2
Decrease sense of smell	16	22.2
Parosmia	14	19.4
Phantosmia	8	11.1
Taste disorder		
Ageusia	34	41.5
Hypogeusia	20	24.4
Parageusia	28	34.1

with their reported sense of smell before their infection. After recovery they reported that the sense of smell was recovered to 81% as it was before the infection. Similar figures were found for taste (respectively 36% and 87%) (Figure 3,4).
Patients who reported to have chronical rhinosinusitis or allergy didn't have a lower pre-infection score than other patients; they reported a normal smell.

54.6% of these patients recovered from their loss of smell and taste between 2 weeks and one month. After 4 months 87.2% had recovered. 8 patients (10.5%) didn't recover from their loss of smell and taste at the end of the study (Table 3). There was no significant difference in recovery time within the three groups of patients (CTC, COVID ward, ICU) p=0.341)

14 patients (13,5%) had parosmia during their infection. Only 8.8 % of them recovered from their reported parosmia.

A paired t-test was conducted to compare sense of smell and sense of taste before and during COVID-19 infection. There was a significant difference in sense of smell score before COVID-19 infection (M= 91.83, SD=11.47) and during COVID-19 infection (M=43.59, SD=36.54); t (102) = 13.051, p <0.0001. There was also a significant difference in the sense of taste scores before COVID-19 infection (M= 94.34, SD=8.22) and during COVID-19 infection (M=40.42, SD=33.87); t (102) =15.494, p <0.0001)
Pearson test showed a significant correlation between the number of symptoms and the change in sense of smell (R=0.293, p=0.003). The number of symptoms was also significantly correlated with change in sense of tase (R=0.348, p< 0.001), There was no correlation found with time of recovery (R=0.251, p= 0.10)

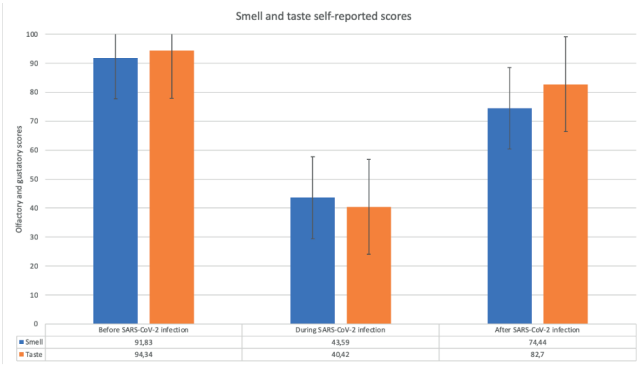

Figure 3. Overall smell and taste self-reported scores after 6 months.

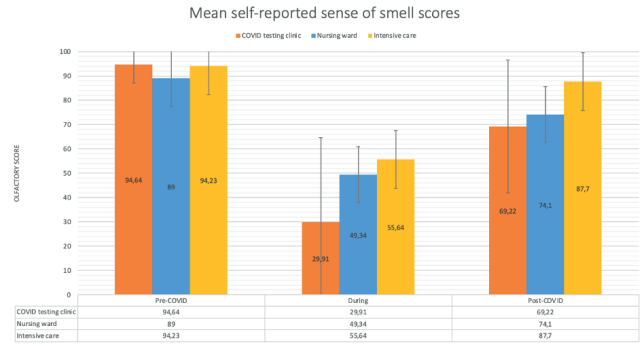

Figure 4. Smell and taste self-reported scores of CTC, nursing ward and ICU.

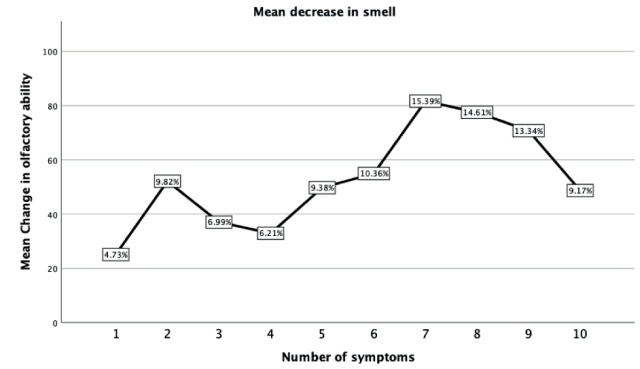

Figure 5. Change in olfactory ability compared to the number of symptoms. In the boxes is noted the percentage of patients suffering from the corresponding number of symptoms.

Using a logistic regression analysis showed that risk factors for change of olfactory sense are dry cough (OR 2.80; 95% CI, 1.17-6.67), dyspnoea (OR 2.47; 95% CI, 1.02-5.10) and dysphagia (OR 5.6; 95% CI, 1.55-20.20).

A Mann-Whitney test indicated that there was no difference in loss of smell and taste between individual symptoms. The number of symptoms was not found to correlate with the number of comorbidities ($p = 0.331$).
None of the comorbidities in contrast to others showed a significant decrease of sense of smell or sense of taste score.
Logistic regression showed that males had a 2.6 times increased chance of developing olfactory dysfunction during COVID-19 than females (OR 2.6; 95% CI: 1.10 – 6.17, $p < 0.001$). There was no difference in gender according to recovery time. Gustatory dysfunction was not significantly correlated to gender nor age.

Table 3. Time of recovery from loss of small and taste.

Days	Cumulative percentage
< 14	11.6
14 - 30	54.6
30 - 60	82.5
60 - 120	87.2
> 120	89.5

Statistical analysis showed that the reported score of smell and taste dysfunction was negatively correlated to severity of the infection. One-way ANOVA analyses pointed out that there was a statistically significant difference between the 3 patient groups ($p = 0.005$). The patients from the CTC and the patients who were admitted at the COVID-19 ward differed significantly ($p = 0.008$), as well as the ICU group ($p = 0.032$). The not hospitalised (CTC) patients who had a milder clinical course of the disease reported a greater olfactory dysfunction. For loss of taste there was no significant effect found.

Discussion

The COVID-19 pandemic has resulted in significant impact for medical health across the world. Although the clinical implications are of the most importance, the economic consequences have also been serious and resulted in substantial damage to the global healthcare system. Most patients with SARS-CoV-2 infection remain asymptomatic, and can be treated with primary care at home whilst in others the infection can cause mild to moderate disease, leading to require admission in hospital and in a lot of cases intensive care support, which has considerable consequences on medical ongoing care of other patients.
One of the much-discussed topics of COVID-19 infection is olfactory loss. The prevalence of anosmia is reported from 5,1% (admitted patients) to more than 70% (admitted and home treated patients)[3]. Beyond anosmia patients also report smell alterations, like parosmia (perceiving flavors in distorted form), or phantosmia (perceiving smells that are not there). Persistent smell and taste loss are associated with a significant reduction in patient's quality of life, including increased depressive symptoms and nutritional issues. The natural course of olfactory dysfunction and how it can be positively influenced by any form of treatment is a still unclear.

We are totally aware of the fact that the results should be interpreted carefully, as the related analyses were based on a limited amount of data and number of patients.
It has been pointed out that the sudden loss of smell and taste can be the only symptom of COVID-19, independent of other symptoms up to 20% [15]. This was not found in our study. One of the reasons could be the lack of knowledge at the start of the study; patients with only smell or taste impairment would not currently be suspected to have COVID-19 infection according to the definitions of disease at that time. Furthermore, the admitted patients were seriously ill due to several symptoms other than smell or taste loss alone.

Fever and headache are one of the major symptoms of COVID -19 infection [4,5]. followed by cough, diarrhea, nausea/vomiting, fatigue and respiratory distress. In our study the number of symptoms was found to be correlate with the mean change of loss of smell and taste as shown in Figure 3; the more symptoms the more dysfunction of smell. The correlation is less above 9 symptoms and more due to the small number of patients. Males seem to have a 2.6 times higher chance of having smell loss than female patients. Age was not a significant factor. Both findings are in contrast with other publications in which female seems to be more affected by smell and taste disorders than males probably as a result of a difference in immunological reaction on the infection [6,10]. Small number of patients can be the explanation of this discrepancy.
Isolated loss of smell is a weaker predictive factor for infection, as this is reported in only 3,81% of the cases. Other studies found corresponding results during COVID-19 infection. There is a positive association between change in olfactory sense and gustatory sense, meaning that most patients experience both. This could be biased by the fact that quantitative based olfactory loss is associated by qualitative bases loss of taste in contrast to the studies who suggested that longstanding impaired olfactory function is associated with decreased gustatory function, which was based on quantitated measurements [13].
Pulmonary disease, diabetes, hypertension and obesity have been identified as risk factors for severe COVID-19. The relative importance of different underlying health conditions is unclear. However, in our study there was no association found between comorbidities and severity of loss of smell and taste, which is backed up by other studies [6].
There is little reported about the relationship of smell and taste dysfunction and the prognosis of COVID-19 infection. The relation of milder or severe course of the disease and the recovery of the dysfunction of smell and taste is not well described as well. The vast majority of patients recovers in a short period of time; persisting smell loss is reported in 6-8 % after 2 months, but may last up to a year [16].
Although our results are geographically limited, 89,5 % of the patients recovered both olfactory and gustatory functions throughout 6 months. Other authors reported similar results. There was no difference in recovery time of smell and taste impairment and severity of disease. Some studies suggest that anosmia is associated in milder disease, probably by the inability of patients with ICU patients to report the presence of olfactory dysfunction during the acute critical illness of their infection. However, our data regarding these patients were collected after discharge of the hospital.
A higher viral load, potentially indicative of more severe disease, does seem to be associated with a shorter duration of anosmia [6]. It suggests that olfactory loss can be seen as a predictor of clinical outcome, as patients with more loss of smell are seen more often in outpatient care. Patients who are hospitalized reported significant less olfactory function. This is also suggested by other authors [7,9].
On the other hand, all patients at the ICU were treated with systematic corticosteroids, which treatment has been associated with better individual components of the clinical outcome; the strongly anti-inflammatory effect of corticosteroid could be the explanation the lack of difference in recovery in smell loss between the serious ill ICU patients and CTC patients who were not treated with corticosteroids.
The pathophysiology of anosmia in SARS-CoV-2 infection is distinct from other coronaviruses due to preferentially targeting olfactory supporting cells. It was demonstrated that the receptors ACE2 and TMPRSS2 were crucial for the entry of COVID-19 in cells, which receptors are expressed in the non-neuronal cells such as basal and sustentacular cells of the main olfactory epithelium [11]. The neural bipolar olfactory cells are presumed not to be damaged by the infection. Therefore, the regenerative ability of the main olfactory epithelium without non neural cell damage is probably the explanation for the good prognosis of the olfactory dysfunction. However, SARS-CoV-2 does not cause sinonasal inflammation in spite of preferred entry factor expression in the nasal respiratory epithelium. This raises doubts about the attention given to ACE2. So other mechanisms may be of importance. An autoimmune response activates lymphocytes causing release of cytokines; this autoimmune reaction against olfactory neurons could differ between patients and could probably explain the variation in recovery of smell and taste loss.
The prognosis for recovery of loss of smell in COVID-19 is excellent by means of progress of quantitative reductions of smell. Parosmia which appears to start after a prolonged period of anosmia, is affecting a growing number of people with COVID-19. This distortion of smell has been neglected in previous reports. A small percentage of patients (13%) in our study experienced parosmia after their recovery. This is in contrast with study results that reports prevalence rates up to 43.1% [15]. Parosmia, which can occur after all kind of viral infections, is typically associated with reduced olfactory sensitivity and not with total

damage. It has been suggested that the presence of parosmia is associated with clinically relevant recovery in olfactory function in patients with post viral smell distortion other than COVID-19 receiving olfactory training [12].

Consideration should be given to the need of further research to investigate recovery, prognosis and medical treatment or olfactory training, giving the growing number of the patients with COVID-19 infection with persistent olfactory dysfunction. Recently studies reported that oral steroids in patients with anosmia after COVID-19 infection could be effective [17,18]. Mometasone furoate nasal spray as a topical corticosteroid in the treatment of post COVID-19 anosmia offers no benefits over the olfactory training [19]. Olfactory training has demonstrated potential benefit for patients with post viral and posttraumatic loss of smell [12,14] and is advised to patient with olfactory dysfunction, but the role of olfactory training on COVID-19 olfactory dysfunction has to be investigated.

Conclusions

The current study has identified olfactory and gustatory dysfunction to be a common symptom of COVID-19 infection. Loss of smell in COVID-19 may be associated with a milder severity of the disease. Acknowledging these symptoms can become a powerful diagnostic tool, leading to early detection of the disease. Almost 90% of patients had spontaneous recovery of the sense of smell and taste, regardless the severity of disease or degree of smell or taste dysfunction. More research concerning the clinical picture of COVID-19 will be essential.

Authorship contribution

DK: study design, study coordination, data collection, text writing; HC: data collection , statistical analysis, contributor of text; HM: statistical analysis , contributor of text.

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Ethics approval and consent to participate

Research involving human participants. The study was was approved by the Central Committee on Research Involving Human Subjects (NL20.076). Patients were invited to participate and the informed consent was obtained.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Conflict of interest

The authors have no conflicts of interest.

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