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Research Article

The SSParoT as a Test in Post-COVID-19 Patients with Parosmia

S.N. Eland[1], B. Bais[2], D.P. Kooper[1*]

[1]Department of Otorhinolaryngology, Reinier de Graaf Gasthuis, Delft, The Netherlands

[2]Department of Medical Research, Reinier de Graaf Gasthuis, Delft, The Netherlands

[*]**Corresponding author:** D.P. Kooper, Department of Otorhinolaryngology, Reinier de Graaf Gasthuis, Delft, The Netherlands

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Abstract

Introduction: Olfactory Dysfunction (OD) is often reported after COVID-19 infection with a prevalence of 47.8 %, which mostly involves temporary anosmia. A subgroup of post-COVID-19 patients with anosmia develop parosmia. Recently, the Sniffin' Sticks Parosmia Test (SSParoT) was described in a healthy population. The SSParoT is the first test to measure qualitative olfactory function. This test uses hedonic estimates of two oppositely odors (pleasant and unpleasant) to assess the Hedonic Range (HR) and Hedonic Direction (HD). These values represent the qualitative olfactory perception. The aim of this study was to characterize post COVID-19 parosmia (PCP) by assessing the HR and HD and comparing them with healthy controls. Furthermore, we described patient characteristics associated with the development of PCP and its severity. **Methods:** The study population consisted of adult patients with parosmia after COVID-19 infection. Patients were retrospectively selected. Exclusion criteria were anosmia, or an olfactory disorder not caused by a COVID-19 infection. The Sniffin' Sticks Parosmia Test (SSParoT) was used to obtain HR and HD. The following data was collected retrospectively: sex, age, T(reshold), D(iscrimination) I(dentification) index , smoking behavior, duration of parosmia in weeks, severity of complaints, COVID-19 symptoms (including hospital admission and admission at the ICU), and comorbidity. With independent sample t-test the difference between groups was studied. Multiple linear regression was used to look for patients characteristics that were associated with more severe parosmia. **Results:** 112 patients were included. 58.9% was female, the median age was 42.5 years. Median values of HR pairs 1 to 4 were 3, 3, 2, and 0, consecutively. For HD pairs 1 to 4 median values were -1, -1.25, 0 and 0.5, consecutively. Mean values for 6 out of 8 pairs were lower than in the general population, reaching statistical significance in 6 values ($p<0.05$). The univariate analyses didn't show any patients characteristics associated with parosmia severity ($p>0.05$). In the multivariate analyses we found that the duration of parosmia and the presence of comorbidity significantly predicted 3 out of the 8 pairs. **Conclusion:** The SSParoT is able to quantify parosmia in post-COVID-19 patients. The SSParoT is therefore suitable for follow up of parosmia in COVID-19 patients.

Keywords: COVID-19; Parosmia; SSParoT, smell, olfactory dysfunction, olfactory distortion

Introduction

Olfactory dysfunction (OD) is a common problem after COVID-19 infection [1,2]. A meta-analysis of almost 30.000 COVID-19 patients found a prevalence of 47.8% [3]. More than 80% of the patients complain about anosmia (absence of smell). The majority of them recovers without any persistent complaints [2,4]. However, a subgroup of patients develop parosmia after the sense of smell has been partially or fully restored [1,2,5,6]. Prevalence of 15 to 20% was reported .[1,6].

Parosmia is an olfactory distortion in which odors are perceived differently. The pathophysiology of an olfactory dysfunction from COVID-19 shows a specific bond from the virus with the ACE2-receptor, using the TMPRSS2-protease receptor. The cell surface protein ACE2 and the protease TMPRSS2 receptors are expressed in sustentacular cells of the olfactory

epithelium. These sustentacular cells of the olfactory epithelium and the pericytes in the bulbus olfactorius become involved in the inflammatory process what leads to a release of mediators causing further inflammation, and loss of smell [7].

Olfactory disorders are divided into two groups: quantitative dysfunction (normosmia , hyposmia and anosmia), and qualitative disorders (parosmia and phantosmia). Parosmia, distortion of smell, has a considerable influence on the quality of life as patients are more likely to have depressive symptoms and may also have reduced appetite [8].

Different studies report different parosmia prevalence rates after a COVID-19 infection. These rates vary between 14% up to 43.1% [5,6]. Parosmia in post-COVID-19 patients is longstanding. After 6 months only 8.5% reported complete resolution of parosmia [5,6].

Olfaction is a measurable sensory modality, which can be assessed by several methods. The Sniffin' Sticks test is the most commonly used in Europe [9]. In this test, patients are offered odor sticks. The test is divided into a threshold determination, a discrimination test and an identification test. The threshold determination indicates the concentration at which the odor is reliably detected and is determined by offering the blindfolded patient odor sticks in decreasing concentration until the odor is no longer smelled. For the discrimination test 16 triplets of sticks are presented, Two sticks of the triplet are impregnated with the same odor and the third stick is impregnated with a different odor. The patient is required to identify which stick of the triplet has a different odor . To establish identification ability of smell, an odor stick is offered to the patient who must make a forced choice from a list of 4 written proposals of odors. Also 16 different sticks are presented. The sum of scores for threshold, discrimination and identification subtests is the TDI ,with a range between 1 and 48 points. [9]. An alternative to the Sniffin' Sticks is the UPSIT (University of Pennsylvania Smell Identification Test). In this test, the discriminatory power of smell is not determined. This test contains several scratch strips that are impregnated with an encapsulated odor that is released after the strip is scratched open. The patient have to identify the released odor.

The Sniffin' Sticks test measures quantitative olfactory dysfunction (normosmia,hyposmia or anosmia) but is less suitable for parosmia. Until recently no sensitive tool was available to measure parosmia. Recently, the Sniffin' Sticks Parosmia Test (SSParoT) was described in a healthy population [10]. In this test eight odors of the 16-item Identification Sniffin' Sticks are used. These are divided into 4 pairs of odors; a pleasant and an unpleasant odor are combined (pair 1: Peppermint and Fish; pair 2: Apple and Garlic; pair 3: Pineapple and Turpentine; pair 4: Banana and Clove). SSParoT uses hedonic estimates of two oppositely odors (pleasant and unpleasant) to assess hedonic range (HR) and hedonic direction (HD), which represent qualitative olfactory perception and is therefore suitable for defining distortion of smell. The HR and HD represent the qualitative olfactory perception. The HR describes the perceptible range and the HD describes the balance or imbalance between the two hedonically oppositely valanced odors [10]. A hedonic value indicates the degree of (un) pleasantness of the smell. It relates to the sensory aspects of smell.

There is little data on quantitative measures of qualitative olfactory dysfunction in a COVID-19 population. A small study investigated a short variant of the SSParoT as a diagnostic test for parosmia in post-viral patients [11]. This study concluded that the short SSParoT was less suitable as a diagnostic test but this study did not seperated post-COVID-19 patients from other post-viral patients.

The aim of this study was to characterize post COVID-19 parosmia (PCP) by assessing HR and HD and comparing them with healthy controls, using the SSParoT. In addition, identified patient characteristics that are associated with parosmia severity were examined.

Methods

Study population

In all patients with an olfactory disorder presenting at the outpatient clinic of the Reinier de Graaf Gasthuis (RdGG) a smell test using Sniffin' Sticks was performed. The SSParoT is integral part of this olfactory test.

The study population consisted of adult patients with parosmia after PCR confirmed COVID-19 infection. Exclusion criteria were anosmia, or an olfactory disorder not caused by a COVID-19 infection.

Data

The following data was obtained retrospectively: sex, age, TDI, smoking behavior, duration of parosmia in weeks, severity of the complaints, COVID-19 symptoms (including hospital admission on the ward or ICU), and comorbidity (none, diabetes mellitus, high blood pressure, obesity, heart and vascular diseases, neurological complains (Parkinson's disease, dementia, Alzheimer's disease), cancer, severe head trauma, thyroid problems, liver diseases, kidney diseases).

The HR was calculated as the difference between the pleasant odor (E1) and the unpleasant odor (E2): HR = E1-E2. The HR can take whole numbers ranging from -8- to +8. The HD is calculated as the average value of the two odors: HD = (E1 + E2)/2. The HD can take whole or half numbers ranging from -4 to +4.

Outcome measures

The primary outcome were HR and HD measured with the SSParoT. Patients scored the smell of odor on a scale from -4 (very unpleasant) to +4 (very pleasant), The score was based on pleasantness and not on the patient's association of the odor. Secondly, we compared these data with the data among healthy controls published by Liu (10).

In addition, we investigated patient characteristics which were associated with more severe parosmia (e.g., age, gender, duration of complaints, comorbidities).

Statistical analysis

Descriptive statistics were used to report baseline characteristics.

Depending on the distribution, the data was presented in means with standard deviations (SD) or medians. If the data was normally distributed, the data was displayed in means and standard deviations. If the data was not normally distributed, the data was displayed in medians and interquartile ranges (IQR). The normality of the data was assessed by histograms, Q-Q plots and with two statistical tests, the Kolmogorov-Smirnov and the Shapiro-Wilk tests.

Statistical significance was tested with a Student's T Test. P-values were reported. Differences between groups were studied using independent sample t-tests. We studied the following groups: male versus female, smokers versus non -smokers and patients with comorbidities versus patients without comorbidities. We tested the differences between each individual HR and HD pair. P-values were reported. Linear regression analyses were used examine patients' characteristics which were associated with more severe parosmia within our study population. For each individual HR and HD pair, we tested for the impact of duration of parosmia, smoking, sex and comorbidities. The coefficient and p-values were reported. A multiple linear regression was used to predict each individual HR and HD pair from the duration of parosmia, smoking, sex and comorbidities.(Table 5)

IBM SPSS 28.0 was used to perform the statistical analyses. The level of statistical significance was set up at $p<0.05$.

Results

Table 1 reports the baseline characteristics of our study population. A slight majority was female. A small group of smoked.

Characteristics	Total 112
Female	66 (58.9%)
Age (years, median) (IQR)	42.5 (27)
Smokers	14 (12.5%)
Comorbidities	21 (18.8%)
Chronic rhinosinusitis or allergy	12
Diabetes Mellitus	1
High Blood Pressure	1
Cardiac or pulmonary diseases	3
Neurological problems	1
Cancer	1
Thyroid disease	3
Parosmia duration (days, median) (IQR)	95 (44)
IQR : Interquartile Range	

Table 1: Baseline patient characteristics.

The first COVID-19 infection was on 1 February 2020 and the last on 30 September 2022. The time between COVID-19 infection and assessment of SSParoT ranged from 2 to 33 months with a median of 11 and an IQR of 7. The HR, HD, age, duration parosmia and the time in months from infection to SSParoT had a non-normal distribution. The TDI had a normal distribution (Table 2).

	TDI	Threshold	Discrimination	Identification
Mean	19.79	1.83	9.31	8.64
SD	6.44	2.09	3.10	3.05
TDI: threshold, discrimination, identification scores; SD: standard deviation				

Table 2: TDI, threshold, discrimination and identification scores.

Results for Sniffin' Sticks Test and the SSParoT

The Sniffin' Sticks Test showed low threshold, discrimination and identification values. Tables 3 and 4 show the median and averages values of the SSParoT.

	HR Pair 1	HR Pair 2	HR Pair 3	HR Pair 4	HD Pair 1	HD Pair 2	HD Pair 3	HD Pair 4
Median	3.00	3.00	2.00	0.00	-1.00	-1.25	0.00	0.50
IQR	3.00	3.00	4.00	3.00	2.40	2.50	2.00	2.00
HD : Hedonic Range, HD: hedonic direction, Pair 1: peppermint and fish, Pair 2: apple an garlic, Pair 3:pineapple **and turpentine, Pair 4: banana and** clove								

Table 3: Medians and IQR's HR and HD.

	Patients	Healthy controls	P-value
HR Pair 1	3.42	5.55	<.001
HR Pair 2	2.53	4.75	<.001
HR Pair 3	2.04	3.65	<.001
HR Pair 4	-0.26	2.95	<.001
HD Pair 1	-1.299	-1.35	0.706
HD Pair 2	-1.219	-0.75	0.002
HD Pair 3	0.040	0.1	0.724
HD Pair 4	0.272	1.7	<.001
HD : Hedonic Range, HD: hedonic direction, Pair 1: peppermint and fish, Pair 2: apple an garlic, Pair 3:pineapple and turpentine, Pair 4: banana and clove			

Table 4: Comparison of our patients' average values with the average norm values of healthy controls.

	HR Pair 1	HR Pair 2	HR Pair 3	HR Pair 4	HD Pair 1	HD Pair 2	HD Pair 3	HD Pair 4
Male versus female	0.767	0.656	0.329	0.929	0.815	0.115	0.203	0.068
Smokers versus non-smokers	0.068	0.677	0.443	0.679	0.871	0.330	0.804	0.186
Comorbidities	0.622	0.202	0.335	0.066	0.328	0.152	0.487	0.425
HD : Hedonic Range, HD: hedonic direction, Pair 1: peppermint and fish, Pair 2: apple an garlic, Pair 3:pineapple and turpentine, Pair 4: banana and clove								

Table 5: The p-values of the differences between the groups.

Comparison with norm values

There were statistically significant differences between the HR of the patients and the control group (Table 4). There were significant differences between the HD of the patients and the control group for HD pair 2 (apple and garlic) and pair 4 (banana and clove).

Associations with parosmia severity

In univariate analysis, we did not find any differences in the HR and HD for each pair between males and females, smokers and non-smokers and in the group with comorbidities versus no-comorbidities.

The variable duration of parosmia significantly predicted HR Pair 2 (β=0.031, p=0.034). The variable comorbidities (having none) significantly predicted HR Pair 4 (β=1.184, p=0.049). The variables duration of parosmia (β=-0.023, p=0.012) and having no comorbidities significantly predicted HD Pair 2 (β=0.891, p=0.025).

We did not find any significant predictable variables for the remaining pairs (HR Pair 1, HR Pair 3, and HD Pair 1, HD Pair 3 and HD Pair 4). (Table 5).

Discussion

A considerable group of post-COVID-19 patients complains of longstanding parosmia. In this study, we calculated HR and HD in post-COVID-19 patients with parosmia complains using the Sniffin' Sticks parosmia test (SSParoT).

Our results differ from the normative values as described by Liu in healthy population [10]. From the 8 pairs in total (HR Pair 1 to 4 and HD Pair 1 to 4) six out of the eight were lower dan the normative values. These lower HR and HD values in patients post-COVID illustrate the long standing parosmia complaints in these patients. It is remarkable that pair 4 (banana and clove) showed a significant difference. Looking at the values it seems that the patients scored banana rather unpleasant than pleasant and clove rather pleasant or neutral. Clove is used in olfactory training , which could be the explanation for this phenomenon. Olfactory training was not corrected in our study

We looked for patient's characteristics which are associated with parosmia severity. For two pairs (HR and HD pair 2) the duration of the parosmia was a determining factor. For the HR, the duration of parosmia has a positive impact, indicating that the longer a patient had parosmia, the higher the chance that the HR value will rise. It could suggest that parosmia will get less severe and hopefully improve. For the HD the duration of parosmia had a negative impact. For HD pair 2 having no comorbidity was also a positive impact factor, indicating less severe parosmia. For HR 4 not having a comorbidity seems to predict a higher HR value, indicating less severe parosmia. We did not find any significant influence on the parosmia severity by patients' characteristics.

We are aware of the limitation of this study as we could not execute all analyses by lack of data retrospectively. Nevertheless the SSParoT seems to be a reliable tool for the assessment of parosmia in post COVID-19 patients and could be used in the follow up of parosmia in these patients population.

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