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STUDY OF OLFACTORY ALTERATIONS AFTER COVID-19 INFECTION AND ITS CLINICAL DEVELOPMENT

***[1]Manar Salloum, [2]Mostafa Ibrahim and [3]Youssef Youssef**

[1]Department of Otorhinolaryngology and Head & Neck Surgery, Tishreen University Hospital, Lattakia, Syria.
[2,3]Department of Otorhinolaryngology and Head & Neck Surgery, Professor, Tishreen University Hospital, Lattakia, Syria.

***Corresponding Author: Manar Salloum**

Department of Otorhinolaryngology and Head & Neck Surgery, Tishreen University Hospital, Lattakia, Syria.

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ABSTRACT

Study Title: Study of olfactory alterations after COVID-19 infection and its clinical development. **Objective:** Evaluating changes in the sense of smell in patients previously infected with Covid-19 with an objective CCCRS test. **Materials & Methods:** The study included 120 patients who visited the Ear, Nose and Throat Clinic at Tishreen University Hospital after a previous infection with Covid-19, and their sense of smell was evaluated after that, during the period between June 2021 and June 2022. After examining the patient, he/she was given a detailed questionnaire about the symptoms of their previous infection with Covid-19 and their medical history. The patient was then subjected to the CCCRS test to evaluate their sense of smell, determine its threshold, and their ability to distinguish different odors. The test should be repeated later after completing a period of six months after active infection with Covid-19 to determine the extent of the clinical development of the sense of smell. **Results:** We did not notice any significant statistical correlation between the overall test result and the variables: age, patient gender, and smoking, while a significant statistical correlation was found between the overall test result and the presence of olfactory symptoms during a previous active infection with Covid-19, expressed in the questionnaire, and the type of this disorder described. There was no statistically significant correlation between the total test result and fever, cough, sore throat, and headache, while there was a significant correlation between the test result and nasal congestion and runny nose. We also noticed that most of the cases had improved results later after several months by repeating the test. **Conclusions:** The possibility of adopting the test to determine the olfactory threshold with butanol as an objective, qualitative and important test to study the olfactory threshold in patients and study its clinical development.

KEYWORDS: Covid-19 - hyposmia - anosmia - CCCRS test.

INTRODUCTION

Smell is considered one of the most important and oldest senses known to humans, which plays a major role in communicating with the environment and identifying potential danger in the surroundings. It also affects nutrition, social and psychological behavior, and memories. Despite this, the field of olfactory research has received less attention than the rest of the other senses. This is often due to the technical challenges in working with olfactory stimuli and the difficulties in measuring brain activity induced by chemical sensory stimuli, but with the coronavirus pandemic sweeping the world and the olfactory disorders it has caused in many patients, it is necessary to give this topic more attention and research.

The incidence of olfactory disorders in the population remains questionable, as researchers found that the incidence rate ranges between 1-3% of the population[1], and in other studies they found a higher incidence rate in the population suffering from nasal sinus complaints, reaching 4.7% for anosmia, 16% for hyposmia, 2.1% for parosmia, and 0.8% for olfactory hallucinations.[2]

Olfactory tests in humans remained poorly researched for a long time due to the difficulty of finding an accurate and selective olfactory stimulant. However, recently, with the development of modern techniques for investigating the olfactory system, this has encouraged increased research in this field, where focus has been placed on three main points: 1- Accurately evaluating olfactory disorder, and thus providing medical advice and the expected prognosis. 2- Evaluating the improvement of the olfactory disorder and its recovery or deterioration for the worse. 3- Evaluating the proposed therapeutic methods.

Olfactory disorders were classified by the World Health Organization in May 2020 as one of the symptoms of Covid-19 syndrome, as it was observed in many studies in different countries that investigated the Covid-19 pandemic, where they were either accompanied by other symptoms and signs or existed in isolation. There was an early onset of olfactory disorder relative to the rest of the symptoms in most cases, with variation from one person to another according to age, gender, clinical condition, accompanying symptoms, medical history, duration, severity, prognosis, and recovery.[3]

Previous studies have shown some types of viruses known to use the olfactory nerves to reach the central nervous system, such as influenza A, parainfluenza, and Japanese encephalitis viruses. Likewise, the SARS coronavirus family, to which the SARS-CoV-2 virus belongs, has shown the ability to travel through the olfactory nerves to the cranium through the olfactory bulb in mouse models, and thus, the SARS-CoV-2 virus has the same characteristics as its ancestors, and this is what we have seen in terms of the occurrence of neurological signs and symptoms.[4][5]

Although the exact mechanism of Covid-19 in olfactory disorders is still under investigation, several hypotheses have been proposed to explain it.

First: Destruction of the supporting cells present in the olfactory epithelium, which have been shown to contain high levels of both proteins (ACE2, TMPRSS2) necessary for the virus to enter the cell, as it was found to be the first site of infection in the olfactory epithelium, as these cells provide structural support to the olfactory nerve cells, supply them with nutrients, and maintain electrolyte balance, and thus disrupting the function of the olfactory epithelium.

Second: The virus destroys the receptors of the olfactory neurons located in the olfactory neuroepithelium, resulting in a decrease in their number and a decrease in olfactory function.

Third: Cytokine storm (excessive and uncontrolled production of cytokines by immune cells) in some patients as a result of the course of the infectious process and its effect on the nervous system, including the sensory organs of smell.

Fourth: The virus harms the olfactory bulb, penetrates the central nervous system through it, and affects the olfactory centers in a few cases.

Accordingly, olfactory changes and their clinical development were studied in patients who suffered from Covid-19 infection.

MATERIALS AND METHODS

Retrospective cohort study.

The data was analyzed using the IBM SPSS STATISTICS 23 statistical program, and the following was adopted.

- Descriptive statistics: Quantitative variables were presented in the form of mean and standard deviation, and qualitative variables were presented in the form of percentages.
- Inferential statistics: Chi-square and Fisher's Exact test were used to study the correlation between qualitative variables.
  The p value < 0.05 was considered statistically significant.

- **OBJECTIVE**

Main Objective: Evaluation of changes in the sense of smell by determining (olfactory threshold - odor differentiation) in patients previously infected with Covid-19 with the objective CCCRC test, and comparison of the results of this test with the questionnaire given to the patients at the same time as the test was performed.

Secondary Objectives: The study of the characteristics of the study group through the following variables: - Age - Gender - Habits and instincts - Symptoms experienced during active infection with Covid-19 - Timing of conducting the test after clinical recovery from Covid-19 - Order of appearance of olfactory symptoms during previous active infection - Evaluation of the development of olfactory changes six months after clinical recovery from Covid-19.

The study included 170 patients who visited the Ear, Nose and Throat Clinic at Tishreen University Hospital after a previous infection with Covid-19, and their sense of smell was evaluated during the period between June 2021 and June 2022.

Inclusion Criteria: Patients previously infected with Covid-19 diagnosed by PCR.

Exclusion Criteria: Children under 12 years (4 patients), pregnant women (1 patient), previous olfactory disorders (2 patients), nasal polyposis (4 patients), chronic sinusitis without polyps (1 patient), previous endoscopic sinus surgery (1 patient), head trauma, radiotherapy for head and neck tumors, neurodegenerative diseases (0 patients), diabetes (8 patients), current use of nasal inhaler medications (cortisone - vasoconstrictors) (12 patients), psychiatric disorders (0 patients), uncooperative patients (8 patients), patients who required admission In the intensive care unit during their active infection (9 patients).

Consequently, 50 patients were excluded and the final sample size was 120 patients.

- **METHODOLOGY**

Organization of patients

First: A comprehensive evaluation of the patient was conducted in terms of the ear, nose, and throat, focusing on examining the nasal cavity accurately with a 0-degree rigid endoscope.
Second: The patient was given a detailed questionnaire about the symptoms of their previous infection with Covid-19 and their medical, surgical, and other medication history, while obtaining their informed consent to enter the research.
Third: The patient was subjected to the CCCRS Test to evaluate their sense of smell and determine its threshold and their ability to distinguish different odors.
Fourth: The results were tabulated and saved.

Olfactory tests used in the study

1- Connecticut Chemosensory Clinical Research Center (CCCRC) test

It is an easy, widespread test approved by the Clinical Research Center for Chemosense in the US state of Connecticut, which based on evaluating smell by determining the olfactory threshold and distinguishing odors using n-butanol at a concentration of 4% diluted with distilled water.[6]

The test is carried out for each patient using n-butanol at the highest concentration of 4% in 60 ml of distilled water, which is bottle (0), and the concentration is diluted in seven steps, where each bottle from 1 to 7 contains a concentration diluted from the previous one by a third (1:3). Hence, the successive concentrations from the highest to the lowest (0.04 -0.01 -0.004 - 0.001- 0.0004- 0.0001-....) are numbered from (0-7) respectively.[7][8]

The patient is asked to close one nostril, two compressible containers are presented below the other nostril, one of which contains butanol, starting with the lower concentration[7], and the other[8] contains only distilled water. The container is placed 2 cm from the nostril and the patient is asked to inhale the odor for 4 seconds with their eyes closed, then the patient is asked which one he/she smelled more intense and the answer is adopted after confirming it 4 times. In the event of an incorrect answer, the patient is moved to a higher concentration and an interval of 30 seconds is left between each concentration.

The final olfactory threshold is determined for each nostril separately by giving points from (0-7) that correspond to the order of the lowest concentration of the bottle that the patient was able to smell. Then, the average value of the points for the two nostrils is calculated to obtain the final value of the point expressing the patient's olfactory threshold value.
Table (1) shows the testing mechanism for each nostril.

Table 1: A table of the patient's answers to the threshold determination test.

Bottle Number	Answer 1	Answer 2	Answer 3	Answer 4
8 (Distilled water bottle)				
7 (Lowest concentration)				
6				
5				
4				
3				
2				
1				
0 (Highest concentration)				

2- Odor Differentiation Test

We conducted an odor differentiation test by giving 10 different odors to patients, placing them in opaque containers that allow the odors to escape from the top when opened, and tested each nostril separately.

The patients were asked to identify the given odors from a list containing 10 correct odors and 10 wrong odors, giving points from 0 to 10 according to the number of correct items answered by the patients, and then the average of the two nostrils was calculated to obtain the final value of the points.

The testing mechanism was based on giving the patient first a list containing the names of the materials used in addition to the names of distracting materials, then starting with the first bottle and having the patient choose the odor he smelled next, then the second bottle, which we started 30 seconds after the first, and so on.

Having finished with the first nostril, we started with the second, but we did not give him/her the bottles in the same order, but rather in a different order so that he did not remember the odors they smelled with the first nostril. Then we calculated the average for both nostrils to get the final point value.

Odors used in the Odor Differentiation Test

The correct odors included in the test: Baby powder, chocolate, coffee, ammonia, menthol, fruit-flavored gum, ketchup, black pepper, soap, orange.

Wrong odors: Chips, leather, sawdust, cinnamon, burnt paper, tobacco, sardines, garlic, rubber, rotten meat.

After analyzing the olfactory threshold test points and the differentiation test points separately, they were converted into composite points through the center's approved point system. Table (2) (3).

Table 2: A table for the composite score of the threshold test and the odor differentiation test.

Olfactory threshold determination test score	Composite result of the olfactory threshold determination test	Odor differentiation test score	Composite result of the odor differentiation test
7	50	8-10	50
6	40	6-7	40
5	30	4-5	30
4	20	3	20
2-3	10	1-2	10
0-1	0	0	0

The final total composite score.

Table 3: A table for the final total composite score for the both tests.

Normal	90-100
Mild hyposmia	70-80
Moderate hyposmia	50-60
Severe hyposmia	20-40
Anosmia	0-10

- **RESULTS AND DISCUSSION**

The study included 120 patients who visited the Ear, Nose and Throat Clinic at Tishreen University Hospital with a history of infection with Covid-19, and their sense of smell was evaluated during the period between June 2021 and June 2022.

The results were as follows, as shown in Table (4).

Table (4): Characteristics and results of the study group according to some variables included in the questionnaire.

		Number of patients	Percentage	
Age	**18-26**	29	24.2%	
	27-35	50	41.7%	
	36-44	11	9.2%	
	45-53	17	14.2%	
	54-62	9	7.5%	
	63-71	4	3.3%	
Gender	**Male**	53	44.2%	
	Female	67	55.8%	
Smoking	**Yes**	66	55%	
	No	54	45%	
Alcohol	**Yes**	23	19.2%	
	No	97	80.8%	
Studied symptoms	**Fever**	106	(88.3%)	
	Cough	67	(55.8%)	
	Nasal congestion	64	(53.3%)	
	Runny nose	58	(48.3%)	
	Sore throat	89	(74.2%)	
	Headache	70	(58.3%)	
	General fatigue	50	(41.7%)	
	Digestive symptoms	10	(8.3%)	
	Thoracic dyspnea	26	(21.7%)	
Olfactory symptoms during the active infection as described in the questionnaire	**Yes**	99(82.5%)	**Hyposmia**	34(34.3%)
			Anosmia	34(34.3%)
			Parosmia	31(31.3%)
	No	21(17.5%)		

Timing of olfactory symptom onset during the active infection in 99 patients	**Beginning of the infection**	27	(27.3%)	
	Mid infection	36	(36.4%)	
	End of the infection	36	(36.4%)	
Timing of the testing in 120 patients	**After 2 weeks**	17	(14.2%)	
	After 3 weeks	19	(15.8%)	
	After 4 weeks	39	(32.5%)	
	After 2 months	33	(27.5%)	
	After 3 months	12	(10%)	

The total number of patients who expressed an olfactory disorder in the questionnaire at the time of the test was about 66 patients, or 55%. The olfactory disorder lasted in 10 patients for less than a week, while in 56 patients it lasted for more than a week.

While the number of patients who expressed in the questionnaire that they continued to have an olfactory disorder until the date of the test was about 54 patients, or 45%.

In a study conducted in the city of Daegu, South Korea in 2020, included 3,191 patients whose clinical data was collected by communicating with them on the phone by doctors, a severe anosmia or ageusia was observed in 15.3% of them in the early stages of infection with Covid-19, and the spread of these symptoms was more significant and clearer in women and young adults (with statistical significance of $p<0.01$ and $p<0.001$, respectively). This study relied on the questionnaire only, without conducting any examination to evaluate smell or taste, while in our study we compared the questionnaire data with the results obtained with the used smell test, and we had superiority for females over males, but without significant statistical significance. Also, the most common age range in our study was adults between 27-35 years.[9]

The distribution of patients in the study group according to the type of olfactory disorder they had, which was detected by the threshold determination and odor differentiation test.

Many studies and literature reviews have found that an olfactory disorder, with or without a gustatory disorder, is one of the most important symptoms of infection with Covid-19, as about a third of those infected with Covid-19 will experience one of these symptoms, which can be considered very indicative of infection with Covid-19, and they should be dealt with accordingly, especially in places where there is no ability to conduct confirmatory diagnostic tests such as PCR, where it was found that a negative PCR swab did not negate infection with Covid-19.[10][11]

The UK Otolaryngology Association suggested that patients who only suffered from an isolated olfactory disorder and did not follow isolation procedures might be The results we obtained are presented in Tables (5) (6) (7).

hidden carriers of the virus and contribute to its general spread in society.

While the American Academy of Otolaryngology and Head & Neck Surgery suggested the possibility of COVID-19 infection in patients who developed sudden olfactory disorder and/or gustatory disorder in the absence of other respiratory symptoms such as pulmonary symptoms, nasal congestion, or rhinorrhea. The Academy suggested that this patient should self-isolate for 14 days to reduce the possibility of transmitting the infection to the surroundings.[12]

We have not previously found an effective and good method for assessing the sense of smell in a relatively accurate manner and identifying its quantitative and qualitative defects in patients. Currently, an effective method has been found using the CCCRC method and n-butanol, and using types of odors that are familiar and common to the patient in order for him/her to distinguish them correctly.

Table 5: A table shows the composite score for the olfactory threshold determination test.

Composite score for the olfactory threshold determination test	Olfactory threshold determination test score	Frequency	Percentage
Valid 10	2-3	3	2.5
20	4	12	10.0
30	5	41	34.2
40	6	38	31.7
50	7	26	21.7
Total	----------	120	100.0

Table 6: A table shows the composite score for the odor differentiation test.

Composite score for the odor differentiation test	Odor differentiation test score	Frequency	Percentage
Valid 10	1-2	5	4.2
20	3	23	19.2
30	4-5	36	30.0
40	6-7	41	34.2
50	8-10	15	12.5
Total	----------	120	100.0

Table 7: A table shows the total composite score for the olfactory test.

	Composite score	Frequency	Percentage
Valid Anosmia	0-10	1	0.8
Severe hyposmia	20-40	9	7.5
Moderate hyposmia	50-60	48	40.0
Mild hyposmia	70-80	33	27.5
Normal	90-100	29	24.2
Total	----------	120	100.0

Upon conducting the test, it was observed that in result there was anosmia in only one patient, at a rate of 0.8%, severe hyposmia in 9 patients, at a rate of 7.5%, moderate hyposmia in 48 patients, at a rate of 40%, mild hyposmia in 33 patients, at a rate of 27.5%, and normal olfaction in 29 patients, at a rate of 24.2%.

The statistical correlation between the total test score and other variables was studied. We note from Table (8) that there is no significant statistical correlation between the total test score and the variables; age, gender of the patient, smoking, alcohol, and the timing of the appearance of the olfactory symptom during the active infection.

While a significant statistical correlation was found between the total test score, the presence of olfactory symptoms during previous active infection with Covid-19, expressed in the questionnaire, and the type of this disorder described.

Table 8: A table shows the statistical correlation between the total test score and some variables.

		Fisher's exact test value	Exact significance (2-sided) (p value)
Total test score	Patient's age	16.497	0.807
Total test score	Patient's gender	1.437	0.938
Total test score	Smoking	4.794	0.278
Total test score	Alcohol	3.459	0.518
Total test score	The presence of olfactory symptoms during the active infection	52.678	0.0001
Total test score	The timing of the appearance of the olfactory symptom during the active infection	6.278	0.632
Total test score	The type of the olfactory disorder described during the active infection	29.852	0.0001

German virologist Hendrik Streeck in Germany reported anosmia and gustatory disorder in more than 65% of 100 people whom he met and were suffering from mild Covid-19 symptoms. In Italy, Massimo Galli, an infectious disease specialist at the University of Milan, noted that anosmia and gustatory disorder in patients were symptoms that appeared later in the course of the

infection, especially when the general symptoms were of limited severity.[12][13]

While in our study, we found that there was no statistically significant correlation between the total test score and fever, cough, sore throat, headache, digestive symptoms, and thoracic dyspnea. However, there was a significant correlation between the test score and nasal congestion, rhinorrhea, and the absence of general fatigue. Table (9).

Table 9: A table shows the statistical correlation between the total test score and some variables.

		Fisher's exact test value	Exact significance (2-sided) (p value)
Total test score	Fever	5.24	0.263
Total test score	Cough	3.972	0.391
Total test score	Nasal congestion	19.756	0.00
Total test score	Rhinorrhea	18.281	0.00
Total test score	Sore throat	7.951	0.71
Total test score	Headache	4.209	0.359
Total test score	General fatigue	18.604	0.00
Total test score	Digestive symptoms	4.927	0.282
Total test score	Thoracic dyspnea	8.189	0.063

- Study of the clinical development of patients with olfactory alterations 6 months after active infection with Covid-19.

We note from Table (10) that the only case of anosmia found with us with the results of the first olfactory test became severe hyposmia in the second test, 6 months after active infection with Covid-19. while the cases of severe hyposmia improved, and 5 patients (55.6%) became moderate in their results, 3 patients (33.3%) became mild, and the result of one case remained a severe hyposmia.

As for cases of moderate hyposmia, the test result improved in 34 patients (70.8%) to become a mild hyposmia, and 4 patients (8.3%) had a normal olfactory test result, while 10 patients remained in their condition of moderate hyposmia.

As for cases of mild hyposmia, the test result improved in 23 patients (69.7%) to normal olfaction, while mild hyposmia remained in 9 patients (27.3%), and the condition of olfaction worsened in only one patient to become moderate hyposmia.

As for the patients who had normal olfaction as a result of the first test, the result of only one of them worsened to become a mild hyposmia, while the rest of the patients remained as they were with a normal olfaction result.

In a study conducted in London, United Kingdom in 2020[14], olfactory symptoms were studied in 382 patients infected with Covid-19 using a questionnaire, where anosmia was observed in 86.4% of patients and 11.5% severe hyposmia. Upon follow-up after a week, the questionnaire evaluation was repeated and it was found that olfaction had improved significantly in 80.1% and had not changed in 17.6% of patients, while it had become worse in 1.9% of them. The study here relied on a questionnaire, and the evaluation and follow-up were repeated after only a week, while in our study we conducted a certified test and followed up with patients several months after the active infection with Covid-19.

Table 10: First total test score * Total test score after 6 months.

			Total test score after 6 months				Total
			Severe hyposmia	Moderate hyposmia	Mild hyposmia	Normal	
First total test score	Anosmia	Count	1	0	0	0	1
		% Total within	100.0%	0.0%	0.0%	0.0%	100.0%
	Severe hyposmia	Count	1	5	3	0	9
		% Total within	11.1%	55.6%	33.3%	0.0%	100.0%
	Moderate hyposmia	Count	0	10	34	4	48
		% Total within	0.0%	20.8%	70.8%	8.3%	100.0%
	Mild hyposmia	Count	0	1	9	23	33
		% Total within	0.0%	3.0%	27.3%	69.7%	100.0%
	Normal	Count	0	0	1	28	29
		% Total within	0.0%	0.0%	3.4%	96.6%	100.0%
	Total	Count	2	16	47	55	120
		% Total within	1.7%	13.3%	39.2%	45.8%	100.0%

In a research study conducted at the University of Cologne in Germany (2020)[15], 91 patients confirmed to be infected with Covid-19 with a PCR test were studied. It was found that 80 patients had suffered a sudden anosmia in the active course of the disease during the time of the test, where the sniffin' sticks test was conducted. Then, 8 weeks after the onset of symptoms, the olfactory function was re-evaluated and it was found that 45.1% of the tested patients still suffered from hyposmia, while 53.8% had their olfaction returned to normal limits. This study is approximately similar to our study in terms of the number of patients, but differs in terms of the duration of follow-up and the type of test used to evaluate the sense of smell.

Finally, some important observations regarding the study sample must be mentioned.

First: A significant percentage of the patients studied are health workers.

Second: It was noted in a small number of patients that they described the occurrence of anosmia initially, then it turned into hyposmia, and finally parosmia, with an interval of days between each sensation and the next. The first appeared symptom was accepted as the main symptom in the questionnaire.

Third: We had some patients studied from one family, and it was observed that they varied in the severity of the symptoms related to Covid-19, and they also varied in their olfactory symptoms. The prevailing rule was that the milder the general symptoms were, the more clearly the olfactory symptoms were apparent. The cause is not known yet, and this is consistent with some studies conducted on the same topic around the world.

Fourth: Many patients reported noticing hyperosmia several days before the general symptoms of Covid-19 infection occurred, and this remains a topic that can be researched later.

- **Conclusions and Recommendations**

1- The possibility of adopting the test to determine the olfactory threshold with butanol as an objective, qualitative and significant test to study the olfactory threshold in patients and study its clinical development.
2- The possibility of adopting the symptom of hyposmia, parosmia, or sudden anosmia as one of the important and clinically oriented symptoms of Covid-19 infection.
3- The rates of olfactory disorder following Covid-19 infection are higher than those after viral upper respiratory infection reported in the medical literature.
4- Among asymptomatic patients and those with mild symptoms, the presence of an olfactory disorder is considered a significant sign to suspect Covid-19 and act accordingly.

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