

Dilemma of prolonged post- COVID 19 anosmia treatment

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ORIGINAL STUDY

dilemma of prolonged post- COVID 19 anosmia treatment

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Abstract

Context: Anosmia is one of the pathognomonic neurological symptoms of COVID-19 since its begging at the end of 2019. Many patients suffered persistently for prolonged time after infected with this virus.

Aims: The aim of this study was to recognise the predisposing factors, to identify possible treatment regimens and to assess the prognosis of prolonged post- COVID-19 anosmia.

Settings and design: Retrospective observational study.

Methods and material: Study conducted among patients with post COVID-19 anosmia. Thirty-four patients sought medical advice for having prolonged post-COVID-19 anosmia between the period of August 2020 and October 2021 and assessed for predisposing factors. They were treated with local and systemic steroid, anti-inflammatory drugs and decongestant, and olfactory training for 2 weeks. The assessment of smell was done using (Visual Analog Scale from 0 to 10). The smell scores were recorded every two weeks, and the duration of smell loss was recorded from the onset of anosmia till the full recovery.

Statistical analysis used: Collection, coding, and verification of data was carried out using Excel software by the researcher. Data was statistically analysed using IBM-SPSS version 26 software (SPSS Inc., Chicago, IL, USA). Data was expressed as mean, standard deviation, frequency, and percentages. Repeated Measure ANOVA (RM-ANOVA) test was used to compare means of VAS-smell scores of same odours in different visits and post-hoc test with Bonferroni correction was used for pairwise time analysis. P-value ≤ 0.05 was considered the accepted level of significance in this work.

Results: thirty-two patients regained smell sense at the end of follow up and two patients showed little or no improvement, the smell scores significantly improved in most of the patients by the end of the second week ($P < 0.001$). Most of the patients had CRS with different causes, which was thought to predispose to prolonged anosmia.

Conclusions: The results suggested that prolonged post covid-19 anosmia can be treated easily considering the predisposing factors, with the combination of medical treatment and olfactory training. Presence of history of chronic rhinosinusitis in patients with prolonged anosmia may be a good prognostic factor.

Keywords: COVID-19, Smell, Prolonged anosmia, Predisposing factors, Chronic rhinosinusitis, Loss of smell, Treatment of anosmia

Key Messages

Post-covid anosmia could be treated easily if the predisposing factors was taken in consideration.

1. Introduction

Anosmia was not that common word to be heard from the public before the infestation of COV-SARS-2 virus at the end of 2019. In the last 2 years any patient complaining of smell disorder considered to have covid 19 infection till proved

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otherwise. Many patients had infection with this virus had wide range of smell disorders ranging from Anosmia, hyposmia, cacosmia and phantosmia.

One of the first papers published to alert physicians about anosmia as a symptom of Covid 19 was by Lechien et al. in Europe. Their study was the first to identify both olfactory and gustatory dysfunctions as significant symptoms in the clinical presentation of the European COVID-19 infection. They found that anosmia may be the first or the only presentation of infection without other significant complaints. They announced that sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19 infection [1].

T. Klopfenstein et al. took the multicentric European study published by Lechien et al. as reference to discuss his study and found that 47% with confirmed COVID-19 reported anosmia with their mean age of the was 47 (± 16) years; 67% were females, 37% were hospitalized due to sever infection. Anosmia began 4.4 (± 1.9) days in their patients after infection onset with the mean duration of anosmia was 8.9 (± 6.3) days and 98% of patients recovered within 28 days and concluded that anosmia was present in half of European COVID-19 patients and was often associated with dysgeusia [2].

Not so many papers discussed prolonged anosmia post COVID 19. Alexander Wieck found that olfactory deficits after COVID-19 often persist for more than a month and are predominantly quantitative. At a mean of 30 days after the patients lost smell sense, only 44% had fully recovered from their olfactory loss and at this time, 28% had not experienced any subjective improvement of their olfactory loss [3].

Nhu Ngoc Nguyen et al. in France found 30 patients from 125 had smell disorder persisted after the onset of COVID 19, with 21/30 partly recovered their smell sense and 7 with no recovery at all, most of them were females (73%) [4].

A prospective, randomized, controlled trial was conducted in Benha, Egypt by Abdelrahman AA. et al., among patients with post COVID-19 anosmia, with 100 patients were randomly assigned to two groups; group I included 50 patients received mometasone furoate nasal spray with olfactory training, group II included 50 patients were advised to keep on olfactory training only. They found no superiority for using mometasone furoate nasal spray as a topical corticosteroid in the treatment of post COVID-19 anosmia offers benefits over the olfactory training [5]. Yo Zahang et al. also recommended Olfactory training for patients with

COVID-19-related smell disorders in Meta-analysis done in China [6].

Le Bon et al. studied the safety and efficacy of combining oral corticosteroids and olfactory training in the management of olfactory dysfunction resulting from COVID-19 infection and he suggests that combination of a short course of oral corticosteroids and olfactory training is safe and may be beneficial in helping patients with enduring anosmia recover from olfactory loss due to COVID-19 [7].

Duika L. et al. studied the impact of post Covid-19 anosmia lasts for months. Anosmia has very serious implications on food, eating, health, work, and well-being, and for some is a profound existential assault disturbing their relationship to self, others, and the world in post COVID 19 patients [8].

The aim of the present study is to identify predisposing factors for developing post-COVID olfactory dysfunction, identify potential treatment strategies and their efficacy, and to determine the recovery course of post-COVID olfactory dysfunction.

2. Subjects and methods

2.1. Patients

This was a retrospective, observational follow up study conducted at Assiut University Hospital, Faculty of medicine, Assiut, Egypt; during the period between August 2020 and October 2021. This study was conducted on patients complained of anosmia after recovery from proven COVID-19 infection. COVID-19 infection diagnosis was based on CT chest and positive real-time reverse transcription-polymerase chain reaction (rRT-PCR) with samples obtained by a nasopharyngeal swab. Recovery was defined as 2 consecutive negative (rRT-PCR) samples.

Using G*Power 3 software, a calculated minimum sample of 34 patients were needed to detect an effect size of 0.3 in the mean VAS-smell score on four repeated occasions, with an error probability of 0.05 and 80% power on a two-tailed test.

Adults aged 18 years or older recovered (2 negative PCR) from COVID 19 infection (positive PCR) and were suffering from recent sudden anosmia, either hospitalized or managed at home were included in the current study. On the other hand, pregnant females and those refused to participate in the study were excluded.

All patients were asked to sign written informed consent prior to participation. The study was performed in accordance with the guidelines of the

Helsinki Declaration of 1975 and its amendments. The study protocol was approved by the Research Ethics Committee at Faculty of Medicine, Assiut University, Egypt (IRB no.17300701).

2.2. Methods

2.2.1. Initial assessment and evaluation

All eligible patients were subjected to.

- A full detailed personal history including age, sex, occupation, residency, and special habits.
- Medical history including detailed history of previous trauma, surgeries, congenital anomalies, and chronic inflammation of the nose.
- Detailed history about the SARS-COV-2 infection (onset, course, duration, and any other complications).
- Associated comorbidities.
- Endoscopic examination of the nose.
- Smell Identification and threshold testing.

2.2.2. Lines of treatment

All Patients had the same medical treatment for two weeks and re-examined in 2-4- and 8-weeks period. The treatment of all the patients for two weeks was in the form of:

1. Prednisolone 20 mg tablet once per day.
2. Combined pseudoephedrine sulphate 120 mg, paracetamol 500 mg and loratadine 5 mg twice tablet daily dose.
3. Montelukast 5 mg tab once per day.
4. Erdosteine 300 mg twice tab per day.
5. Intranasal steroid in the form of Fluticasone furoate twice per day.
6. Vitamin B complex and folic acid tablets twice per day.
7. Olfactory training.

2.2.3. Follow up

As regards the assessment of smell, the patients were assessed for smell sensation with “a visual analogue scale (VAS)-smell score” using familiar substances with a distinctive odour, with caution to avoid any irritants. The substances like mint, clove, lemon and rose were used to test identification of smell. Patients reported the degree of anosmia subjectively with VAS-smell score from 0 to 10 (0 means total loss of smell and 10 refers to completely normal smell sensation). Assessment of smell was performed initially in the first visit before treatment, 2, 4 and 8 weeks after treatment for all patients. The

duration of smell loss was recorded from the onset of anosmia till full recovery of the sensation.

2.3. Statistical analysis

Collection, coding, and verification of data was carried out using Excel software by the researcher. Data was statistically analysed using IBM-SPSS version 26 software (SPSS Inc., Chicago, IL, USA). Data was expressed as mean, standard deviation, frequency, and percentages. Repeated Measure ANOVA (RM-ANOVA) test was used to compare means of VAS-smell scores of same odours in different visits and post-hoc test with Bonferroni correction was used for pairwise time analysis. P-value ≤ 0.05 was considered the accepted level of significance in this work.

3. Results

Thirty-four patients with confirmed COVID-19 reported anosmia were included in this study. Among these patients, the mean age was 30.1 (± 9.2) years and 22 (64.7%) were females. No associated comorbidities were found in these patients (asthma, arterial hypertension, and cardiovascular disease, COPD, diabetes, malignancy, and thyroid dysfunction). Among the 34 patients, the mean duration of anosmia was 104.7 (± 92.3) days ranging from 1 week after first two weeks of isolation to 1 year [Table 1].

Twenty eight of the thirty-four patients had history of allergic rhinitis (82.4%) confirmed by history and examination, while only one patient had history of chronic infective rhinosinusitis (2.9%). Two patients had gastro-esophageal reflux disease GERD (5.9%) which is known to predispose CRS. No other predisposing factors was found in all patients (Nasal bony deformities, Nasal tumors, Previous nasal surgery, Head trauma).

Thirty-two patients (94.1%) regained their ability to smell and identify odors with twenty-seven patients improved after 2 weeks (82.4%), three patients in 4 weeks (11.8%) and one patient (2.9) after 8 weeks from the beginning of treatment. Only two patients showed no improvement at all.

As shown in [Table 2], By comparing means of smell scores after 2 week, 4 weeks and 8 weeks of treatment, there were statistically significant differences between the first visit (before treatment) and the other visits, P-values were (0.000, 0.000 and 0.000) respectively. The average time for complete recovery of smell was 16.62 ± 8.29 days and the recovery rate was (94.12%) by the end of the eight's week [Table 2]. summarized the comparison between smell scores over the period of the study;

Table 1. Baseline demographic and clinical characteristics of the study cohort.

Parameter	n = 34
Age in years	• Mean \pm SD 30.24 \pm 8.9
	• Median (Range) 28 (18–55)
Sex	• Female 22 (64.7%)
	• Male 12 (35.3%)
Occupation	• Non-working (HW/Student) 24 (70.6%)
	• Working 10 (29.4%)
Post COVID Anosmia Duration/weeks	• Mean \pm SD 13.59 \pm 12.2
	• Median (Range) 8 (1–48)
Predisposing Factors	• Allergic Rhinitis 28 (82.4%)
	• Chronic Bacterial Rhinosinusitis 1 (2.9%)
	• GERD 2 (5.9%)
Complete improvement	• Yes 32 (94.1%)
Treatment Duration/weeks	• Mean \pm SD 2.38 \pm 1.2
	• Median (Range) 2 (2–8)

there were significant improvements over the period of the study, the median of smell scores was 0 initially and by the end of the eighth week it improved to 10 ($P < 0.001$). Fig. 1 shows the VAS-smell Score differences among the studied odours over Time.

4. Discussion

In the last two years, great changes happened worldwide after the outbreak of COV-SARS-2 started in Wuhan, China at the end of 2019 not only in health but in many life aspects. Every day there were a newly discovered symptoms and signs caused by this virus the mechanism of most of them are not yet understood. Smell sense disorders were one of the first described symptom of infection by COV-SARS-2 and helped to diagnose many patients.

Post-viral infection anosmia is one of the main causes of olfactory dysfunction in adults, viruses that cause common cold are well known to cause post-infectious smell disturbance, and over 200 different viruses known to cause upper respiratory tract infections [9]. Olfactory dysfunction is a characteristic finding of COVID-19 patients, which can be the only symptom or associated with other symptoms, but its pathogenesis is still not well understood. It may result from viral induced local inflammation and obstruction of the nasal cavity, olfactory nerve damage, or both [10].

This retrospective observational study included thirty-four patients came to our outpatient clinic in Assiut university hospital between August 2020 and October 2021, included in the research complained of anosmia for a long period after infection with SARS-COV-2. All patients were diagnosed to have infection by CT chest and PCR of nasopharyngeal samples. Of the 34 patients, twenty-two were females (64.7%) and twelve males (35.3%). The average age of the subjects was 30.2 ± 8.9 years (mean \pm SD) with a wide range (18–55 years), and the mean duration of anosmia was 104.68 ± 92.27

Table 2. Smell scores (VAS) over the study period among the studied cohort.

Variable	Baseline (I)	2-weeks (II)	4-weeks (III)	8-weeks (VI)	P-value ^a
Lemon	0.50 \pm 0.1	8.68 \pm 1.2	9.15 \pm 1.4	9.41 \pm 1.7	< 0.001
• P-value ^b	I vs. II < 0.001	II vs. III = 0.125	III vs. VI = 0.325	I vs. VI < 0.001	
Clove	0.65 \pm 0.2	8.53 \pm 1.3	9.12 \pm 2.1	9.41 \pm 2.3	< 0.001
• P-value ^b	I vs. II < 0.001	II vs. III = 0.117	III vs. VI = 0.325	I vs. VI < 0.001	
Mint	0.56 \pm 0.1	8.47 \pm 1.4	9.18 \pm 1.8	9.41 \pm 2.1	< 0.001
• P-value ^b	I vs. II < 0.001	II vs. III = 0.068	III vs. VI = 0.325	I vs. VI < 0.001	
Rose	0.50 \pm 0.1	8.38 \pm 1.5	9.26 \pm 1.7	9.41 \pm 1.4	< 0.001
• P-value ^b	I vs. II < 0.001	II vs. III = 0.054	III vs. VI = 0.325	I vs. VI < 0.001	
	I vs. III < 0.001	II vs. VI = 0.045			

^a One-way RM-ANOVA test was used to compare means over the study period.

^b Post-hoc test was used for Pairwise Comparisons.

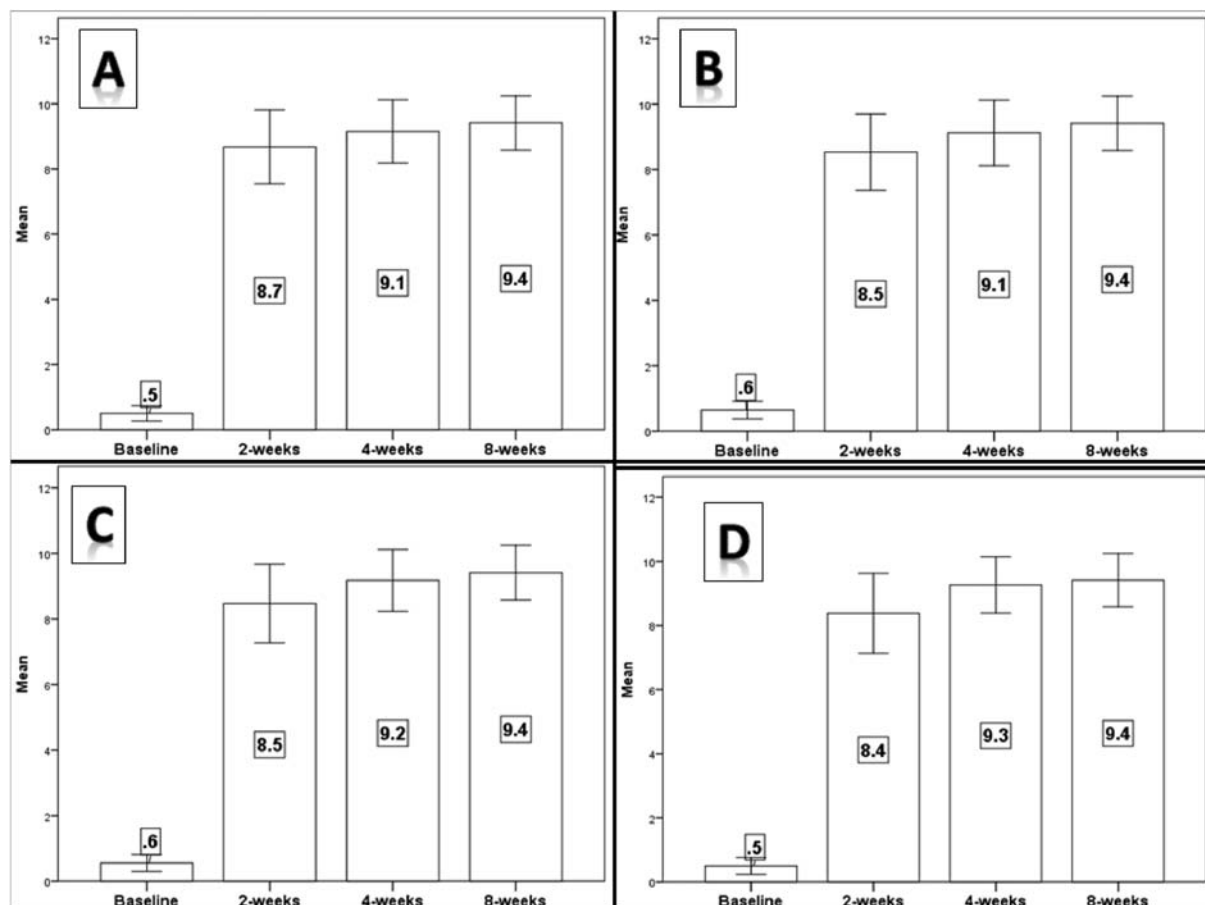


Fig. 1. VAS-smell Score Differences among the studied Cohort over Time. A: Lemon B: Clove C: Mint D: Rose.

days. No one of the patients had an associated comorbidity (Asthma, Hypertension, Diabetes, cardiovascular disease, COPD, Malignancy, Thyroid dysfunction) and no one had treatment for anosmia except one patient had oral corticosteroid for one week.

Anosmia was more common in females than males in all researches published to study post viral infection anosmia without a probable explanation which suggest more sexual predisposition to females, the reason for this female preponderance is unclear but may relate to the fact that women tend to have more URIs as known before the era of COVID 19 [11–14].

Most of the patients were already known allergic patients (82.4%), two patients had gastro-esophageal reflux disease (5.9%) and one had chronic infective rhinosinusitis (2.9%) before the onset of COVID 19 disease and no one of them suffered of smell disorder before. No other predisposing factors for anosmia (Nasal bony deformities, Nasal tumors, Previous nasal surgery, Head trauma) detected in the patients. Chronic rhinosinusitis (allergic,

infective, or none-allergic none-infective) could be a predisposing factor to persistent and prolonged anosmia after recovery from COVID 19 virus infection.

Treatment used to these patients targeted to relieve nasal obstruction, thick mucus aggregations, edema and inflammation around the olfactory nerve endings, allergic inflammation, and vitamins to support the nerve function. Short course of oral steroids used as known that systemic steroid management reverses anosmia in most patients with nasal obstruction that is caused by chronic rhinitis [11,12,15,16].

Most of the patients (28) included in the study show significant improvement in the first 2 weeks (82.4%), 3 after 4 weeks (11.8%) and one patient at the end of the 8 weeks (2.9%). Scangas et al. and Heilmann et al. stated that topical steroid treatment has been reported to improve the recovery in post-infectious olfactory dysfunction patients but not in COVID 19 Infection [17,18].

A case report by Touisserkani and Ayatollahi found a female patient with COVID-19 anosmia did

not recover after 2 weeks of its onset and for 10 days on the topical nasal steroid without improvement. Then oral prednisolone was prescribed and after 6 days of consuming prednisolone, her anosmia reversed [19]. Abdelrahman AA. et al. in 2021 used the local corticosteroid nasal spray in the form of mometasone furoate with olfactory training shows good results on improvement of anosmia but with no advantages over olfactory training alone in the treatment of anosmia in patients recovered from COVID-19 infection [5]. Yo Zahang et al. also recommended Olfactory training for patients with COVID-19-related smell disorders in Meta-analysis done in China. Unlike other studies done on post COVID 19 Anosmia either with short or long duration, in this study, the researcher preferred to use both oral and intranasal steroid to study the additive effect of both [6].

Pseudoephedrine sulphate add to treatment to relieve nasal blockage, loratadine and Montelukast to subside the inflammations and decreasing discharge and Erdosteine for its mucolytic effect.

The results of the study suggest that the pathogenesis of prolonged anosmia in most of the studied patients is local nasal obstruction and inflammation, with no one of the patients who showed improvement suffered of relapse at the end of follow up, with the exception of the 2 patients that showed no improvement at all at the end of the study that may had neurological origin of anosmia.

Many theories were put to try to describe or distinguish the etiology of post viral infection anosmia before the appearance of COVID 19 disease like Conductive or obstructive theory, Disruption of olfactory epithelium following local infection, Retrograde propagation to higher-order neurons in the olfactory pathway, Hematologic spread to the CNS and direct or indirect CNS injury causing demyelination. Only the obstructive theory can be proved by treating the obstruction medically or surgically, but the other theories need more evaluation and studying. Albert Y. Han et al. postulated that depending on the true distribution of ACE2 receptors (which is used by COV- SARS-2 virus as a receptor to enter the cells), virulence potential, and resulting immune and inflammatory response, olfactory dysfunction may indicate a peripheral injury of the first cranial nerve and branches or a harbinger of a more global neurological manifestation of the disease [20].

Imaging studies done on post COVID 19 anosmia using CT and MRI showed no significant changes in the olfactory area. Amal Hajjij et al. didn't find any abnormality of signal or morphology of olfactory region, neither in the sinuses and nasal cavities [21],

in contrast to S.B Strauss et al. and Letterio S. Politi et al. who founded in 4 of 12 patients a cortical hyper intensity in the gyrus rectus and olfactory bulbs at the critical phase of infection and disappeared after healing. This finding suggested edema and inflammation of the olfactory tract [22,23].

Finally, future prospective studies are needed to study the possible causes and predisposing factors of post COVID 19 anosmia and to study combinations of effective remedies.

5. Conclusion

The results of our study suggest that using short course oral steroid, intranasal spray as a topical corticosteroid, decongestants, with autoinflammatory drugs and mucolytic therapy along with olfactory training in the treatment of post COVID- 19 anosmia offers a great benefit in combination for most of the patients with good smell scores over the period of the study and recovery rates.

Conflict of interest

No conflict of interest.

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