



Case Control Study

Psychiatric outcomes in outpatients affected by long COVID: A link between mental health and persistence of olfactory complaint

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Abstract

BACKGROUND

Anosmia was one of the main symptoms of coronavirus disease 2019 (COVID-19). A psychiatric history (*i.e.*, depression) may be an independent contributor to the risk of COVID-19 diagnosis, and COVID-19 survivors appear to have an increased risk of neuropsychiatric sequelae (bidirectional association).

AIM

To compare the rate of psychiatric disorder among post-COVID patients without anosmia *vs* patients with persistent olfactory complaints.

METHODS

We conducted a prospective case control study from March 2020 to May 2021. Patients recruited at the ENT department of Nice University Hospital had a subjective olfactory complaint (visual analogue scale) for over 6 wk and a molecular or CT-proven severe acute respiratory syndrome coronavirus 2 diagnosis confirmed by serology. Post-COVID patients without persistent olfactory disorders were recruited at the university hospital infectiology department. Psychiatric medical histories were collected by a psychiatrist during the

assessments.

RESULTS

Thirty-four patients with post-COVID-19 olfactory complaints were included in the first group of the study. Fifty percent of the patients were female ($n = 17$). The group's mean age was 40.5 ± 12.9 years. The control group included 32 participants, of which 34.4% were female ($n = 11$), and had a mean age of 61.2 ± 12.2 years. The rate of psychiatric disorder among post-COVID patients with olfactory complaints was significantly higher (41.7%) than among patients without (18.8%) ($\chi^2 = 5.9$, $P = 0.015$).

CONCLUSION

The presence of a psychiatric history may constitute a potential risk factor for the development of long COVID due to persistent anosmia. It therefore seems important to establish reinforced health monitoring after a COVID 19 infection in at-risk patients. Further prospective, translational, and collaborative studies are needed to extrapolate these results to the general population.

Key Words: COVID-19; Anosmia; Psychiatry; Stress; Neuroplasticity; Psychiatric history

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Core Tip: Our study reveals a significant association between a psychiatric history and persistent anosmia in post-coronavirus disease 2019 (COVID-19) patients. With a higher rate of psychiatric disorder observed in individuals experiencing long-COVID symptoms, our findings underscore the need for reinforced health monitoring of at-risk patients. This emphasizes the importance of considering psychiatric factors in the assessment and management of post-COVID-19 sequelae. This study will thus contribute to a broader understanding of the multifaceted impact of the virus on mental health.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic originated in China. It was first identified in Wuhan (Hubei province) in December 2019 before spreading to other continents[1]. It resulted in a still active global pandemic.

Olfactory loss was one of the main symptoms among European patients with mild-to-moderate COVID-19 (70.2%)[2]. Even if several pathogenic mechanisms of olfactory dysfunction in patients with COVID-19 were postulated, the precise mechanisms remain unclear. Neuroplasticity is known to play a major role in recovery after loss of smell[3]. However, it has been observed that the plasticity of the human brain can be affected by (certain) stressful events, by a psychiatric history (e.g., depression) and by lifetime sensory experiences[4]. Thus, Taquet *et al*[5] (2021) have suggested bidirectional associations between COVID-19 and psychiatric disorders.

Interestingly, in their study, a psychiatric diagnosis in the previous year was shown to be an independent risk factor of COVID-19 diagnosis[5]. In a further study, Taquet *et al*[6] (2021) suggested that a COVID-19 diagnosis was associated with psychiatric and neurological outcomes at 6 months in one third of patients.

Based on these results, we can hypothesize that the persistence of an olfactory complaint could also be affected by the patient's psychiatric history.

The main objective of our study was to compare the psychiatric history within the previous year of post-COVID patients without olfactory complaints (with a total recovery < 1 month) *vs* patients with persistent post-viral olfactory complaints.

The secondary objectives were: (1) To assess the rate of post-traumatic stress disorder (PTSD) among patients with post-viral olfactory complaints (COVID-19) and to compare it with the rate of PTSD among patients without olfactory complaints (with a total recovery < 1 month); and (2) for patients with persistent olfactory complaints, to correlate the intensity of post-traumatic symptoms with self-reported olfactory recovery.

MATERIALS AND METHODS

Study registration

The study was approved by the institutional review board of Nice University Hospital (CNIL number: 412). This study is

part of a large prospective work registered under a ClinicalTrials.gov number (ID: NCT04799977). For this large trial, we prospectively recruited patients of the ENT department of Nice University Hospital, starting in March 2020. All had been contaminated by COVID-19 and had persistent olfactory disorders lasting more than 6 wk (3 to 15 months).

We retrospectively extracted the patients' demographic data and clinical features, including subjective taste impairment, subjective olfactory impairment (qualitative and quantitative dysosmia), weight (measured at home in the previous week on a personal scale), nasofibroscopy (assessing nasal cavity patency and differential diagnosis), and olfactory loss using Sniffin' Sticks Test® (SST; Medisense, Groningen, The Netherlands).

Population

In this study, patients with persistent olfactory disorders were recruited at the ENT department of Nice University Hospital during the period from March 2020 to February 2021. Patients were self-referred or referred by colleagues, general practitioners or recommended by the infectiology department that recorded all COVID-19 declared patients (city guidelines). Patients had an olfactory complaint for over 6 weeks and a molecular-proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnosis or a CT-proven SARS-CoV-2 diagnosis secondarily confirmed by serology. Patients with other pathologies that could affect the olfactory system were excluded, as confirmed by their medical history and nasofibroscopy results: olfaction disorders, ENT cancer, head radiotherapy history, and post viral (before the pandemic) olfactory history.

Post-COVID patients without persistent olfactory disorders were recruited at the university infectiology department during the same period.

Measures and trial design

For patients with persistent olfactory complaints, olfactory function was evaluated by an otorhinolaryngologist using a visual analogue scale (VAS) assessing the subjective perceived olfactory recovery.

A psychiatric interview performed by an experienced psychiatrist explored the psychiatric history, the diagnostic categories (according to the DSM 5), the presence of stress factors, and exposure to recent or past psychotrauma. Psychiatric assessments included validated self-report questionnaires for PTSD (PCL-5).

Patients without olfactory complaints were interviewed by a psychiatrist who conducted a medical and psychological evaluation. Special attention was paid to their psychiatric history. They also completed the PCL-5 questionnaire at home using Google Forms.

Statistical analysis

Data are presented as mean (SD) for quantitative variables and as frequency and percentage for qualitative variables. To compare age between groups (patients with persistent olfactory complaints *vs* patients without olfactory complaints), we used independent-sample *T* tests for normally distributed variables (age), and Mann-Whitney *U* tests for non-normally distributed variables (PCL-5). To investigate gender differences across groups, we performed Chi2 analyses. We also ran an exploratory logistic regression analysis to verify whether the presence of previous mental disorders could have had an impact on the presence of olfactory disorders lasting more than one month.

To investigate correlations between subjective reports (VAS) and PCL-5 scores, we performed bivariate correlation analyses. As data were not normally distributed (as suggested by the Kolmogorov-Smirnov test), non-parametric Spearman's correlations were made.

RESULTS

Demographic features

The patients' demographic and clinical features are presented in Table 1. Thirty-four patients with post-COVID-19 olfactory complaints were included in the first group of the study. Fifty percent of the patients were female ($n = 17$). The patients' mean age was 40.5 ± 12.9 years. They were interviewed 5.3 ± 2.8 mo after COVID-19 infection. The day of the interview, patients reported having recovered only $37.7\% \pm 27.5\%$ of their olfaction (ranging from 0% to 90%). The control group included 32 participants, of which 34.4% were female ($n = 11$), and had a mean age of 61.2 ± 12.2 years. The two groups differed in terms of mean age ($t_{(64)} = 6.7$, $P < 0.001$), while gender did not differ between groups ($\text{Chi}^2_{(1)} = 1.6$, $P = 0.199$).

Psychiatric history

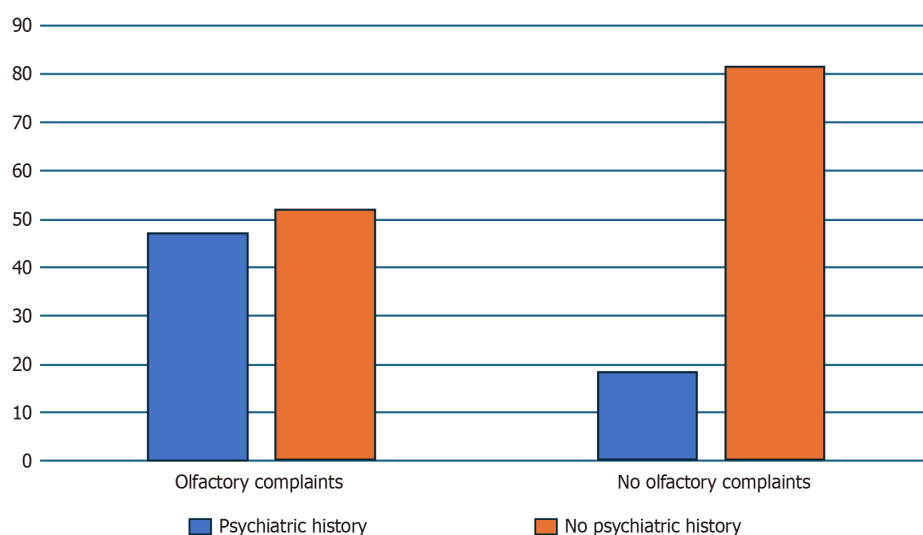
In the group with olfactory complaints, 47.1% of the subjects ($n = 16$) reported a psychiatric history prior to SARS-CoV-2 infection. Only 18.8% of subjects in the control group ($n = 6$) reported a psychiatric history prior to SARS-CoV-2 infection (Figure 1). Chi2 analysis confirmed that the proportion of people with a previous psychiatric history was significantly higher in the patients with persistent olfactory complaints compared to the control group ($\chi^2_{(1)} = 5.9$, $P = 0.015$). Logistic regression analysis suggested that the presence of a previous psychiatric history had a significant impact on the probability of having post-COVID-19 olfactory complaints ($B = 1.35$, $P = 0.018$).

Presence of post-traumatic stress symptoms

Subjects with olfactory complaints had a mean PCL-5 score of 17.8 (SD = 22.4), while control subjects had a mean score of 18.1 (SD = 20.0). The difference was not statistically significant ($U = 461.5$, $P = 0.285$). In the olfactory complaint group, no

Table 1 Demographic and clinical characteristics of the patients in the two groups

	Olfactory complaints, <i>n</i> = 34	No olfactory complaints, <i>n</i> = 32	<i>P</i> value
Age, mean (SD)	40.5 (12.9)	61.2 (12.2)	< 0.001 ¹
PCL-5, mean (SD)	17.8 (22.4)	18.8 (20.0)	0.285 ²
Sex, <i>n</i> (%)			0.199 ³
Female	17 (50.0)	11 (34.4)	
Male	17 (50.0)	21 (65.6)	
Psychiatric history, <i>n</i> (%)			0.015 ³
Yes	16 (47.1)	6 (18.8)	
No	18 (52.9)	26 (81.3)	

¹*t*-test.²Mann-Whitney test.³ χ^2 test.**Figure 1** Link between psychiatric history and olfactory complaints.

significant correlation was found between the percentage of subjective olfactory recovery (VAS) and PCL-5 ($\rho_{(32)} = 0.02$, $P = 0.925$).

DISCUSSION

Several factors have been shown to influence the likelihood of developing persistent olfactory disorders after COVID-19 infection, such as belonging to an ethnic minority, socioeconomic deprivation, smoking, and obesity[7]. Here we investigated whether a psychiatric history before SARS-CoV-2 infection was more frequent in patients with and without olfactory complaints. Our results suggest that psychiatric history and certain psychological conditions such as stressful events were more common in patients with persistent olfactory complaints.

Olfactory complaint was one of the main symptoms among European patients with mild-to-moderate COVID-19 (70.2%); in a seminal study that included 1420 patients, Lechien *et al*[2] (2020) found that olfactory complaints persisted at least 7 d in 37.5% of these cases. Since the beginning of the COVID-19 pandemic, several pathogenic mechanisms of olfactory dysfunction have been postulated. However, the precise mechanisms still remain unclear. Reichert *et al.* (2018) conducted research on the role of neuroplasticity in recovery after loss of smell, focusing on the decrease in white and grey matter[3]. They also highlighted the efficacy of olfactory training programs. In a large review, McEwen[4] (2007) suggested that the plasticity of the human brain could be affected by stressful life events, a psychiatric history (*e.g.*, depression), lifetime sensory experiences, and stress-related social problems. Taquet *et al*[5] (2021) suggested bidirectional associations between COVID-19 and psychiatric disorders. They observed that a psychiatric diagnosis in the previous year was an independent risk factor of COVID-19 diagnosis. In a further study, they showed that COVID-19 diagnosis was associated with psychiatric and neurological outcomes in one third of patients 6 months after the infection[6]. These

results are supported by evidence that COVID-19 can have an impact on the brain. As mentioned above, McEwen has shown that stress can have a damaging effect on the brain, and that the brain can also respond to stress by manifesting behavioral and physiological symptoms[8]. More broadly, life experiences modify brain function *via* synaptic transmission[8].

The data presented in this study suggests that a psychiatric history and certain psychological conditions, such as stressful events, may have a negative impact on the persistence of an olfactory complaint. These results are consistent with several hypothesized mechanisms of brain involvement in SARS-CoV-2 infection. Indeed, it has been shown that SARS-CoV-2 can infect the Central Nervous System by crossing the neural-mucosal interface and more specifically by crossing the olfactory mucosa and following neuroanatomical structures due to its neurotropism[9]. Moreover, in a large systematic review, Rogers *et al*[10] (2020) have pointed out that depression, anxiety, PTSD, and other neuropsychiatric syndromes can appear after COVID-19. Once infected, people with pre-existing mental disorders are at high risk of experiencing persistent symptoms of COVID[11]. In our study, we failed to demonstrate that PTSD was a risk factor for developing persistent anosmia, but we did not explore the risk of developing PTSD after COVID infection.

Limitations

The main limitation of this study is the small sample size, which is not representative of the whole population. Furthermore, the two samples of participants with and without persistent anosmia were recruited in different facilities, making it impossible to exclude a recruitment bias. Patients in both groups also differed in age, which limits comparability between them. These results should be interpreted with caution and should be replicated in bigger samples.

CONCLUSION

In conclusion, the human brain might be affected by a psychiatric history (including stressful events). This brain damage could partially be an explanation for olfactory complaint persistence months after a SARS CoV-2 infection, showing the key importance of post COVID-19 psychiatric follow-up and of preventive mental health care.

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FOOTNOTES

Author contributions: Askenazy F, Dumas LE, Vandersteen C and Metelkina-Fernandez V initiated the project and designed the experiment; Dumas LE, Chirio D, Gros A, Fernandez A and Metelkina-Fernandez V conducted clinical data collection; Manera V conducted several collation and statistical analyses; Metelkina-Fernandez V wrote the original manuscript; Chirio D, Gros A, Manera V, Metelkina-Fernandez V and Fernandez A revised the paper; and all authors reviewed and approved the paper and approved the final manuscript.

Institutional review board statement: The study was approved by the institutional review board of Nice University Hospital (CNIL number: 412).

Informed consent statement: This study was carried out as part of routine care. Patients were informed of their inclusion in this study and gave their informed consent to participate. Patients' non-objection to study participation was requested orally and recorded in the patient's medical record. Patients were informed that they could refuse to participate or withdraw their consent at any time during the study. Data were anonymized before the analyses.

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