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Case Control Study

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

COVID-19 anosmia and mental health.

victoria Metelkina-Fernandez, Louise-Emilie Dumas, Clair Vandersteen, David Chirio, Auriane Gros, Arnaud Fernandez, Florence Askenazy, Valeria Manera

victoria Metelkina-Fernandez, psychiatry, CHU de Nice, Nice 06000, France

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 patients' psychiatric histories 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 University Department of Nice either had a subjective olfactory

complaint (visual analogue scale) for over 6 wk and a molecular or CT-proven SARS-CoV-2 diagnosis confirmed by serology. Patients without persistent olfactory disorders were recruited at the university 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 study. Fifty percent of patients were female ($n = 17$), with a mean age of 40.5 ± 12.9 years. The control group included 32 participants. 34.4% of patients were female ($n = 11$), with a mean age of 61.2 ± 12.2 years. The rate of patients' psychiatric histories 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 psychiatric history seems to 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 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 psychiatric history and persistent anosmia in post-COVID-19 patients. With a higher rate of psychiatric

histories observed in individuals experiencing long-COVID symptoms, our findings underscore the need for reinforced health monitoring in at-risk patients. This emphasizes the importance of considering psychiatric factors in the assessment and management of post-COVID-19 sequelae, contributing to a broader understanding of the multifaceted impact of the virus on mental health.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) pandemic originated in China. It was first identified in Wuhan (Hubei province) in December 2019 and spread to other continents (Zhu *et al.*, 2019). 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%) (Lechien *et al.*, 2019). Even if several pathogenic mechanisms of olfactory dysfunction in patients with COVID-19 were postulated, the precise mechanisms remain unclear. Neuroplasticity plays a major role in the recovery after loss of smell (Reichert *et al.*, 2018). However, the plasticity of the human brain could be affected by (certain) stressful events, by a psychiatric history (e.g depression) and is dependent on lifetime sensory experiences (McEwen, 2007). Thus, Taquet *et al.*, (2021) 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 (Taquet *et al.*, 2021). On the other hand, Taquet *et al.* (2021b), suggested in another study that COVID-19 diagnosis was associated with psychiatric and neurological outcomes in one third of patients at 6 months.

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

The main objective of our study was to compare the rate of patients' psychiatric histories in previous year among post-COVID patients without olfactory complaints (or

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 (or with a total recovery < 1 month); 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 the Nice University Hospital (CNIL number: 412). This study is part of a large prospective work registered under a ClinicalTrials.gov number (ID: NCT04799977). In this large trial, we prospectively recruited patients in the ENT division of Nice University Hospital since March 2020. All were contaminated by COVID-19 with 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 of March 2020 to February 2021. Patients were self-referred or referred by colleagues, general practitioners or advised by the infectiology department that received all COVID-19 declared patients (city guidelines). Patients had an olfactory complaint for over 6 wk and a molecular-proven SARS-CoV-2 diagnosis, or a CT-proven SARS-CoV-2 diagnosis secondarily

confirmed by serology. Other pathologies that could affect the olfactory system were excluded by recording the medical history and nasofibroscopy results: olfaction disorders, ENT cancer, head radiotherapy history and post viral (before the pandemic) olfactive history.

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 underwent an interview with a psychiatrist for 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 employed independent-sample T tests for normally distributed variables (age), and Mann-Whitney U tests for non-normally distributed variables (PCL-5). To investigate gender differed across groups, we performed Chi2 analyses. We also run an exploratory logistic regression analysis to verify whether the presence of previous mental history could have 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 Kolmogorov-Smirnov test), non-parametric Spearman's correlations were employed.

RESULTS

Demographic features

The demographic and clinical patients' features are presented in Table 1. Thirty-four patients with post-COVID-19 olfactory complaints were included in the study. Fifty percent of patients were female ($n = 17$), with a mean age of 40.5 ± 12.9 years. They were seen after 5.3 ± 2.8 months after the COVID-19 infection. The day of consultation, patients reported to have recovered only $37.7 \pm 27.5\%$ of their olfaction (ranging from 0% to 90%). The control group included 32 participants. 34.4% of patients were female ($n = 11$), with 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 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 previous psychiatric history had a significant impact of the probability to have 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 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 Covid19 infection, such as belonging to an ethnic minority, socioeconomic deprivation, smoking, and obesity (Subramanian *et al.*, 2022). Here we investigated whether psychiatric history before their 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, Lechien *et al.*, (2019), included 1420 patients, and found that and olfactory complaints persisted at least 7 days in 37,5% of them. Since the beginning of the COVID-19 pandemic, several pathogenic mechanisms of olfactory dysfunction were postulated. However, the precise mechanisms remain still unclear. Reichert *et al.*, (2018) conducted research on the role of neuroplasticity in the recovery after loss of smell, focusing on the decrease in white and grey matter. They also highlighted the efficacy of olfactory training programs. In a large review, Mc Ewen (2007) suggested that the plasticity of the human brain could be affected by stressful life events and a psychiatric history (*e.g.*, depression), and depends on lifetime sensory experiences and stress-related social problems. Taquet *et al.*, (2021)suggested bidirectional associations between COVID-19 and psychiatric disorders. They also showed, in another study, that COVID-19 diagnosis was associated with psychiatric and neurological outcomes in one third of patients at 6 months after the infection (Taquet *et al.*, 2021b).

As suggested by Taquet *et al.* (2021), a psychiatric diagnosis in the previous year was shown to be an independent risk factor of COVID-19 diagnosis (Taquet *et al.*, 2021).

These results are supported by evidence that COVID-19 can have an impact on brain. It is well known that stress can have a damaging effect on the brain, and that the brain's response to stress can also manifest with behavioral and physiological

symptoms. (McEwen, 2017). More broadly, life experiences modify brain function *via* synaptic transmission (McEwen, 2017).

The data presented in this study suggests that psychiatric history and certain psychological conditions, such as stressful events, may have a negative impact on the persistence of 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 (CNS) by crossing the neural-mucosal interface and more specifically by crossing the olfactory mucosa and following neuroanatomical structures due to its neurotropism (Meinhardt *et al.*, 2021). Moreover, in a large systematic review, Rogers *et al.*, (2020) emphasized that depression, anxiety, PTSD, and other neuropsychiatric syndromes can manifest after COVID-19. Once infected, people with pre-existing mental disorders are at high risk of experiencing persistent symptoms of COVID (Molero *et al.*, 2023). 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.

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

The COVID-19 pandemic, originating in China, has been associated with olfactory loss in a significant proportion of patients. Despite various proposed mechanisms, the precise causes of this dysfunction remain unclear. Notably, previous research suggests bidirectional associations between COVID-19 and psychiatric disorders, with psychiatric diagnoses identified as independent risk factors for COVID-19.

Research motivation

The study addresses a critical gap in understanding the potential interplay between psychiatric history and persistent olfactory dysfunction in the aftermath of COVID-19, contributing valuable insights to the broader understanding of the virus's long-term effects.

Research objectives

the current study aims to compare the prevalence of psychiatric histories among post-COVID patients with and without persistent olfactory complaints.

Research methods

The study, conducted between March 2020 and May 2021, employed a prospective case-control design involving patients from the ENT University Department of Nice with persistent olfactory complaints lasting over 6 wk and confirmed SARS-CoV-2 diagnoses. Patients without persistent olfactory disorders were recruited from the university infectiology department, and psychiatric medical histories were systematically collected by a psychiatrist during the assessments.

Research results

The study included 34 patients with post-COVID-19 olfactory complaints, predominantly female (50%) with a mean age of 40.5 years. A control group of 32 participants, with a mean age of 61.2 years, was also examined. The analysis revealed a significantly higher rate of psychiatric histories among post-COVID patients with olfactory complaints (41.7%) compared to those without (18.8%), indicating a potential association between psychiatric history and persistent olfactory dysfunction in post-COVID individuals ($\chi^2 = 5.9$, $P = 0.015$).

Research conclusions

his study proposes to accurately collect the psychiatric history of people who have been infected with COVID-19 when they present persistent symptoms, and to consider this history as a potential marker of vulnerability to the risk of developing long COVID.

Research perspectives

This study underlines the importance of comprehensive patient care and interdisciplinary collaboration (in this case psychiatrist, infectiologist and ENT specialist). It shows the need for multi-center, even international, collaboration to set up cohorts with a large number of patients and regular re-evaluations if we hope to demonstrate, beyond correlations as in the present study, a possible cause-and-effect relationship that would pave the way for the study of underlying mechanisms.

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