Prolonged Olfactory Dysfunction in the COVID-19 Era; Etiological Analysis in a Single-centered Cohort

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February 22, 2024

Abstract

Key Points: ? COVID-19 often cause prolonged olfactory dysfunction. ? This study evaluated the relative burden of the COVID-19-related disease in a single-centered cohort of POD patients. ? COVID-19-related POD was diagnosed serologically. ? In the COVID-19 era, the local burden of POD increased two-fold. ? It is important to use pleiotropic approach and robust measures, when we assess OD.

Key Points:

- COVID-19 often cause prolonged olfactory dysfunction.
- This study evaluated the relative burden of the COVID-19-related disease in a single-centered cohort of POD patients.
- COVID-19-related POD was diagnosed serologically.
- In the COVID-19 era, the local burden of POD increased two-fold.
- It is important to use pleiotropic approach and robust measures, when we assess OD.

Introduction:

Among other etiologies, such as the airway obstruction and neural disorders, viral illnesses have always been the most common cause of prolonged olfactory dysfunction (POD). The emerging coronavirus disease 2019 (COVID-19), which is now increasingly recognized to be accompanied by an impairment in odor sensation, may have contributed to an increase in the overall prevalence of POD, but to what extent is unknown. While once thought to have a good prognosis, recent reports on long-term follow-up data estimate that a significant proportion of patients with the COVID-19-related odor sensation impairment, ranging from 1% to 48%[1,2], develop POD. In this study, we evaluated the relative burden of the COVID-19-related disease in a single-centered cohort consisting of patients with POD of previously undetermined etiology. The clinical characteristics of COVID-19-related POD were compared with those of POD from other etiologies.

Methods:

This study was cross-sectional study, and took place at "Blind for review".

Participants of the study were 16 people (11 of 16 were women, 69%), with a median age of 42 years (interquartile range 15–83), self-reporting of prolonged (lasting more than four weeks) impairment in odor sensation, and visiting the outpatient clinic at "Blind for review" from December 2020 to January 2022. Clinical data from their medical records were collected, including symptoms, laboratory variables, endoscopy and CT findings, and final diagnosis. The outcome was the pattern and severity of odor sensation impairment. The following methods were used to assess the outcome qualitatively and quantitatively. (i) Participant completed the Self-Administered Odor Questionnaire (SAOQ), which was developed by the Japan Rhinology

Society to assess an individual's ability to identify 20 different odorants. The percentage of correct answers indicated the degree of impairment[3]. (ii) The Open Essence (OE) smell identification card assessed an individual's ability to identify 12 different odorants familiar to the Japanese population. The number of correct answers reflected the severity of impairment[4]. (iii) Intravenous olfactometry (IO) measures the latency in recognizing the garlic-like odor and the duration of its perception, following an injection of thiamine propyl-disulfide. The worst score was used for analysis of participants who were assessed longitudinally at multiple time points. This study was approved by the institutional review board of "Blind for review". All participants have given their informed consent to participate.

Participants were assessed for the etiology of their POD. They were tested for anti-SARS-CoV-2 antibodies using the Elecsys Anti-SARS-CoV-2 assay (Roche, Basel, Switzerland). One participant with a "high-negative" result was further tested with the Architect SARS-CoV-2 IgG and IgG II Quant (Abbott, Chicago, Illinois, USA) immunoassays, targeting nucleocapsid and spike proteins, respectively. In the absence of a SARS-CoV-2 vaccination, the participant had "positive" results on both confirmatory immunoassays and was thus classified as having a positive serology. Participants with positive serology against SARS-CoV-2 were diagnosed with COVID-19-related POD. CT was used to diagnose paranasal sinus abnormalities. Non-SARS-CoV-2 post-viral POD was defined as a persistent impairment in odor sensation after recovery from acute rhinitis. Participants with POD were otherwise classified as "idiopathic."

The Strengthening the Reporting of OBservation studies in Epidemiology statement was used to report the findings.

Results:

Surprisingly, 9 of 16 (56%) of our cohort were serologically diagnosed with COVID-19-related POD. Other causes of POD included eosinophilic sinusitis (1), non-SARS-CoV-2 post-viral (2), and idiopathic (4). COVID-19-related POD patients were more likely to expwrience gustatory dysfunction than other miscellaneous PODs (6 of 9, 67% vs. 2 of 7, 29%). Despite not reaching statistical significance due to the limited sample size of the study, the degree of POD assessed by all three presented methods showed a trend toward increased severity for COVID-19-related disease (Table). When the patterns of impairment in OE odor discrimination were evaluated odorant by odorant, patients with COVID-19 were more frequently non-recognizable of menthol (4 of 8, 50% vs. 2 of 7, 29%).

Discussions:

In the contemporary COVID-19 era, the local burden of POD increased a surprising two-fold. Thus, COVID-19-related POD has indeed caused a non-negligible threat to the quality of life of the affected, as well as the Japanese public health system. Surprisingly, 5 of 7 COVID-19 patients lacked an acute diagnosis and were later diagnosed serologically. This may reflect the local situation in Japan, which once faced a severe shortage of molecular diagnostics. Comparisons to preceding findings from the UK, also indicated that seroprevalence of the COVID-19-related impairment in the odor sensation[5]had relied on subjective assessment of impairment lacking quantitative data. Our findings confirmed the previously reported magnitude of an increase in the disease burden, by further using robust indices of both qualitative and quantitative features (SAOQ, OE, IO).

The intranasal trigeminal system, like the gustatory system, is now recognized as a frequent neuronal target of the SARS-CoV-2[6]. OE, which is widely used in Japan, contains menthol as one of the 12 odorants and allows for the screening of any coexisting intranasal trigeminal dysfunction. In line with previous research, non-recognition of the cooling sensation in menthol, which is an expression of trigeminal dysfunction, rather than olfactory dysfunction, was more commonly observed in our cohort of patients with COVID-19-related POD. However, some participants reported a subjective improvement in their POD during interviews, despite inconsistent unimprovement in the OE scoring. This could be due to the patient's difficulty in distinguishing trigeminal sensation from olfaction. Thus, assessing POD in the clinic must use pleiotropic approaches and robust measures. The prognostic value of differentiating the POD etiologies in the era of COVID-19 shall be studied further in the future.

Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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