Ref: Ro J Infect Dis. 2020;23(2)
DOI: 10.37897/RJID.2020.2.13

Anosmia – an independent predictor in the persistence of SARS-CoV-2 infection?

Stefan Lazar[1,2], Daniel Codreanu[2], Adela Neculai[2], Loredana Musetescu[2], Carmen Apostol[2], Andra Carnaru[2], Marius Serbanoiu[2], Simina Dinu[2], Ariana Marcu[2], Sorina Vasile[2], Emanoil Ceausu[2,3], Simin-Aysel Florescu[1,2]

[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]"Dr. Victor Babes" Clinical Hospital of Infectious and Tropical Diseases, Bucharest, Romania
[3]Academy of Medical Sciences of Romania

ABSTRACT

Knowledge about the manifestations of SARS-CoV-2 infection is constantly enriching as more reports of the disease appear. Anosmia, which had not been linked to SARS-CoV-2 infection at the beginning of the pandemic outbreak, later became, through evidence, an important symptom of the disease. In the presented paper we studied the correlation between this symptom and the complex pathological context of patients. Using statistical analysis we demonstrated that anosmia can be considered an independent predictor for the extended period of hospitalization in patients in the study group.

Keywords: SARS-CoV-2, anosmia, smell, myalgias, independent predictor, infection days, hospitalization days

INTRODUCTION

SARS-CoV-2 infection put the medical world in front of special challenges due to its novelty, the pleomorphism of the symptoms, and the complications presented. Observations and studies conducted around the world rapidly changed the perspective on this condition, enriching knowledge about the disease in a evolutionary way. Although in the first articles, fever, cough and dyspnea were the most important elements for the definition of clinical case [1,2], later other symptoms completed the clinical picture of the disease. Anosmia was recognized to be a common symptom in all current studies, although did not appear in the first reports of researchers in China [3], and was initially reported anecdotally on social networks during February and March 2020. Recent studies report that olfactory disorders appear with a frequency between 38-86% [4,5,6]. This big variation between percentages can be explained by the difficulty of making an objective assessment of this symptom, the data presented in most published works being obtained subjectively by self-assessment of patients. The mechanism of anosmia is not yet fully understood, but most authors believe that there is no neuronal damage, and the mechanism is most likely in correlation with local inflammation of the olfactory epithelium. Unlike neurons that do not have the ACE2 receptors that are involved in the intracellular penetration of the virus, olfactory epithelial cells express large amounts of this receptor [7]. These findings indicate that olfactory dysfunction is an important symptom of COVID-19 [8] and can be considered a highly suggestive marker of infection in the population.

The present paper evaluates anosmia in correlation with the symptomatology and the severity of the dis-

Corresponding author:
Stefan Lazar, MD, PhD student
E-mail: stefan.d.lazar@gmail.com

Article History:
Received: 31 May 2020
Accepted: 20 June 2020

ease, and also with the duration of hospitalization, comparing our results with data from the literature.

OBJECTIVE

Evaluating anosmia as a predictive factor of evolution of SARS-CoV-2 infection.

MATERIALS AND METHODS

Cluster composition

We used the medical data of some patients hospitalized in "Dr. Victor Babes" Hospital for Infectious and Tropical Diseases in Bucharest, after signing an informed consent. We considered eligible 100 patients hospitalized in Clinical Department II of Adult Infectious Diseases from 28th of March 2020, when the first patients infected with SARS-CoV-2 were admitted here. The exclusion criteria were: patients who did not sign the informed consent and those who could not give information on the sense of smell. Thus, 8 patients were excluded: 2 children under 5 years of age and 6 elderly patients with degenerative neuropsychiatric disorders, the group being completed with the following 8 chronologically hospitalized patients, who met the inclusion criteria. The evaluation method was through direct questioning and by offering to smell strong odorizing substances (alcohol-based disinfectants), patients being invited to evaluate both the presence of the sense of smell and its quality.

Statistical methods used

Patient data was collected in an Excel file and statistical processing was performed using IBM SPSS v.20 and Medcalc® – the online version. Scalar data (continuous data) were analyzed with the F test (for those with normal distribution) and with non-parametric tests for those with non-normal distribution. Categorical data were analyzed with the Pearson-Chi square test (for 2x2 type tables) and with the Fisher accuracy test (for tables larger than 2x2). To identify the risk factors, linear regressions (for continuous data) and binomial logistic regressions (dichotomous data) were performed. The critical probability level for statistical tests was $p < 0.05$.

RESULTS AND DISCUSSIONS

The studied group consisted of 49 women and 51 men, aged between 5 and 72 years, the median age being 41 years. The median age was 41 years for women and 40 for men. The age distribution is shown in figure 1.

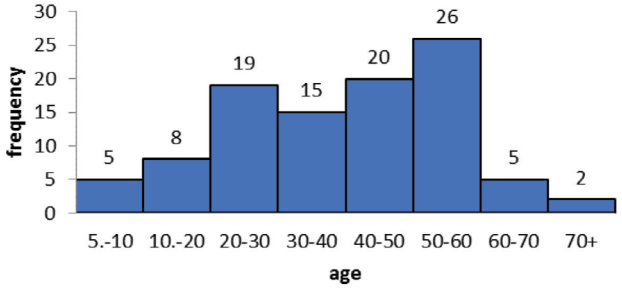


FIGURE 1. *Distribution by age groups*

In symptomatic patients, the clinical onset was 4 days before the time of hospitalization (median values). In the asymptomatic patients group, the clinical onset was considered the first day of hospitalization, which most often corresponded with the day that these patients were tested positive for SARS-CoV-2.

The symptoms described by patients at the time of clinical onset or occurring later are summarized in figure 2.

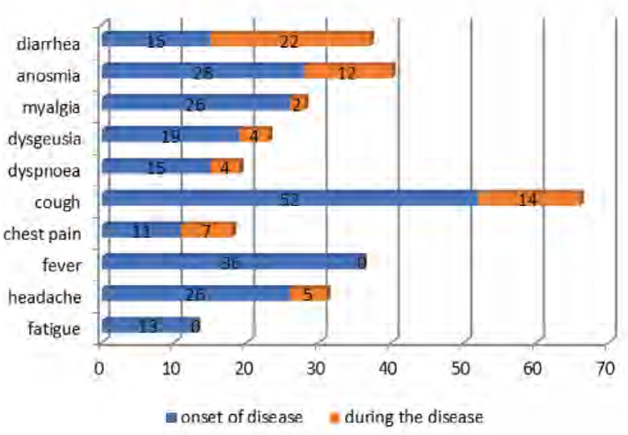


FIGURE 2. *Main symptoms in hospitalized patients*

We found that cough was the most common inaugural symptom in the study group, followed by fever, anosmia, headache and myalgia. In patients with fever and fatigue, these were found only at the onset of the disease, while the rest of the symptoms appeared both at the beginning and during the course of the disease. Overall, the symptoms encountered were (ordered by frequency): cough (66%), anosmia (40%), diarrhea (37%), fever (36%), headache (31%), and myalgias (28%). In the studied group, asthenia was encountered with the lowest frequency (13%). Compared with other studies [3,9,10] we found that fever

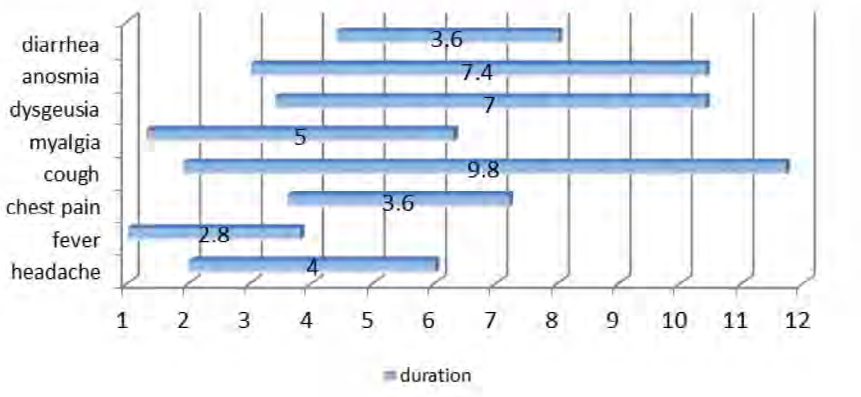


FIGURE 3. *Appearance and persistence of the main symptoms (number of days – average values)*

and asthenia occurred with a lower frequency in our group, while diarrhea and headache had a higher frequency of occurrence. Anosmia and dysgeusia were within the percentage ranges described in the literature.

Next, we evaluated the days of occurrence and the persistence of the main symptoms in the patients studied. Below we have represented graphically, calculating the average values, the days of appearance and the persistence of the main symptoms (figure 3).

As expected, the main symptom (cough) had the longest period of manifestation (9.8 days), followed by anosmia and dysgeusia with an average duration of about 7 days, both appearing about 3 days after onset. The last element that appeared chronologically in the evolution of the disease seems to be diarrhea, more than 4 days after the onset. The appearance of this symptom may have a mixed causality, both in the context of SARS-CoV-2 infection and of hydroxychloroquine administered according to the national treatment protocol [11,12].

Being the second symptom in frequency and persistence, we studied anosmia in correlation with the other symptoms and with the evolution of the disease (table 1).

The table 1 shows that the age and body mass index of patients (BMI) do not influence the appearance of anosmia, but females are much more affected than males, an observation that has been found in the literature [5,6]. Regarding females, neither age (p = 0.685), nor BMI (p = 0.253) correlated with anosmia. In addition, we compared patients with BMI over 31 with those with BMI below 25 (obese vs. normal weight), but without showing significant differences.

We studied the presence of anosmia in correlation with pre-existing comorbidities, which is shown in the table below. Depending on the presence of anosmia, we compared patients with at least one comorbidity with those without comorbidities, later detailing in the case of patients with the most important comorbidities (table 2).

TABLE 2. *Comorbidities vs. anosmia*

Variable / population, N = 100	Normosmia n = 60	Anosmia n = 40	p-value
Comorbidities (n, %)	39(65.0)	17(42.5)	**P = 0.026**
Hypertension (n, %)	14(23.3)	6(15.0)	P = 0.307
DM (n, %)	5(8.3)	2(5.0)	P = 0.522

Other comorbidities (neoplasms, autoimmune diseases, chronic hepatitis etc.) were not taken into account due to the small number of patients, not statistically interpretable in our group. The table above shows that patients without comorbidities had more frequent anosmia (p = 0.026), but, taken separately, the presence of diabetes mellitus (DM) or hypertension was not statistically significant.

TABLE 1. *General characteristics of the group*

Variable / population, N = 100	**Normosmia n = 60**	**Anosmia n = 40**	**p-value**
General age (mean, CI 95%)	40.13(35.53-44.74)	36.48(32.04-40.91)	P = 0.276
Gender n (%)	M37(61.7), F23(38.3)	M12(38.3), F28(70.0)	**P = 0.002**
BMI (kg/mp)	26.80 (25.15-28.45)	26.08(24.32-27.83)	P = 0.546

Next, we evaluated the presence of anosmia in correlation with the severity of the clinical disease. For this, we divided the patients according to severity from 0 = asymptomatic to 3 = severe evolution. The studied group did not include critical patients. We did not find statistically significant differences in these categories (p = 0.546).

Taking into account the data from the literature [13,14], we followed the biological samples considered to be predictors of severe evolution: lymphocytes, neutrophil / lymphocyte ratio (N / L), LDH value, inflammatory syndrome (CRP), D-dimer value and of interleukin-6. We considered their values at hospitalization and followed them during the first 10 days after the onset of the disease, which coincided with the average period of anosmia. ANOVA analyzes of these values found no statistically significant differences between patients with or without anosmia. Correlating these results with the clinical classification of patients, it results that anosmia was not predictive for the clinical evolution (favorable or not) of the patients in the studied group.

Since anosmia is considered to be a direct consequence of the presence of the virus in the olfactory mucosa, which is a route of penetration of many viral infections to the central nervous system [15], we compared the headache with a significant duration (over 48 hours) with the presence or not of anosmia in the hypothesis of a possible subclinical encephalitic involvement. In the statistical analysis we did not find a significant correlation between these two symptoms (p = 0.226). It should be noted that none of the patients in the study group showed neurological changes during hospitalization.

We also evaluated the other symptoms described by patients (fig. 2), which appeared both at the beginning and during the disease, but even in these situations we did not find correlations with statistical significance.

In our study we evaluated both the hospitalization period and the period until we obtained negative SARS-CoV-2 RT-PCR samples depending on the main symptoms described both at the clinical onset and at the time of hospitalization. Regarding the period of evolution of the infection and the period of hospitalization, we found that anosmia was a factor in prolonging the period of hospitalization and the number of days until we obtained negative RT-PCR samples, both values having statistical significance, while in the case of myalgias, the statistical significance was present only in the case of the hospitalization period (table 3). The other symptoms do not appear to significantly influence the periods of infection or hospitalization.

TABLE 3. *Period of hospitalization / negation of samples*

Variable / population, N = 100	**Normosmia n = 60**	**Anosmia n = 40**	**p-value**
Hospitaliza ys (mean, CI95%)	12.50 (11.48-13.52)	14.33 (13.19-15.46)	**P = 0.021**
Days un taining nega e samples (mean, CI95%)	15.50 (14.21-16.79)	17.63 (16.01-19.24)	**P = 0.040**
	No myalgia n = 72	**Myalgia N = 28**	
Hospitaliza ys (mean)	12.71	14.57	**P = 0.031**
Days un taining nega e samples (mean)	15.85	17.64	P = 0.114

The following table, which shows the averages of the calculated days, shows that in patients who had both symptoms present, the periods were longer compared to those who presented only anosmia, this not necessarily compared to patients who had only myalgias (table 4).

TABLE 4. *Mean number of hospitalization days / days until negative sample*

Variable	**Myalgia + Anosmia**	**Anosmia**	**P-value**
Hospitaliza ys	16.15	13.44	**P=0.022**
Days un a e sample	20.23	16.37	**P=0.021**
	Myalgia + anosmia	**Myalgia**	
Hospitaliza ys	13.14	12.30	P=0.493
Days un a e sample	15.43	15.52	P=0.952

Because only myalgias and anosmia had statistical significance, following bivariate analysis, only these symptoms were selected, to see which of them influences as an independent predictor the number of hospitalization days or obtaining a negative RT-PCR result. For this, linear regression equations were performed for each of the periods:

1. Number of days of hospitalization (days of anosmia and days with myalgias). The linear regression equation is not statistically significant (p = 0.066), the two predictors not statistically significantly influencing the result (anosmia p = 0.060, myalgias p = 0.710).

2. Number of days until negativity (days with anosmia and days with myalgias). The regression equation is not statistically significant (p = 0.815), the two predictors not statistically significantly influencing the result (anosmia p = 0.740, myalgias p = 0.532).

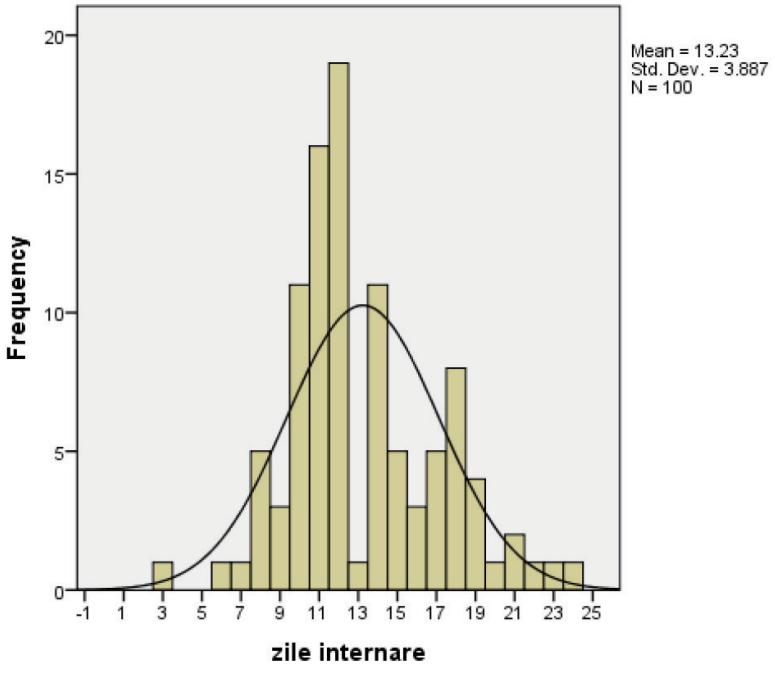
Because the average values of the days of presence of anosmia and myalgias do not describe from a statistical perspective the number of days of hospitalization and the number of days until obtaining a negative sample, we performed a binomial logistic regression. The days of hospitalization or evolution of the infection were ordered by categories, taking into account the distribution of the number of cases so that the group is distributed as evenly as possible. Thus the number of days of hospitalization was divided into ≤ 12 and > 12 and the number of days until obtaining a negative sample was divided into ≤15 and >15.

Following the binomial logistic regression to identify independent predictors of prolongation of hospitalization days, it is demonstrated that both the presence of anosmia (p = 0.008) and myalgias (p = 0.040) increases the possibility that the patient has a hospital stay longer than 12 days.

Following the binomial logistic regression to identify independent predictors of prolongation of the infection period, it was identified that anosmia (p = 0.011) increases the possibility that the patient will be negative in more than 15 days. Myalgias did not show a statistically significant value (p = 0.515).

CONCLUSIONS

In the group of 100 patients evaluated in the present study, we found the presence of the same symptoms found in the literature, but with different frequencies. If cough is a common symptom, in the case of fever the percentage in our group was lower (36% vs. 43%). We found a higher frequency of patients with diarrhea (37% vs. 19%) compared to the data in the literature. Regarding anosmia, the data presented in other studies are very variable, the percentage in the present study being 40%, a percentage that falls

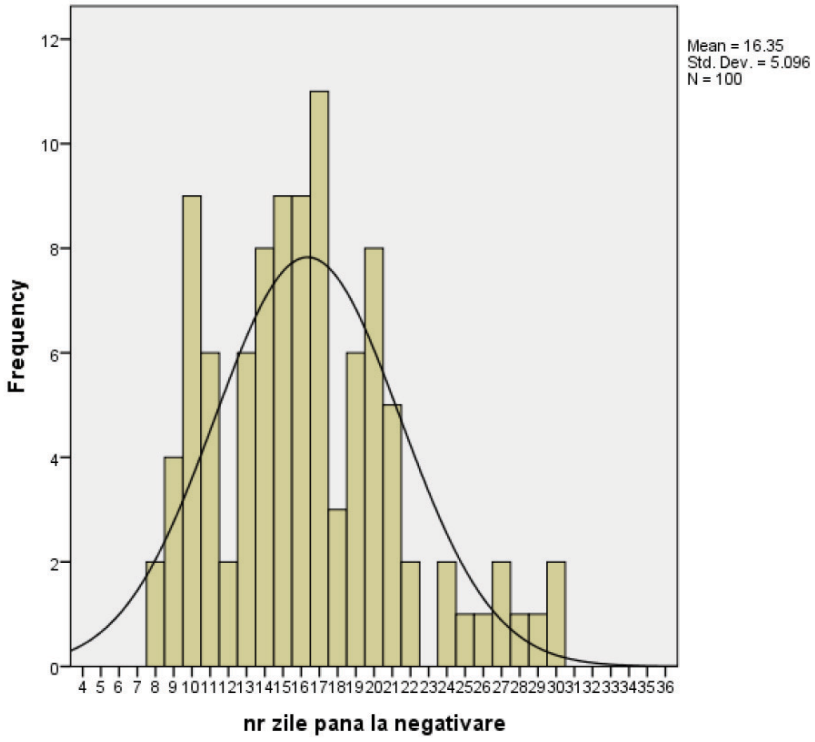


Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	mialgie_da_nu(1)	-.979	.476	4.228	1	.040	.376	.148	.955
	categdebaza(1)	-1.155	.436	7.032	1	.008	.315	.134	.740
	Constant	1.093	.481	5.167	1	.023	2.982		

a. Variable(s) entered on step 1: mialgie_da_nu, categdebaza.

FIGURE 4A,B. *Logistic regression – categories of hospitalization days*



Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	mialgie_da_nu(1)	-.306	.469	.424	1	.515	.737	.294	1.848
	categdebaza(1)	-1.098	.434	6.407	1	.011	.334	.143	.781
	Constant	1.058	.478	4.901	1	.027	2.880		

a. Variable(s) entered on step 1: mialgie_da_nu, categdebaza.

FIGURE 5A,B. *Logistic regression – days until negativity*

within the reports in the literature. Although the study group was relatively small, it can be deduced that the patients studied had some peculiarities compared to those described in other regions of the world.

Discussing anosmia, we found that this symptom was more common in women without comorbidities, other characteristics (age, BMI) having no influence. Regarding the evolution of the disease, anosmia does not seem to be a favorable indicator, nor a predictor of severity, both by global assessment and by comparison with biological factors considered as predictors of severity.

The hospitalization period was prolonged in patients with myalgia and anosmia, while the period of infection was prolonged in the context of anosmia. Since the hospitalization period depends on the date of admission, which has a fairly important variability, we consider that the period from the onset of symptoms until obtaining negative RT-PCR SARS-CoV-2 samples is a better indicator for the period of infection. In this context, by logistic regression, only anosmia showed statistical significance. For this reason, we can consider that the presence of anosmia is an independent predictor of prolongation of the infection period in the studied group.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Centers for Disease Control and Prevention. 2019 Novel coronavirus, Wuhan, China. Information for Healthcare Professionals. https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html.
2. World Health Organization. Novel Coronavirus (2019-nCoV) technical guidance. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance.
3. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
4. Giacomelli A, Pezzati L et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis.* 2020.

5. Spinato G, Fabbris C et al. Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. *JAMA*. 2020;323(20):2089-2090.
6. Lechien JR, Chiesa-Estomba CM et al. Loss of Smell and Taste in 2013 European Patients With Mild to Moderate COVID-19. *Ann Intern Med*. 2020.
7. Hoffmann M, Kleine-Weber H, Schroeder S et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280.e8.
8. Pellegrino R, Cooper KW, Di Pizio A, Bhutani S, Parma V. Corona viruses and the chemical senses: Past, present, and future. *OSF Preprints,* 15 Apr. 2020.
9. Stokes EK, Zambrano LD et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(24):759.
10. Goyal P, Choi JJ, Pinheiro LC et al. Clinical Characteristics of COVID-19 in New York City. *N Engl J Med.* 2020;382:2372.
11. Ministerul Sănătăţii. Protocolul de tratament al infecţiei cu virusul SARS-Cov-2, din 26.03.2020.În vigoare de la 27 martie 2020. Publicat în Monitorul Oficial, Partea I nr. 253 din 27 martie 2020. Formă aplicabilă la 30 martie 2020.
12. Ministerul Sănătăţii. ORDIN nr. 860 din 21 mai 2020 privind modificarea anexei la Ordinul ministrului sănătăţii nr. 487/2020 pentru aprobarea protocolului de tratament al infecţiei cu virusul SARS-Cov-2. Monitorul Oficial nr. 432 din 22 mai 2020.
13. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* 2020;395:1054.
14. Wu C, Chen X, Cai Y et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020.
15. https://www.sciencealert.com/covid-19-can-target-the-entire-nervous-system-causing-dizziness-and-delirium.