Long-COVID olfactory dysfunction: allele E4 of apolipoprotein E as a possible protective factor

Disfunção olfativa na COVID longa: o alelo E4 da apolipoproteína E como um possível fator protetor

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Arq. Neuro-Psiquiatr. 2024;82(9):s00441788272.

Abstract

Background Olfactory dysfunction (OD) represents a frequent manifestation of the coronavirus disease 2019 (COVID-19). Apolipoprotein E (APOE) is a protein that interacts with the angiotensin-converting enzyme receptor, essential for viral entry into the cell. Previous publications have suggested a possible role of APOE in COVID-19 severity. As far as we know, no publications found significant associations between this disease's severity, OD, and APOE polymorphisms (E2, E3, and E4).

Objective To analyze the epidemiology of OD and its relationship with APOE polymorphisms in a cohort of Long-COVID patients.

Methods We conducted a prospective cohort study with patients followed in a post-COVID neurological outpatient clinic, with OD being defined as a subjective reduction of olfactory function after infection, and persistent OD being defined when the complaint lasted more than 3 months after the COVID-19 infection resolution. This cross-sectional study is part of a large research with previously reported data focusing on the cognitive performance of our sample.

Results The final sample comprised 221 patients, among whom 186 collected blood samples for APOE genotyping. The persistent OD group was younger and had a lower hospitalization rate during the acute phase of the disease ($p < 0.001$). Furthermore, the APOE variant E4 allele frequency was lower in this group ($p = 0.035$). This study evaluated OD in an outpatient population with COVID-19. In the current literature on

Keywords
- COVID-19
- Olfaction Disorders
- Postacute COVID-19 Syndrome
- Anosmia
- Apolipoproteins E

received
April 19, 2023
received in its final form
March 19, 2024
accepted
May 27, 2024

DOI https://doi.org/10.1055/s-0044-1788272.
ISSN 0004-282X.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

this disease, anosmia is associated with better clinical outcomes and the E4 allele is associated with worse outcomes.
Conclusion Our study provides new information to these correlations, suggesting APOE E4 as a protective factor for OD.

Resumo

Antecedentes A disfunção olfatória (DO) é uma manifestação frequente da doença do coronavírus 2019 (COVID-19). A apolipoproteína E (APOE) é uma proteína que interage com o receptor da enzima conversora de angiotensina, essencial para a entrada viral na célula. Publicações anteriores sugeriram um possível papel da APOE na gravidade da COVID-19. Até onde sabemos, nenhuma publicação encontrou associações significativas entre a gravidade dessa doença, DO e polimorfismos da APOE (E2, E3 e E4).
Objetivo Analisar a epidemiologia da DO e sua relação com os polimorfismos do gene APOE em uma coorte de pacientes com COVID longa.
Métodos Um estudo de coorte prospectiva com pacientes acompanhados em ambulatório neurológico pós-COVID, com DO sendo definida como uma redução subjetiva da função olfativa após a infecção e a DO persistente sendo definida quando a queixa durou mais de 3 meses após a resolução da infecção por COVID-19. Este estudo transversal é parte de uma pesquisa maior com dados anteriormente relatados, focando na performance cognitiva dos pacientes.
Resultados Foram selecionados 221 pacientes para esse estudo, dos quais 186 haviam coletado amostras de sangue para genotipagem APOE. O grupo DO persistente foi mais jovem e apresentou menor taxa de internação na fase aguda da doença ($p < 0{,}001$). Além disso, a frequência do alelo E4 da APOE foi menor nesse grupo ($p = 0{,}035$). Este estudo avaliou a DO em uma população com COVID longa. Na literatura atual sobre essa doença, a anosmia está associada a melhores desfechos clínicos e o alelo E4 está associado a piores desfechos.
Conclusão Nosso estudo acrescenta novas informações a essas correlações, sugerindo a APOE E4 como um fator de proteção para DO.

Palavras-chave
- COVID-19
- Transtornos do Olfato
- Síndrome de COVID-19 Pós-aguda
- Anosmia
- Apolipoproteínas E

INTRODUCTION

Postviral anosmia is a dysfunction of the olfactory system. It constitutes a common etiology of olfactory dysfunction (OD) among adults, accounting for around 11 to 40% of cases, with a greater incidence in females. Typically, this condition manifests between the fourth and eighth decades of life following an upper respiratory tract infection.[1,2] The anosmia represents a frequent manifestation of the coronavirus disease 2019 (COVID-19), with research indicating a range of incidence rates between 11 and 84% during the acute phase of the illness.[3]

Anosmia may manifest during the acute phase of the illness or beyond 12 weeks from the onset, either in isolation or accompanied by other symptoms, such as cognitive impairment, sleep disturbances, and headache.[3,4] For instance, a study with 138 outpatients identified that 7.2% of patients assessed by olfactory tests[5] persisted with smell alterations after 60 days of illness. Furthermore, a prospective observational study with 4,182 COVID-19 patients identified anosmia as the third most prevalent symptom in Long-COVID through patient self-report.[6] Hintschich et al. evaluated 303 patients and showed that smell and taste complaints persisted objectively after 6 months of infection in 18 and 32% of patients respectively.[7] Likewise, a systematic review by Jafar et al. selected studies that evaluated the recovery of anosmia in patients after 1, 2, and between 3 and 6 months after COVID-19, showing the persistence of hyposmia in 37.4, 36.7, and 36.5% of patients[8] respectively.

Apolipoprotein E (APOE) is a protein that results from the transcription of the APOE gene, which presents three frequent allelic variants (E2, E3, and E4).[9] This protein plays a crucial role in the cholesterol metabolism and interacts with the angiotensin-converting enzyme (ACE2) receptor, a key factor in the binding process of the viral spike protein, thereby enabling its cellular entry.[9] Previous publications have suggested a possible role of APOE in conferring protection against COVID-19 or its more severe clinical manifestations.[10,11] To our knowledge, no published studies have reported significant correlations between APOE polymorphisms, olfactory dysfunction, and COVID-19 severity.

We aimed to analyze the epidemiology of OD and its relationship with APOE polymorphisms in a cohort of Long-COVID patients.

METHODS

Subjects

We conducted a prospective cohort study involving patients being followed up at a post-COVID neurological outpatient clinic at the Walter Cantídio University Hospital in Fortaleza, located in the Northeastern region of Brazil. Patient recruitment occurred between July and August 2020 and was performed in the context of our research group's ongoing prospective longitudinal investigation.

Eligibility criteria for participation included a confirmed diagnosis of COVID-19 within the preceding 12 months. The study inclusion criteria required that patients be aged between 18 and 90 years old, with a positive nasal swab RT-PCR or serological test for COVID, and post-COVID neurological symptoms that persisted for more than 3 months from the onset and were referred to our outpatient clinic. The exclusion criteria were absence of neurological symptoms, negative test for COVID-19, pregnancy, need of oxygen support after acute COVID-19 infection, and patients with an operative approach in the period between the acute infection and the study evaluation.

In this study, OD was defined as a subjective reduction in olfactory function following a COVID-19 infection and was confirmed by means of a simple olfactory examination involving the use of coffee as a test odor in both nostrils. The duration of disfunction was estimated from the patient's clinical history and the day of evaluation. We defined persistent OD as persistent complaints for more than 3 months following the resolution of COVID-19 infection. This cross-sectional study is an integral part of a larger study that had previously reported data on the cognitive performance of our sample.[12]

The clinical evaluation was conducted by two neurologists, who worked independently from each other. The clinical evaluation and identification forms were the same for all patients. Several patient characteristics were recorded during the evaluation, including age, sex, years of schooling, initial neurological symptoms, hospitalization, type of COVID-19 test performed, complementary exams, comorbidities, history of alcohol abuse, and tobacco use. The Medical Research Council (MRC) dyspnea scale was utilized to assess dyspnea levels before and after the COVID-19 infection. We also looked for control patients without COVID-19 infection but, unfortunately, the country was undergoing a severe health crisis during the pandemic, and patients without the disease were afraid to participate in the research within a hospital environment.

APOE genotyping analysis

The patient's blood specimens were gathered in EDTA containers per the manufacturer's directives. Subsequently, genomic DNA was derived from leukocytes in peripheral blood using the Invitrogen commercial PureLink Genomic DNA Mini Kit (ThermoFisher Inc., Waltham, MA, USA). The APOE genotypes were ascertained through real-time polymerase chain reaction (qPCR), utilizing the TaqMan SNP Genotyping Assay (ThermoFisher Inc.) allelic discrimination system.[13] For this purpose, we utilized probes under the manufacturer's supplied sequences: C____904973_10 (rs7412) and C___3084793_20 (rs429358), while considering the data provided in the catalog number 4351379, and similar techniques described in previous literature. All evaluations were executed using the QuantStudio(Applied Biosystems, Foster City, CA, USA) real-time PCR platform.

Statistical analysis

Categorical data were presented as absolute counts and percentages. The associations between categorical data were assessed using chi-square tests. The normality of continuous data was first checked using the Kolmogorov-Smirnov test. Normally distributed data were reported as mean $\pm$ standard deviation (SD), while non-normally distributed data were expressed as median and interquartile range. The one-way analysis of variance (ANOVA) with the Tukey post-test was used for normal data, and the Kruskal-Wallis test with the Dunn post-test was utilized for non-normal data. The data were analyzed with the IBM SPSS Statistics for Macintosh (IBM Corp., Armonk, NY, USA) software, version 23.0. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 241 individuals were subjected to screening procedures, out of which 20 were deemed ineligible for inclusion in the study (10 for absence of neurological symptoms and 10 for testing negative for COVID-19). Thus, the final sample size comprised 221 patients, among whom 186 provided blood specimens for APOE genotyping, and all subsequent analyses were performed on this subset. The patients were evaluated at an average of 4.5 months after diagnosis.

►**Table 1** describes patients' clinical and sociodemographic characteristics dichotomized according to OD. Patients were predominantly female (65.4%). The OD group was characterized by younger age and a lower rate of hospitalization during the acute phase of COVID-19 infection, as indicated by statistical analysis ($p = 0.003$). No significant differences were observed between the OD and non-OD groups in terms of depression and cognitive impairment.

An independent analysis was conducted for the group of 29 patients without APOE genotyping to determine if the analyzed group was representative of the cohort. Despite the small sample size, the correlations of age ($p = 0.03$) and hospitalization ($p = 0.02$) remained statistically significant.

►**Table 2** describes olfactory dysfunction in comparison to patients' APOE polymorphism. In both groups, the E3/E3 genotype was found to be the most prevalent. No significant intergroup differences were observed concerning this particular genotype. However, the frequency of the E4 allele was found to be lower in the OD group, a finding that reached statistical significance ($p = 0.035$).

DISCUSSION

This study evaluated OD in an outpatient population with COVID-19. Our patients had lower hospitalization incidence,

Table 1 Comparison of demographics and clinical evaluation between patients with and without olfactory dysfunction

		Olfactory dysfunction		*p*-value
		No ($n = 133$)	Yes ($n = 53$)	
Gender: n (%)	Female	87 (65.4)	36 (67.9)	0.744*
	Male	46 (34.6)	17 (32.1)	
Age: mean(±standard deviation)		49(±14.4)	41.1(±13.4)	< 0.001**
Years of schooling: n (%)	0	4 (3.0)	0	0.031*
	1–4	6 (4.5)	1 (1.8)	
	5–8	22 (16.5)	3 (5.7)	
	9–12	38 (28.6)	11 (20.8)	
	> 12	63 (47.4)	38 (71.7)	
Cognitive impairment: n (%)	Normal	39 (29.4)	22 (41.5)	0.110*
	Cognitive decline	94 (70.6)	31 (58.5)	
Hospitalization: n (%)	No	86 (64.7)	50 (94.3)	0.003*
	Yes	47 (35.3)	3 (5.7)	
Depression: n (%)	No	117 (88.0)	44 (83.0)	0.798*
	Yes	16 (12.0)	9 (17.0)	

Notes: *Chi-squared test; **Student *t*-test.

were younger, and had a lower APOE E4 allele frequency when compared with the non-OD group.

In our sample, patients who experienced persistent OD had a lower incidence of hospitalization, which is consistent with prior research studies.[14–16] Mendonça et al. evaluated 261 patients prospectively and showed that patients with mild flu-like syndrome had olfactory dysfunction more frequently (OR = 4.63) than those with severe COVID-19.[14] In a retrospective study, Talavera et al. evaluated 576 patients in whom OD was associated with lower mortality (OR = 0.180).[15] Furthermore, a systematic review by von Bartheld et al. included 104 studies and reported a lower prevalence of OD in hospitalized patients.[16]

Our OD group was younger, which is also in agreement with previous studies.[16,17] Giacomelli et al. evaluated 59 patients hospitalized with COVID-19, and those with

Table 2 Comparison of APOE polymorphism between patients with and without olfactory dysfunction

		OD		*p*-value*
		No ($n = 133$)	Yes ($n = 53$)	
APOE: n (%)	E2/E2	1 (0.8)	0	0.100
	E2/E3	11 (8.3)	4 (7.5)	
	E2/E4	0	1 (1.9)	
	E3/E3	81 (60.9)	41 (77.4)	
	E3/E4	36 (27.1)	7 (13.2)	
	E4/E4	4 (3.0)	0	
Alleles: n (%)				
E2	No	121 (91.0)	48 (90.6)	0.930
	Yes	12 (9.0)	5 (9.4)	
E3	No	5 (3.8)	1 (1.9)	0.514
	Yes	128 (96.2)	52 (98.1)	
E4	No	93 (69.9)	45 (84.9)	0.035
	Yes	40 (30.1)	8 (15.1)	

Abbreviations: APOE; apolipoprotein E; OD, olfactory dysfunction.
Note: *Chi-squared test.

olfactory and taste disorders were younger (median 56 vs. 66 years, $p = 0.035$).[18] In a systematic review, besides age, other factors associated with a higher probability of OD were Caucasian ethnicity and being female.[16]

Our study found that patients with OD had a lower APOE E4 allele frequency. The study of APOE polymorphism in post-COVID-19 OD patients is essential, since this disfunction and APOE genotype are known risk factors for neurodegenerative diseases, notably the Alzheimer disease (AD).[19,20] To date, no other study has evaluated such an association. However, Manzo et al. suggested investigating APOE E4-positive patients, post-COVID-19 hyposmia, and future neurodegenerative diseases' subsequent onset.[21] This association deserves to be investigated since Dong et al. found an association between mild cognitive impairment (MCI), the presence of amyloid and neurodegeneration biomarkers, and OD, postulating this disfunction as a potential biomarker of prodromal dementia.[22]

Numerous theories have been proposed to explain the onset of OD following COVID-19, encompassing factors such as obstruction of odorant transit to the olfactory receptors due to nasal congestion and damage to the olfactory bulb resulting from cytokine release.[23] Nasal congestion was postulated because of the resemblance of OD presence post-COVID-19 and after other viral infections.[24,25] For example, Chapurin et al. demonstrated in a case-control study that there was no significant difference between objective scores in olfactory tests between the post-COVID-19 OD groups and other viral infections.[25] However, OD patients post-COVID-19 had no symptoms of nasal congestion and rhinorrhea when compared with other viral infections.[24] Olfactory bulb injury and atrophy were described in COVID-19 patients, possibly related to astrogliosis and cytokine release in the acute phase of the disease.[26,27]

Regarding a possible explanation for the association found between post-COVID-19 OD and a lower E4 allele frequency, Zhang et al. showed that, among the APOE alleles, E4 is the one that least inhibits the entry of SARS-CoV-2, thus conferring a greater risk for severe forms of COVID-19, which was also shown by Kuo et al.[9,10] Thus, the lower frequency of E4 found in our OD group may explain the lower severity found in these same patients.[7,28] Conversely, APOE E4 is a well-known risk factor for AD. There is existing neuroimaging evidence that has documented structural damage to brain tissue in individuals diagnosed with COVID-19. The affected regions have been identified as those exhibiting functional connectivity with the primary olfactory cortex, such as the hippocampus, parahippocampal cortex, and amygdala.[29] These same sites are also greatly affected in patients with AD. Thus, it would be reasonable to assume that patients with olfactory dysfunction and APOE E4 polymorphism could be AD patients in the initial stage of the disease.

Several significant limitations are present in our investigation. The absence of a control group limits the interpretation of our findings. Our study solely recruited patients with neurological manifestations and approximately 16% of the recruited patients lack of APOE genotyping and only 19% of the sample was over 60-years-old, which might lead to selection bias. We did not conduct a standardized olfactory assessment, which could have enhanced the reliability of our results, primarily in older patients. We did not have information about SARS-CoV2 genotype in our patients, as previous study shows that different variants may have different symptoms epidemiology.[30] Lastly, the absence of neuroimaging investigations prevented us from establishing a correlation between complaints and radiological findings.

Nevertheless, our sample of Long-COVID-19 outpatients is noteworthy, as it highlights the persistent nature of OD symptoms following the acute phase of the disease, particularly in individuals with mild manifestations. Additionally, the inclusion of APOE polymorphism analysis and its potential correlation with other symptoms strengthens our research's overall contribution.

Within the existing body of literature on COVID-19, anosmia has been linked with favorable clinical results, whereas APOE E4 has been associated with unfavorable clinical outcomes.

The association between Long-COVID and cognitive decline is still unclear. A study conducted by Llana et al. applied cognitive tests to 42 individuals with Long-COVID, pointing out deficits in procedural memory consolidation and in the immediate recall of declarative information in patients with anosmia compared with patients without anosmia and a control group. The average age in the study was 43 years.[31] Another study by Pirker-Kees et al. examined the relationship between anosmia and cognitive impairment in a small sample of 7 patients with Long-COVID, with an average age of 79 years. Patients with COVID-19 showed significantly lower ability to identify odors and lower scores on the Montreal Cognitive Assessment (MoCA) compared with healthy controls, suggesting that olfactory dysfunction may be a clinical biomarker for cognitive impairment.[32]

Our research contributes novel insights into these associations by identifying the APOE E4 allele as a possible protective factor against OD. It is of utmost importance to conduct longitudinal monitoring of these patients and assess biomarkers of neurodegenerative disorders in their cerebrospinal fluid or plasma to ascertain the persistence of the impairment in olfactory functioning after a certain timeframe and determine whether there is any correlation with the onset of neurodegenerative diseases.

Ethical Aspects

The study protocol was authorized by the Research Ethics Committee of the Walter Cantídio University Hospital following Opinion no. 4.092.933. All patients or their legal representatives provided written Informed Consent Forms, ensuring the privacy and confidentiality of the collected data, as well as the right to refuse participation in the study activities and inquiries.

Authors' Contributions

DNO, JTJ, MSN, PBN: conception and design of this study; DNO, JTJ, PBN: performed data acquisition, analysis, and

interpretation; DNO, JTJ, PBN: conducted the drafting of the manuscript. DNO, JWLTJ: Both authors equally contributed to the article. All authors contributed to the critical review of the manuscript and provided significant intellectual input.

Conflict of Interest

The authors have no conflict of interest to declare.

Acknowledgments

The authors would like to thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for the provision of a fellowship grant to Caroline Aquino Moreira-Nunes, Raquel Carvalho Montenegro, and Pedro Braga Neto. Additionally, Pedro Braga Neto and Raquel Carvalho Montenegro acknowledge the financial support from Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; 88881.505364/2020–01). Finally, Carmem Meyve Pereira Gomes received funding from Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico (FUNCAP).

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