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RESEARCH PAPER

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Magnetic resonance spectroscopy findings of brain olfactory areas in patients with COVID-19-related anosmia: A preliminary comparative study

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Abstract

Objectives: 2019 novel coronavirus disease (COVID-19) infection is commonly associated with olfactory dysfunctions, but the basic pathogenesis of these complications remains controversial. This study seeks to evaluate the value of magnetic resonance spectroscopy (MRS) in determining the molecular neurometabolite alterations within the main brain olfactory areas in patients with COVID-19-related anosmia.

Methods: In a cross-sectional study, seven patients with persistent COVID-19-related anosmia (mean age: 29.57 years) and seven healthy volunteers (mean age: 27.28 years) underwent MRS in which N-acetyl-aspartate (NAA), choline (Cho), creatine (Cr), and their ratios were measured in the anterior cingulate cortex, dorsolateral prefrontal cortex, orbitofrontal cortex (OFC), insular cortex, and ventromedial prefrontal cortex. Data were analyzed using TARQUIN software (version 4.3.10), and the results were compared with an independent sample *t*-test and nonparametric Mann–Whitney test based on the normality of the MRS data distribution.

Results: The mean duration of anosmia before imaging was 8.5 months in COVID-19-related anosmia group. MRS analysis elucidated a significant association between MRS findings within OFC and COVID-19-related anosmia ($P_{disease} < 0.01$), and NAA was among the most important neurometabolites ($P_{interaction} = 0.006$). Reduced levels of NAA ($P < 0.001$), Cr ($P < 0.001$) and $^{NAA}/_{Cho}$ ratio ($P = 0.007$) within OFC characterize COVID-19-related anosmia.

Conclusions: This study emphasizes that MRS can be illuminating in COVID-19-related anosmia and indicates a possible association between central nervous system impairment and persistent COVID-19-related anosmia.

KEYWORDS
anosmia, COVID-19, magnetic resonance spectroscopy, neuroimaging, olfaction

Key points

- Magnetic resonance spectroscopy (MRS) provides valuable data to identify the basic pathogenesis of various central nervous system disorders, such as 2019 novel coronavirus disease (COVID-19).
- Orbitofrontal cortex neurochemical dysfunction is significantly associated with persistent COVID-19 induced anosmia.
- N-acetyl-aspartate (NAA) within the orbitofrontal cortex was significantly lower in patients with persistent COVID-19-related anosmia comparing normal volunteer participants.
- According to the results, NAA was among the most important neurometabolites.
- The main findings of this study could shed light on future studies to find more specific pharmacologic or nonpharmacologic treatments based on MRS findings.

INTRODUCTION

Magnetic resonance spectroscopy (MRS) is a noninvasive quantitative imaging technique with a high impact on diagnosing and managing central nervous system (CNS) disorders. MRS can assess regional levels of metabolites based on chemical alterations. Generally, N-acetyl-aspartate (NAA), choline (Cho), creatine (Cr), and their ratios are the most common metabolites of the brain that are detected by MRS.[1]

In the last years, 2019 novel coronavirus disease (COVID-19) infection has been a common cause of olfactory dysfunction. Although most of these anosmic patients will eventually improve within a few months, a considerable number of patients will develop prolonged smell loss more than 2 years after diagnosis.[2,3] Overall, olfactory disorders could be classified as conductive sensory-neural or due to a CNS impairment.[4] Until now, the basic pathogenesis of these complications remains controversial, and evidence suggests that the main pathogenesis of anosmia in the setting of COVID-19 infection can probably depend on CNS dysfunction.[5] The most important current discussions in COVID-19-related anosmia are the controversies about the biochemical basis of these pathologies, diagnosis, and treatment.[6] Therefore, using advanced CNS imaging to fill the lack of knowledge in the context of COVID-19-related anosmia and introduce more sensitive and specific methods for diagnosis is reasonable. Importantly, understanding the basic pathogenesis of anosmia can potentially shed light on further trials to find a cure.[7]

This study seeks to investigate the neurometabolic alterations in the brain structural regions associated with the olfaction process in cases with COVID-19-related anosmia. In this light, single-voxel spectroscopy (SVS) was performed on five regions of interest (ROI), including anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), insular cortex (IC), orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (VMPFC) in the right hemisphere.[8–11]

MATERIAL AND METHODS

Participants

The strengthening of the reporting of observational studies in epidemiology (STROBE) statement was used for reporting the study. Between October 2021 and October 2022, two groups were included in the study to investigate MRS data in cases with COVID-19-related anosmia and those with normal olfactory function.

The exclusion criteria for both groups were as follows: (i) history of neurological, psychiatric, sino-nasal disorders, sinus or olfactory disorders; or (ii) current Symptoms of rhinovirus infection. (iii) Any evidence may suggest other possible pathophysiology for the anosmia in two anosmic groups.

Normal healthy volunteers with an age between 18 and 60 were considered Group 1 and included in the study if they had no exclusion criteria. All healthy controls underwent the Iran smell identification test (Ir-SIT) to confirm normal olfactory function.

COVID-19-related anosmia patients (Group 2) were recruited based on the following criteria: (i) COVID-19 infection and subsequent anosmia; (ii) documented positive severe acute respiratory syndrome coronavirus 2 tests (direct antigen detection or reverse transcriptase-polymerase chain reaction) on nasopharyngeal swab specimen before the onset of anosmia; (iii) persisting the anosmia for at least 3 months; (iv) fulfillment of criteria for anosmia based on Ir-SIT[12]; (v) excluding all possible pathological etiologies by CT-scan and structural MRI; and (vi) age between 18 and 60 years.

Institutional Review Board approval and patient informed consent was obtained. All the visits, physical examinations, and MRS acquisitions were performed concerning health protocols against COVID-19.

Ir-SIT

Ir-SIT is a modified version of the University of Pennsylvania Smell Identification Test for the Iranian population.[13] The cut point for the anosmia was 9. A score between 10 and 13 and 14 and 18 is considered severe and mild microsomia, respectively. A score between 19 and 24 indicates that the participant has a normal olfactory function. Patients with COVID-19-related anosmia were completely anosmic. All participants in the control group were utterly normosmic (Table 1).

MRS protocol

Clinical evaluation was performed at a 1.5 Tesla Siemens scanner using an eight-channel receive-only head coil. A conventional 3-dimensional brain image (sagittal T1 MPRAGE, TR/TE = 1800/3.5, the field of view = 256 × 256 × 160 mm^3, Resolution = 1 × 1 × 1 mm^3) as a reference image for the volume of interest (VOI) positioning was performed for all patients before MRS sequence. For SVS, MRS was obtained using a point-resolved spectroscopy sequence. Four 2 × 2 × 2 cm^3 voxels were located on the ACC, DLPFC, IC, and VMPFC. One 2 × 2 × 1 cm^3 voxel was located at OFC to accurately estimate cerebral cortex neurometabolites' concentration and to prevent the effect of surrounding bone tissue on the spectroscopy. The voxels were carefully placed to avoid subcutaneous fat, skull, vasculature, arachnoid space, and cerebrospinal fluid. Manual shimming was performed for all acquisitions. The parameters were set as TR/TE = 1500/135 and NEX = 128. Six saturation bands were placed around the VOI to suppress the outer volume signals. The average time for each MRS duration was (25 ± 2) min (5 min for each region).

TABLE 1 Demographic data of enrolled cases in each group.

Groups and cases number	Gender	Age (year)	Anosmia duration (month)	Ir-SIT score
Group 1				
C1	M	25	–	20
C2	M	24	–	20
C3	M	34	–	21
C4	M	38	–	19
C5	F	20	–	20
C6	F	22	–	20
C7	F	28	–	21
Group 2				
C8	M	26	7	9
C9	M	28	8	9
C10	M	34	7	7
C11	M	41	9	5
C12	F	18	9	7
C13	F	29	9	8
C14	F	31	11	8

Note: Group 1, healthy volunteer cases; Group 2, COVID-19 induced anosmia cases; Iran-SIT score (anosmia =0–9, severe microsmia = 10–13, mild microsmia = 14–18, normosmia = 19–24).

Abbreviations: C, case; F, female; Ir-SIT, Iran Smell Identification Test; M, male.

MRS data processing

Data were preprocessed by the administration of a water removal algorithm for the reference offset of 4.65 ppm to remove the residual water signals. SVS raw data were fitted using TARQUIN (version 4.3.10).[14] Targeted approaches select a predefined group of metabolites such as NAA, Cho, and Cr for peak fitting and metabolite concentration. The metabolite ratios of NAA to Cr ($^{NAA}/_{Cr}$), NAA to Cho ($^{NAA}/_{Cho}$), and Cho to Cr ($^{Cho}/_{Cr}$) were measured by dividing the metabolite values in the same spectrum for each ROI.

Statistical analysis

Statistical analyses were performed using SPSS version 26. Shapiro–Wilk test was used to determine the normality of MRS data distribution, including absolute and relative values of neurometabolites. The relative values of neurometabolites were calculated by dividing the arbitrary unit (au.) levels of NAA/Cr, NAA/Cho, and Cho/Cr.

Parametric independent *t*-test and nonparametric Mann–Whitney test were carried out for the comparison of quantitative variables with and without normal distribution between groups. Repeated measured ANOVA was used to determine the effect of the ROI and spectroscopic data on the anosmia as well as the interaction between MRS data in different brain regions. $P < 0.05$ were considered significant.

RESULTS

Clinical characteristics

Considering the risk of exposure to COVID-19 in the hospital, the cost and time of data acquisition and spectroscopy, we included only seven healthy volunteers in the study as control group (four males and three females; mean age: 27.28, range: 20–38; Ir-SIT mean score: 20.1).

Seven patients (four males and three females; mean age: 29.57 years. range: 18–41; Ir-SIT mean score:7.5) met the inclusion criteria in COVID-19-related anosmia. Mean duration of anosmia before imaging was 8.5 months in these patients. Demographic characteristics relating to participants are summarized in Table 1.

MRS results

As illustrated in Figure 1A, the NAA level within OFC ($P = 0.001$) and VMPFC ($P = 0.026$) detected by MRS in patients with COVID-19-related anosmia was significantly lower than the control group. Interestingly, anosmic patients exhibited a lower NAA level than the control group in all ROI (Table 2).

As opposed to NAA, there was no significant difference between groups for Cho levels. Nonetheless, as represented in Figure 1A,B diffuse nonsignificant decrease of the Cho level in anosmic patients compared to the control group was observed (Table 2).

As reflected in Figure 1C, there was a significant reduction of Cr level within OFC in anosmic patients comparing the control group ($P = 0.001$, Table 2).

$^{NAA}/_{Cho}$ ratio within OFC was significantly different between groups ($P = 0.007$, Figure 1D, Table 2).

We found no significant differences in $^{NAA}/_{Cr}$ or $^{Cho}/_{Cr}$ ratios among the two groups (Figure 1E,F, Table 2).

Our results demonstrated a significant association between OFC-neurometabolite impairment and COVID-19-related anosmia ($P_{disease} < 0.001$, Figure 2). Repeated measured ANOVA analysis revealed that the interactions of NAA ($P_{interaction} = 0.006$) and Cr ($P_{interaction} = 0.043$) within OFC were significantly different between the two groups (Table 2).

Gnuplot of Tarquin examples shown in Figure 3 provided a visual display of the distribution of brain neurometabolites of the OFC spectroscopy in each group.

DISCUSSION

Two processes can disrupt the sense of smell: conductive olfactory deficit and sensorineural olfactory deficit. Processing of olfaction starts in the olfactory sensory neurons of the nasal olfactory epithelium. From there, efferent information travels through the olfactory tract to the primary olfactory cortex and subsequently to the secondary olfactory centers, including the IC, OFC, thalamus, hippocampus, and ACC.[11,15] Therefore, the central olfactory system is closely interconnected with limbic structures and olfactory memory processes.[15] Furthermore, the limbic loop of the basal ganglia, including the ACC, VMPFC, and DLPFC, has a critical role in olfactory processing.[9,15] These parts of the brain are also involved in olfactory memory.[16] Interestingly, literature has emphasized that right hemisphere structures play a more prominent role in olfaction.[8–11]

Loss of smell sensation in the setting of COVID-19 infection

Relatively high occurrence of COVID-19-related anosmia led us to use MRS to compare brain MRS data in normal control volunteer participants

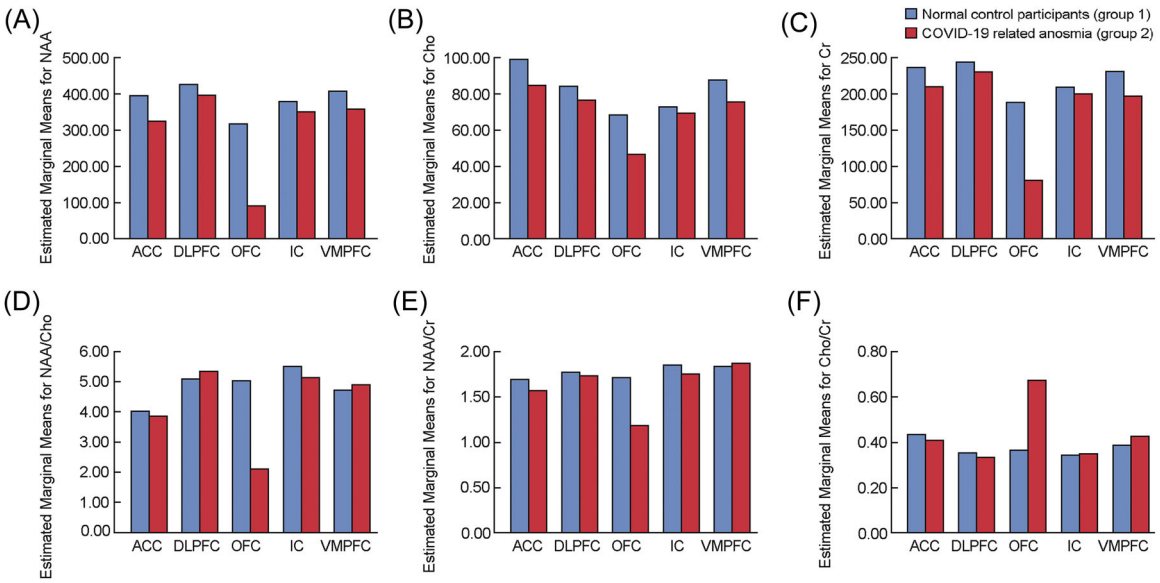

FIGURE 1 The difference in the magnetic resonance spectroscopy data between groups for each region of interest (ROI) including anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), insular cortex (IC), and ventromedial prefrontal cortex (VMPFC). (A) Estimated marginal means of N-acetyl-aspartate (NAA); (B) Estimated marginal means of choline (Cho); (C) Estimated marginal means of creatine (Cr); (D) Estimated marginal means of NAA/Cr ratio; (E) Estimated marginal means of NAA/Cho ratio; (F) Estimated marginal means of Cho/Cr ratio.

TABLE 2 Magnetic resonance spectroscopy results from all regions of interest and the main statistical findings of this study (Mean ± SD).

MRS data	Region	Group 1	Group 2	Group differences P_{value}	Repeated measure ANOVA analysis $P_{interaction}$
NAA	ACC	395.6 ± 87.3	324.4 ± 42.5	0.073	0.006[a]
	DLPFC	425.7 ± 66.6	397.0 ± 37.0	0.620	
	OFC	317.3 ± 34.8	90.9 ± 53.5	0.001[a]	
	IC	379.3 ± 26.5	349.5 ± 17.8	0.053	
	VMPFC	401.1 ± 18.8	357.9 ± 40.7	0.026[a]	
Cho	ACC	99.2 ± 15.7	84.6 ± 8.0	0.097	0.637
	DLPFC	84.3 ± 14.0	76.5 ± 13.8	0.259	
	OFC	68.5 ± 21.0	46.6 ± 24.4	0.097	
	IC	72.7 ± 20.4	69.4 ± 11.5	0.719	
	VMPFC	87.9 ± 15.8	75.6 ± 12.4	0.259	
Cr	ACC	236.32 ± 67.59	210.0 ± 32.4	0.379	0.043[a]
	DLPFC	244.38 ± 61.45	230.6 ± 28.3	0.605	
	OFC	188.08 ± 23.62	80.9 ± 36.0	0.001[a]	
	IC	209.42 ± 40.87	199.9 ± 13.0	0.949	
	VMPFC	230.85 ± 63.98	197.3 ± 51.8	0.304	
$^{NAA}/_{Cho}$	ACC	4.022 ± 836	3.85 ± 0.53	0.805	0.120
	DLPFC	5.088 ± 0.617	5.33 ± 1.08	0.805	
	OFC	5.036 ± 1.636	2.10 ± 1.46	0.007[a]	
	IC	5.499 ± 1.274	5.14 ± 0.79	0.620	
	VMPFC	4.719 ± 0.608	4.89 ± 1.23	0.949	
$^{NAA}/_{Cr}$	ACC	1.699 ± 0.192	1.57 ± 0.29	0.383	0.341
	DLPFC	1.777 ± 0.200	1.73 ± 0.22	0.710	
	OFC	1.714 ± 0.312	1.19 ± 0.62	0.128	
	IC	1.85 ± 0.26	1.75 ± 0.16	0.456	
	VMPFC	1.84 ± 0.34	1.87 ± 0.31	0.850	
$^{Cho}/_{Cr}$	ACC	0.43 ± 0.08	0.41 ± 0.06	0.620	0.442
	DLPFC	0.35 ± 0.06	0.33 ± 0.07	0.633	
	OFC	0.36 ± 0.11	0.67 ± 0.46	0.133	
	IC	0.34 ± 0.04	0.35 ± 0.06	0.805	
	VMPFC	0.38 ± 0.05	0.42 ± 0.12	0.902	

Abbreviations: ACC, anterior cingulate cortex; Cho, choline; Cr, creatine; DLPFC, dorsolateral prefrontal cortex; IC, insular cortex; NAA, N-acetyl-aspartate; OFC, orbitofrontal cortex; VMPFC, ventromedial prefrontal cortex.

[a]$P < 0.05$.

and patients with COVID-19-related anosmia.[2] To the best of our knowledge, only one study had utilized MRS to evaluate olfactory dysfunction in a variety of causes, including head injury (four patients), postviral (five patients), and idiopathic causes (nine patients). Nevertheless, none of them were COVID-19-induced anosmia.[17]

We performed five single voxel spectroscopies in ACC, DLPFC, VMPFC, IC, and OFC in the right hemispheres as the ROI to compare neurometabolite concentrations in normal volunteer participants and patients with COVID-19-related anosmia. The main findings of the study show that OFC neurochemical dysfunction is significantly associated with COVID-19-induced anosmia, and the most critical neurometabolite was NAA.

We have observed that COVID-19-related anosmic patients present a diffuse reduction of NAA, Cr, and Cho levels in most brain

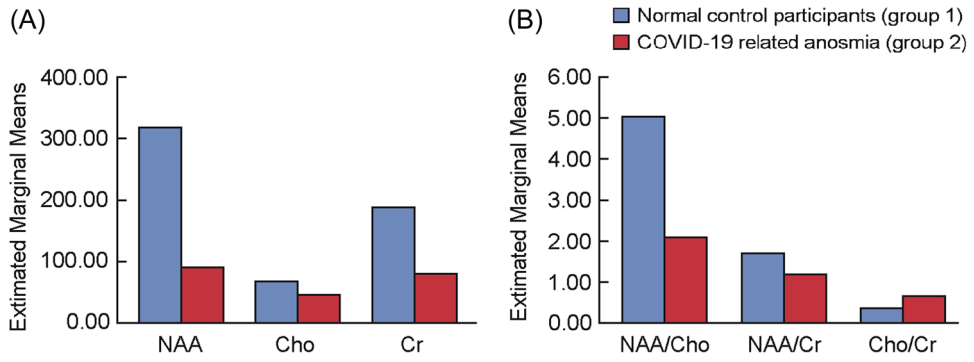

FIGURE 2 Comparison of magnetic resonance spectroscopy results within the orbitofrontal cortex between the healthy control group and COVID-19-related anosmia patients (Cho, choline; Cr, creatine; NAA, N-acetyl-aspartate). Based on repeated measured analysis of variance, orbitofrontal cortex neurometabolite impairment was significantly associated with COVID-19-related anosmia ($P_{disease} < 0.001$). (A) NAA, Cho, and Cr; (B) NAA/Cho, NAA/Cr, and Cho/Cr.

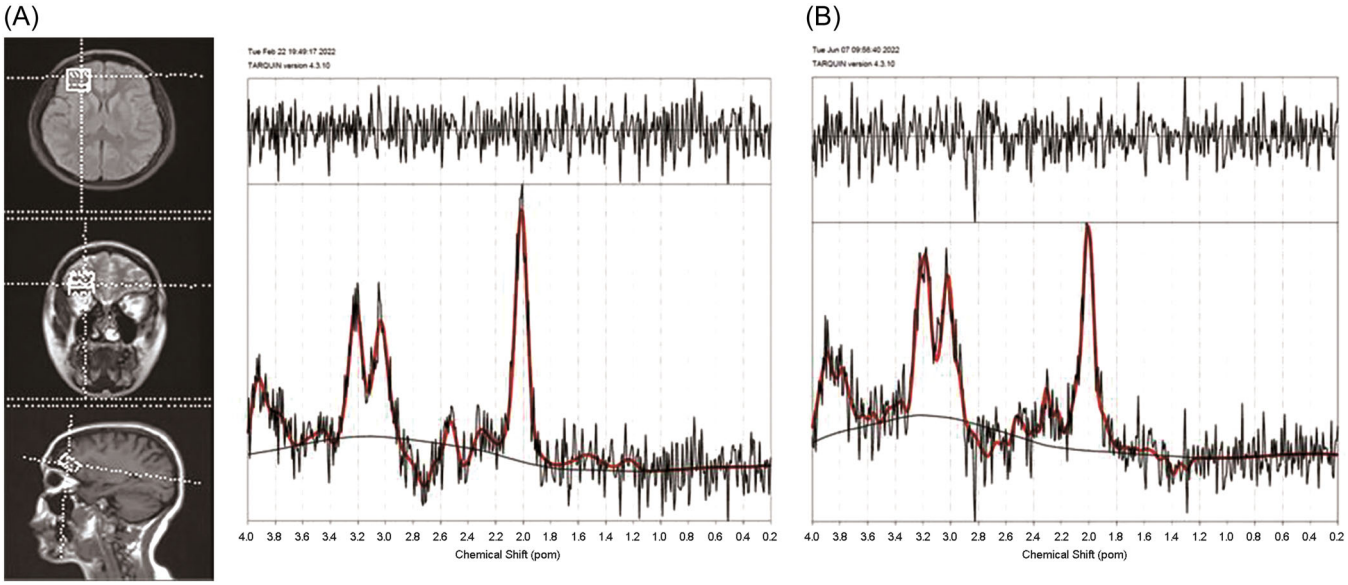

FIGURE 3 Voxel placement within orbitofrontal cortex and examples of Tarquin gnuplot results in a healthy control volunteer (A) and a patient with COVID-19-related anosmia (B).

regions, comparing the control group, especially in OFC. However, these findings were significant only for the NAA and Cr levels and $^{NAA}/_{Cho}$ ratio within OFC and NAA levels within VMPFC.

There are limited data on radiographic practice on patients with postinfectious olfactory loss, which lead to some controversies. Previously, Kollndorfer et al. reported gray matter volume reduction in the right OFC in patients with postinfectious olfactory loss.[10]

It is well known that the loss of sense of smell after COVID-19 infection is much more common than previous reports of postinfectious olfactory loss before the COVID-19 pandemic. Moreover, COVID-19-related anosmia is less related to inflammation, rhinorrhea, or other obstructive mechanisms.[18] A few radiological studies (e.g., MRI, Diffusion tensor imaging, and olfactory functional magnetic resonance imaging) have indicated that the main pathology in COVID-19-related olfactory dysfunction is better justified by CNS dysfunction.[19]

Contrary to our results, Ho et al. suggest that COVID-19 infection may not have a role in frontotemporal cortex function because of the relatively normal oxyhemoglobin area under the curve in COVID-19-related anosmic patients comparing the healthy control group.[20] In our opinion, normal oxyhemoglobin AUS based on the functional near-infrared spectroscopy study could not rule out biochemical changes in neuronal damage.[20]

Overall, the findings of this study suggest that olfactory dysfunction in patients with COVID-19-related anosmia is significantly associated with CNS impairment. Since the NAA originates from mitochondria, it can reflect neuronal integrity and viability; the significant decrease of NAA and $^{NAA}/_{Cho}$ in the OFC in COVID-19-related anosmia strongly suggests regional neuronal OFC impairment in the context of persistent COVID-19 anosmia. The second significant alteration in our patients was a reduction in Cr levels

within OFC. Cr works as an indirect intermediator of cellular energy and previous studies have shown its reduction following nerve injuries.[1] Although this cellular dysfunction emphasized the hypothesis that impairment of OFC function is significantly associated with permanent anosmia, these results could not answer a controversy about the cause-and-effect relationship between brain neurometabolite dysfunction and COVID-19-related anosmia.

Despite the promising results of the study, as we focused on patients with COVID-19-induced anosmia and those with normal olfactory function, therefore, we could not address a certain address about the cause or effect relationship between OFC-neurometabolite alterations and COVID-19-related anosmia. In this regard, to make a stronger case for COVID-19, it would have been of interest to consider additional anosmia groups, particularly ones in which peripheral, including olfactory bulb (viral, toxic exposure, Kallmann syndrome, olfactory fila transection) or central (e.g., epilepsy) is evident. However, it should be noted that the results of recent clinical trials that did not achieve significant improvement from intranasal corticosteroids raise the property of CNS mechanisms for COVID-19-related anosmia.[21–23]

Limitations and comments of the study

The small number of patients is certainly a major limitation of our study, but this is a well-designed preliminary study. Another limitation of our study was the nature of our scanner. More powerful scanners and multivoxel spectroscopy can detect extra metabolites such as Myo-inositol, glutamate, glutamine, glutathione, gamma-aminobutyric acid, and lactate.

Another limitation of this study is the lack of additional anosmia groups, particularly ones in which peripheral, including olfactory bulb (viral, toxic exposure, kallman syndrome, olfactory fila transection) or central (e.g., epilepsy, AD) is evident. According to the evidence that damage to the olfactory bulbs influences central structures, notably various neurotransmitter levels, those additional groups would strengthen the case to infer that the smell loss of COVID-19 is central.

Despite the limitations of this study, we believe that the MRS is a valuable advanced neuroimaging technique and could provide very important landmarks in the diagnosis, treatment and follow-up of patients with anosmia.

Interestingly, as MRS provides valuable, quantifiable data, it would be possible to build a predictive score based on future longitudinal studies and neural network to predict the outcomes of patients with acquired anosmia.

According to a suggestive origin of injury in patients with COVID-19-related anosmia, pharmacologic, or nonpharmacologic therapies to increase NAA levels using electroconvulsive therapy, cognitive behavioral therapy, and physical exercise or short-course pharmacological therapies with lithium, valproate, or antipsychotics could be tried in these patients as they can lead to a widespread increase in brain NAA levels.[24,25]

CONCLUSIONS

MRS is an exciting and novel approach for evaluating prolonged olfactory dysfunction after COVID-19-related anosmia. However, it is still not entirely clear that abnormalities in the CNS are the cause or the effect of olfactory loss due to COVID-19 infection. We believe further neuroimaging studies and clinical trials with additional groups, particularly ones in which peripheral or central cause of anosmia is evident, could answer some controversies about the cause-and-effect relationship between the neurometabolic alterations within OFC in COVID-19 anosmia.

AUTHOR CONTRIBUTIONS

Mohammad Haghani Dogahe, Shadman Nemati designed the work; Mohammad Haghani Dogahe, Alia Saberi, Pejman Kiani, Tofigh Yaghubi Kalurazi, Ehsan Kazemnejad Leili, Sara Seddighi, and Abbas Monsef acquired and analyzed data; all authors contributed in drafting the manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study was approved by Guilan University of Medical Sciences Ethical Committee: IR. REC.1400.170.

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