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Grey matter analysis in non-severe COVID-19 points out limbic-related cortex and substantia nigra

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Abstract

Background & Objective: It is unknown whether occult neurological damage exists in mild COVID-19 patients. Obtaining direct histopathological evidence is difficult and often inappropriate. Radiological tools provide important clues regarding this issue. We aimed to investigate any overt or subtle changes in brain magnetic resonance (MR) scans of patients who recovered from non-severe COVID-19 at subacute stage. *Methods:* Cortical thicknesses/areas were measured in the olfactory bulb (OB), gyri recti, amygdalae, hippocampi, entorhinal cortices, perirhinal cortices, insulae, and substantia nigrae (SN) and compared with controls. Gross findings have also been reported. We assessed the correlations between radiological and clinical parameters. *Results:* Twenty percent of the patients had abnormal MR scans (mild ventriculomegaly, a hyperintense lesion, a lacune and hydrocephalus) although their relevance to COVID-19 was unknown. We found increased cortical thickness in bilateral OB, left entorhinal cortex, right perirhinal cortex, bilateral insulae, and bilateral gyri recti ($p<0.05$ for all). Right OB was thinner in patients with anosmia ($p=0.015$) and ageusia ($p=0.004$). Left perirhinal cortex and left gyrus rectus were thicker in patients with vertigo ($p=0.040$; $p=0.032$ respectively). Sleep disturbance was associated to increased thickness in left perirhinal cortex ($p=0.033$). Patients with brain fog had smaller SN bilaterally (right $p=0.028$ and left $p=0.011$). Patients with anxiety symptoms after COVID-19 had increased right hippocampal area($p=0.023$). Neutrophil-to-lymphocyte ratio was correlated to the thickness of right perirhinal cortex ($r=-0.57$, $p=0.02$) while CRP, time since COVID-19 and age were not.
Conclusion: These changes in limbic areas, insula and SN necessitate close monitoring of patients for autonomic complications, and secondary neurodegenerative processes.

Keywords: COVID-19; cortical thickness; brain fog; insula; hydrocephalus; perirhinal cortex.

INTRODUCTION

Since the first case in 2019, SARS-CoV2 has caused 504 million confirmed cases and 6.2 million deaths all over the world.[1] Respiratory failure and multisystem inflammatory syndrome consist the main causes for mortality and determine disease severity.[2] There is also abundant evidence for the neuroinvasive potential of this virus.[3] Neurological involvement in COVID-19 may manifest as severe central nervous system (CNS) complications, besides, it may also cause *long COVID* symptoms in the subacute period and long term, which are now being increasingly recognized.[4]

Until the recent variants of SARS-CoV2, anosmia and ageusia have been among the most frequent initial symptoms of COVID-19.[5] Based on this fact, olfactory and gustatory pathways have been proposed as possible routes for viral invasion of CNS via transsynaptic propagation.[6] There are studies that clearly show the presence of ACE2 and TMPRSS2 in the brain, which are SARS-CoV2 entry points.[7,8] Direct histopathological evidence for neuroinvasion in humans is obscure.[9] However, there are some radiological data which suggest alterations in the structures which are anatomically related or connected to the olfactory and gustatory pathways.[10,11] These structures are mainly components of limbic system. On severe cases, microangiopathic or major vascular pathologies can be seen or severe hypoxemia

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can also result in some lesions in brain magnetic resonance imaging (MRI).[12,13] However, in mild cases the major point of concern is delayed effects of virus in the brain parenchyma which may cause post-infectious neurodegenerative changes in the long term as in the case of postencephalitic parkinsonism.[14] Routine MRI investigations of COVID-19 patients may not reveal any lesions or pathology especially if the case is mild. In this study we aimed to investigate if there are any changes in the cortical thicknesses particularly at the limbic areas which are anatomically connected to olfactory and gustatory systems, in addition to any gross findings in the routine sequences. We identified the patients who had brain MRI from our COVID-19 database and measured cortical thicknesses in a blind manner at 16 grey matter regions of interest (ROI). We compared our findings with an age- and sex- matched control group. Clinical parameters that correlate with cortical thickness changes were also identified.

METHODS

This is a cross-sectional case-control study in which the clinical and laboratory data were collected retrospectively from medical records.

Subjects

The participants were recruited from the COVID-19 database of our unit. This database included any patient who was assessed in our outpatient clinics with a confirmed COVID-19 medical history. Sample size was determined after power calculation with the preliminary data given the following study parameters: type I error rate 0.05; type II error rate 0.2. Accordingly, we included 40 subjects (20 per group) for the radiological analysis. Inclusion criteria were: (a) 18-65 years of age, (b) nasopharyngeal swab polymerase chain reaction (PCR) test confirming SARS-CoV2 infection, (c) having a brain MRI scan at least two weeks after recovery from acute symptoms of COVID-19.

Control group consisted of the patients that admitted to our department with non-specific neurological complaints. None of these subjects had had COVID-19 based on their self-report. No confirmatory test (e.g. antibody titer or PCR) was applied due to ethical issues.

Exclusion criteria for both groups were as follows: Any neurodegenerative disease, malignancy, history of head trauma, stroke, brain tumors, or an epileptic disorder. Our research was approved by local Clinical Research Ethics Committee (KAEK no:118/102). Informed consent was obtained from each subject.

Clinical assessment

The clinical information included age, sex, date of SARS-CoV-2 infection, comorbidities, severity of COVID-19 (according to WHO guidelines)[2], need for hospitalization, COVID-related symptoms such as presence of fever, numbness in the extremities, vertigo, headache, disturbance of smell and taste sensations, as well as sleep problems, brain fog, and anxiety later on. We also included serum C-reactive protein (CRP) level and neutrophil/lymphocyte ratio (NLR) from the laboratory tests to see whether these inflammatory markers were predictive of or associated to cortical thickness changes. The laboratory tests were performed at admission. For non-COVID19 subjects, information about age, sex and comorbidities were recorded.

Neuroimaging

Data acquisition

All the subjects were scanned with a 3T scanner (Ingenia, Philips Medical System, Netherlands) with a 16-channel head array coil. The protocol included T1W, T2W, SWI, DWI, T2-FLAIR (slice thickness/gap of 4/1 mm matrix size of 256 × 256, FOV of 240 × 240 mm2) and thin slices 3D T1W (slice thickness/gap of 1.1/0.55 mm, matrix size of 252x250, FOV of 250x250 mm2) sequences. Images were evaluated by a radiologist blind to the groups of subjects. Any abnormal gross finding was reported as an initial evaluation. Special attention was given for i) microhemorrhages or microthrombi in SWI, ii) grey or white matter hyperintensities. In addition to that, several regions of interest were selected for cortical thickness measurements.

Regions of Interest

The selection of ROIs was based on their anatomical relation to olfactory system or limbic function. The ROIs included olfactory bulbi (OB), gyri recti, amygdalae, hippocampi, entorhinal cortices, perirhinal cortices, insulae, and substantia nigrae (SN).

Area measurements were performed for amygdalae, hippocampi, SNs and *thickness* measurements for the rest.

Correlation analysis

We assessed correlations among the radiological measurements and the clinical parameters such as suffering anosmia, ageusia, headache, sleep disturbance, brain fog, anxiety, fever, vertigo, numbness in the extremities, time since COVID-19, CRP and neutrophil-to-lymphocyte ratio (NLR) values.

Statistical analysis

Descriptive statistics were presented as mean ± standard deviation or median and interquartile range based on the normal distribution or not, respectively. Comparisons between independent groups were performed using Mann-Whitney U test, and correlations between non-normally distributed continuous data were analyzed using Spearmen correlation. A p value <0.05 was considered as statistically significant, and all analyses were performed in SPSS 21 (IBM Inc., Armonk, NY, USA) software.

RESULTS

The mean (± standard deviation) age of the study group was 35.5 ± 9.5 and the control group was 36.3 ± 6.7 (p>0.05). The patient group consisted of 10 females and 10 males; the control group consisted of 11 females and 9 males. The groups were similar with respect to the prevalence of comorbidities.

None of the cases were found to have respiratory failure due to COVID-19 and there were not any intensive care unit admissions in our patients. Therefore, our patient group represented non-critical SARS-CoV2. Mean duration of recovery since COVID-19 was 107 days (min 16 days and max 210 days; median 112 days).

In four of the patients (20%) the MRI scans were reported to be abnormal by the radiologist. These cases are summarized briefly as follows:

Patient 1: A 32-years old woman with no comorbidities. Her complaints on admission were fatigue and anxiety. She was reported to have minimal dilatation of the cerebral ventricles in brain MRI. There was no prior brain imaging verifying whether this finding existed before. She had COVID-19 four weeks ago.

Patient 2: A 36-years old man with no comorbidities. He admitted with headache. His brain MRI showed a non-enhancing hyperintensity near the left lateral ventricle (figure 1a). There was no prior brain imaging verifying whether this lesion existed before. It was considered to be unrelated to his symptom. The patient had COVID-19 three months ago.

Patient 3: A 18-years old boy with no comorbidities. His complaints were fatigue and headache on admission. There was a right parietal lacune in the white matter in his brain MRI (figure 1b). He had no prior brain imaging. He had COVID-19 four months ago.

Patient 4: A 32-years old man with no comorbidities. He was admitted to emergency room and consulted to neurology department on having seizures. He did not have any seizure or febrile convulsion before. His past medical history and family history were unremarkable. His brain MRI revealed hydrocephalus. His EEG recording exhibited multifocal epileptic activity. He had COVID-19 four months ago with intractable headache and fever for several days at home (figure 1c).

Grey matter measurements and correlations

The comparisons between COVID-19 recoverers and controls revealed increased cortical thickness in bilateral OB, left entorhinal cortex, right perirhinal cortex, bilateral insulae, and bilateral gyri recti (Table 1).

We also checked for the effects of different clinical parameters on cortical thickness. The measurements did not differ between sexes. As for the COVID-related symptoms, numbness and headache did not have an effect in any of the ROIs measured.

Right OB was *thinner* in the patients who had anosmia (median 3.7 mm vs. 4.1 mm) and in the patients who had ageusia (median 3.7 mm vs. 4.1 mm) compared to patients without these symptoms ($p = 0.015$ and $p = 0.004$, respectively).

The thicknesses of left perirhinal cortex and left gyrus rectus were increased in patients who had vertigo compared to the patients without vertigo (median 3.1 mm vs 2.6 mm; $p = 0.040$, and median 3.5 mm vs 3 mm; $p = 0.032$, respectively).

The area of right amygdala was increased in the patients who had fever (median 1.7 vs 1.6 mm; $p = 0.031$).

Sleep disturbance had an effect on the thickness of left perirhinal cortex. It was thicker when sleep disturbance was present after COVID-19 (median 2.9 mm vs 2.5 mm; $p = 0.033$).

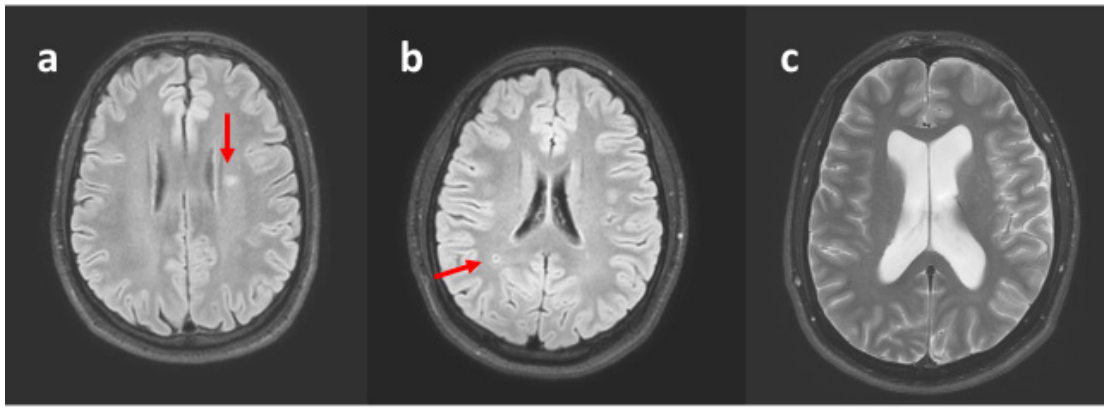

Figure 1. Examples to the brain magnetic resonance images of the patients with overt lesions on routine evaluation. a. FLAIR sequence, axial section, arrow depicting a hyperintense lesion adjacent to the left lateral ventricle in a 36-year-old man. b. FLAIR sequence, axial section, arrow depicting a right parietal lacune in the white matter in an 18-year-old boy. c. T2-weighted axial section showing hydrocephalus in a 32-year-old man.

The patients with cognitive disturbance after COVID-19 had smaller SNs bilaterally compared to the ones without (for right SN, median 0.6 mm vs 0.7 mm, p = 0.028; for left SN median 0.6 mm vs 0.8 mm, p = 0.011).

Patients who had anxiety symptoms after COVID-19 were shown to have increased right hippocampal area compared to the ones who did not suffer anxiety (median 1,7 cm2 vs 1.5 cm2; p = 0.023).

When we checked the correlations between cortical thickness/area and CRP, neutrophil-

Table 1: Thickness or area measurements of grey matter structures that are regions of interest

	Patients	**Controls**	
	Median [IQR]	**Median [IQR]**	**p**
R OLFACTORY BULBUS, mm	3.8 [3.6-4.1]	3.5 [3.3-3.8]	**0.007**
R AMYGDALA, cm2	1.6 [1.6-1.7]	1.6 [1.5-1.6]	0.465
R HIPPOCAMPUS, cm2	1.5 [1.4-1.6]	1.5 [1.5-1.5]	0.579
R ENTORHINAL CORTEX, mm	2.8 [2.5-3.1]	2.5 [2.4-2.7]	0.077
R PERIRHINAL CORTEX, mm	2.8 [2.6-3]	2.7 [2.5-2.7]	**0.016**
R INSULA, mm	3.1 [2.7-3.3]	2.6 [2.5-2.7]	**<0.001**
R GYRUS RECTUS, mm	3.1 [2.7-3.6]	2.8 [2.7-3]	**0.050**
R SUBSTANTIA NIGRA, cm2	0.6 [0.6-0.7]	0.6 [0.6-0.7]	0.440
	Median [IQR]	**Median [IQR]**	**p**
L OLFACTORY BULBUS, mm	3.8 [3.6-4.1]	3.6 [3.4-3.8]	**0.025**
L AMYGDALA, cm2	1.6 [1.6-1.7]	1.6 [1.5-1.6]	0.066
L HIPPOCAMPUS, cm2	1.5 [1.3-1.5]	1.5 [1.4-1.5]	0.202
L ENTORHINAL CORTEX, mm	2.8 [2.5-3.1]	2.5 [2.4-2.7]	**0.009**
L PERIRHINAL CORTEX, mm	2.7 [2.6-3.1]	2.6 [2.5-2.7]	0.130
L INSULA, mm	3.2 [2.9-3.6]	2.8 [2.6-2.9]	**<0.001**
L GYRUS RECTUS, mm	3.1 [2.9-3.5]	2.7 [2.6-2.9]	**0.003**
L SUBSTANTIA NIGRA, cm2	0.7 [0.6-0.8]	0.6 [0.6-0.7]	0.685

R: right, L: left, IQR: interquartile range

to-lymphocyte ratio on admission, time since COVID-19 and age, we found that NLR was moderately and inversely correlated to the thickness of right perirhinal cortex ($r = -0.57$, $p = 0.02$). *Age* did not show a correlation with the measured cortical regions of interest in our study.

DISCUSSION

The main finding of this study is that even in a group of non-severe COVID-19, many cortical areas including olfactory bulbus, entorhinal cortex, perirhinal cortex, insula and gyrus rectus were affected and were enlarged compared to controls.

Among these regions, insula deserves special attention. It is directly connected to the primary olfactory cortex.[15] It has been the center for nociception, self-awareness, introception and contributes to many autonomic functions.[16] It has been linked to sudden death.[17] On the other hand, all types of heart disease risk at 1-year after COVID has been shown to be substantial even among individuals that suffered mild disease[18] and fatality due to cardiac arrest was found to be increased in people infected with SARS-CoV2.[19,20] Considering these, our finding of increased cortical thickness in bilateral insulae may be in support of central autonomic dysfunction as the cause of increased sudden deaths associated to COVID-19. This anatomical site is also involved in gustatory processing. Yet, there was not an association of ageusia with insular thickness in our group.

Olfactory bulbus, entorhinal and perirhinal cortices are anatomical parts of the olfactory system.[21] Entorhinal and perirhinal cortices also function in the network associated with memory processing.[22,23] In our study, the olfactory bulbi appeared thicker in the patient group, however, right olfactory bulbus was significantly thinner if the patients had anosmia and ageusia. Decrease in OB volume has been documented at the chronic stage (10-12 months) after COVID-19, previously.[24] Our findings on OB may reflect the early course of this evolution. The thicknesses of entorhinal and perirhinal cortices were increased in COVID-recoverers compared to controls in our study. Indeed, mesial temporal structures were shown to exhibit altered function in fMRI studies, hypometabolism in PET studies and low CBF in perfusion studies on COVID-19.[11,25,26] These mostly belonged to severe cases. Now, we document that left entorhinal and right perirhinal cortices were particularly affected at the subacute stage in the patients who recovered non-severe COVID-19. A large study from UK also identified reduction in grey matter thickness of these structures in addition to a global decline in brain size and cognitive function following SARS-CoV-2 infection.[27] We found no correlation of brain fog with these structures. However, vertigo in the acute stage and sleep disturbance were related to thicker left perirhinal cortex. As for the laboratory markers, neutrophil-to-lymphocyte ratio on admission was also negatively and moderately correlated to right perirhinal cortical measurements. Disruption of the circuitry in perirhinal cortex might be expected to be involved in genesis of diverse neurological symptoms, as it acts as a polymodal associative area and a gateway between cortex and hippocampus.[28]

We found no difference in hippocampal measurements between study groups. In a previous study by Qin et al., hippocampal grey matter was thinner in a group of patients who had severe COVID-19 and they reported a correlation between hippocampal thickness and inflammatory markers (CRP, IL-6).[11] Considering this finding and the fact that all of our patients were non-severe COVID-19, it was plausible to find hippocampal thickness indifferent compared to controls. On the other hand, right hippocampus appeared thicker in the patients that suffered anxiety after COVID-19. There was also an association between fever and amygdala area. Its biological relevance is unknown.

The inflammatory parameters (CRP and NLR) belonged to the time that the patients showed up in the neurology clinics. We referred to them as an indicator of ongoing systemic inflammation. Viewed individually, these values were all in the normal range.[29] Nevertheless, NLR in the subacute stage still had an inverse correlation with the thickness of right perirhinal cortex.

Headache has been repeatedly reported to be one of the most frequent neurological symptoms in COVID-19.[30,31] It was not related to a change in any cortical regions of interest. This raises the possibility that headache may occur as a constitutional symptom rather than as a direct result of central nervous system involvement.

An important finding of this study was the decrease in the area of substantia nigra bilaterally in COVID-19 recoverers who suffer brain fog. Although it may seem unrelated at first glance, any influence on the dopaminergic innervation of the mesoprefrontal system may cause disturbance in executive cognitive functions. Based on this radiological finding, monitoring COVID-19 patients with brain fog for the development

of neurodegenerative diseases and also for Parkinson's disease in the long term may be suggested.

In 2020, early in the course of pandemic, a case with COVID-19 and sudden anosmia was reported with her acute stage MRI scan revealing cortical hyperintensity in the right gyrus rectus, as well as bilateral olfactory bulbs. Gyrus rectus is adjacent to olfactory tract. Its specific function is unknown. Hypometabolism of this structure was also shown in COVID-19 patients previously.[32] In our analyses, gyri recti were bilaterally and significantly thicker in the patient group.

The cases that we presented individually in the results section were all young patients. It is noteworthy that none had any known co-morbidities. One of them was admitted with the newly-onset seizures. Although rare, there are some reports of seizure after recovery from COVID-19[33,34] and seizures are now included in the post-COVID-19 syndrome.[35] Our patient had the acute infection quite a long time ago (4 months). However, his EEG revealed multiple foci with epileptic activity and brain MRI revealed hydrocephalus. Even it is impossible to prove that COVID-19 had been the underlying etiology in this patient, it was the strongest suspect given his symptoms (fever and severe headache) in the acute stage and EEG. These cases unveil the existence of overt brain MRI lesions even in non-severe cases. We did not encounter any microthrombus or microbleed in our group of patients.

Major limitation of this study is its cross-sectional nature. Therefore, it is not possible to confirm that the findings arose from COVID-19. Longitudinal COVID series of brain imaging documenting pre-infection baseline MRI are very scarce in the literature and indeed hard to establish.[27] However, the changes that we detected in the patient group were statistically significant and worth of consideration. The cases in our study all had some sort of neurological complaints that made them admit to neurology department. We are aware that it is not possible to link these admission symptoms/complaints directly to COVID-19 and accept all of these patients as *post-acute COVID*. However, our control subjects were also the patients with some neurological complaints, with the only difference that they did not have SARS-CoV2 infection. This increases the reliability of our findings.

Another limitation might be the fact that the symptoms declared in this study were all based on patients' self-reports. We did not apply a neuropsychological test or a scale to assess cognitive disturbance, anxiety, headache etc. since this was out of our scope.

We performed manual tracing for the cortical thickness and subcortical grey matter area measurements. Automated post-processing tools for images were not available to us. However, we do not take this as a weakness since the validation studies of these computer-aided estimations have been done utilizing the traditional methods like manual tracing or histologic measurements.[36,37] All our measurements were performed in the same way by a single radiologist who was blind to the study groups.

In conclusion, COVID-19, which affected millions of people within a two-year period, seems to have the capacity to make significant changes in cerebral grey matter and might cause overt lesions in some, even if it is non-severe. The fate of these cortical changes remains undisclosed yet, though some studies appeared reporting reversal of some, at 10 months.[38] The changes identified in the limbic structures, insula, and in the substantia nigra (in people with cognitive complaints), necessitate caution, especially in terms of autonomic complications, and justify the concerns about secondary neurodegenerative changes in the long run.

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DISCLOSURE

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