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Cranial Catastrophe Beyond Respiratory Symptoms: COVID-19's Hidden Neurological Damage Revealed by MRI DTI Tractography

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Neuroimaging, Tractography, Diffusion Tensor Imaging, Recovered Covid-19 Patients, Cranial Nerves

ABSTRACT
Emerging evidence suggests that coronavirus disease 2019 (Covid-19) can significantly affect cranial nerves, resulting in various neurological complications. Predominant issues include anosmia, ageusia, and severe headaches. This study involved 30 recovered Covid-19 patients who underwent MRI Tractography with a Superconductor 1.5 Tesla machine and Diffusion Tensor Imaging (DTI). We analyzed correlations between gender, age, Covid-19 symptoms, pathological findings, diffusion metrics, motor and cognitive functions, and other clinical characteristics. Probabilistic constrained spherical deconvolution tractography and tract quantification were performed following diffusion tensor parameters, utilizing fiber tracking methods and fractional anisotropy (FA) metrics. Tractography reconstructions of cranial nerves were successfully achieved in all patients. Affected cranial nerves showed decreased FA and disrupted fibers, with lower axonal density in clinically recovered patients. Patients with moderate and severe symptoms had lower FA in the cranial nerves and slightly more brain abnormalities. Motor and cognitive deficits were prevalent among recovered patients. This study demonstrates that DTI provides essential qualitative and quantitative insights into the pathophysiology underlying neurological disorders in Covid-19 patients. These insights can be used to improve clinical outcomes and quality of life for patients' post-recovery.

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INTRODUCTION

Since its emergence in late 2019, Coronavirus Disease 2019 (Covid-19) has become the cause of death for approximately 6,823,213 people worldwide, out of a total of 670,203,160 cases. According to data released by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) on January 29, 2023, around 663,379,947 individuals have successfully recovered. Several other studies conducted in various countries have identified complications in the brain and nervous system following Covid-19 infection (Neishaboori et al., 2020). These complications include confusion, restlessness, brain inflammation, strokes, structural micro changes in white matter, lesions in the frontal and parietal subcortical lobes, memory delay, cognitive impairment, neurological disorders, changes in brain microstructure, decreased cerebral blood flow, and lower axonal density in patients recovering from Covid-19(Huang et al., 2022; Wesselingh, 2023). These conditions tend to be more severe in patients with comorbidities such as diabetes, high blood pressure, and obesity (Bozkurt et al., 2016; Iglay et al., 2016; Sarma et al., 2021).

The majority of Covid-19 positive cases who have successfully recovered fall within the age group of 15-64, which is considered the productive working-age category (Comisión Económica para

América Latina y el Caribe et al., 2021). In this age range, individuals are typically engaged in completing formal education, seeking employment, building careers, starting families, actively participating in community development, and more. The Covid-19 pandemic's long-term effects could lead to a surge in diseases due to potential serious damage to the brain and nervous system (Wang et al., 2022). Even after recovery, Covid-19 may cause serious brain and nervous system damage (Berger, 2020; Koralnik & Tyler, 2020; Marshall, 2020; Pelizzari et al., 2022; Spudich & Nath, 2022). Approximately 25% of Covid-19 cases show manifestations of the Central Nervous System (CNS), along with neurological symptoms, hippocampal and cortical memory impairment, concentration disorders (acute and chronic), and delirium. Magnetic Resonance Imaging (MRI) is crucial for evaluating these conditions, providing detailed anatomical and physiological images (Prezzi & Goh, 2016; Weiskopf et al., 2021).

Brain MRI protocols encompass various sequences, including SWI (Susceptibility Weighted Imaging) for detecting iron and microbleeding, ASL (Arterial Spin Labeling) to measure blood flow (MacDonald & Frayne, 2015; Murray, 2021), T2-FLAIR (Fluid-Attenuated Inversion Recovery) for identifying inflammation and white matter changes, DWI (Diffusion Weighted Imaging) for providing data on immune cell activity in Covid-19 patients, T1-weighted imaging for muscle fiber evaluation, and STIR (Short Tau Inversion Recovery) sequences for mapping nerve denervation. Additionally, DTI (Diffusion Tensor Imaging) offers insights into white matter structure.

The aims of this research are to evaluate the long-term neurological effects of Covid-19 using advanced MRI techniques and to understand the structural and functional changes in the brain and nervous system among recovering patients. This study will also investigate the correlation between these changes and the severity of Covid-19, along with the presence of comorbidities.

METHOD

Researchers selected 30 samples at Banjarmasin Hospital from July 2020 to April 2023. The patients were aged between 18 and 65 years and had been infected with Covid-19, with or without symptoms. The severity of Covid-19 symptoms was categorized into five levels. Post-recovery MRI scans were conducted to identify brain pathological findings, focusing on lesions and vascular abnormalities. Participants reported various neurological symptoms post-Covid-19, including cognitive impairments and motor disturbances. FA values were analyzed to assess white matter integrity in the brain, indicating the extent of nerve fiber damage and anisotropy levels. Spearman's Rho Correlation Test and Mann-Whitney U Test were used in three statistical tests to examine gender differences in Covid-19 symptom severity, explore gender disparities in MRI brain pathological findings, and evaluate the relationship between age and Covid-19 symptom severity

RESULT AND DISCUSSION

Based on age categories, there is variation in the number of samples, where the age category with the highest number of samples is 26-35 years old, with 10 samples (33.3% of the total). The age categories with the second-highest number of samples are 36-45 years old and 46-55 years old, each with 7 samples (23.3% of the total). The age categories with the lowest number of samples are 17-25 years old and 56-65 years old, each with 3 samples (10% of the total). The data collected on the severity of Covid-19 symptoms in relation to pathological findings in post-recovery Brain MRI scans reveals significant differences. Among the samples, those with mild Covid-19 symptoms exhibited the highest number of pathological findings (12 samples). In contrary, samples without symptoms still showed a substantial number of pathological findings (9 samples), while samples with moderate symptoms had 8 samples with such findings. Remarkably, samples with severe Covid-19 symptoms exhibited a significantly lower incidence of pathological findings, with only 1 sample indicating such abnormalities. Samples experiencing neurological disturbances after recovering from Covid-19 are categorized into three indications: motoric, cognitive, and other neurological disorder indications. Out of the total samples, 16% exhibited cognitive disturbances, 25% experienced motoric disturbances, and 59% of the samples showed indications of other neurological disorders.

Table 1.

Classification of Covid -19 severity and Brain MRI Expertise Post Covid-19

Age (year)	Classification of Covid-19 Symptom				Post Covid-19 Expertise MRI Finding			
					With Pathology		Without Pathology	
	No Symptom	Mild	Moderate	Severe	♀	♂	♀	♂
17-25	2	1	0	0	1	0	1	1
26-35	7	2	1	0	1	4	2	3
36-45	0	6	1	0	5	0	0	2
46-55	0	2	5	0	3	4	0	0
56-65	0	1	1	1	2	1	0	0
Total	9	12	8	1	12	9	3	6

From the Tabel 1 based on the severity of their symptoms, the age group of 26-35 years has the highest percentage in the "Moderate" category at 23.33%. Meanwhile, in the age group of 56-65 years, there is one sample (3.33%) experiencing severe symptoms. The brain MRI revealed that 3 samples (14%) had pathological findings on the right side, 2 samples (10%) had pathological findings on the left side, and 16 samples (76%) had pathological findings on both sides (bilateral).

Table 2.
Neurology Disorder Post Covid-19 and Diffusion Tensor Imaging on Cranial Nerves
(Surbakti et al., 2023)

MRI Samples	Neurological Disorder Post Covid-19		
	Cognitive (a)	Motoric (b)	Others (c)
No Disorder	8 (26,67%)	13 (43,33%)	30 (100%)
Single Disorder	5 (16,67%)	1 (3,33%)	19 (63,33%)
Multiple Disorder	5 (16,67%)	5 (16,67%)	5 (16,67%)

From the Table 2**,** the statistical results of the sample population that underwent Brain MRI scans with Post Covid-19, Neurological Disorders was obtained. The diagnosis results before the MRI examination revealed the following: Cognitive disorders were present in 8 samples (26.67%), Motoric disorders were observed in 13 samples (43.33%), Other disorders were found in all samples (100%). There were samples that experienced only one type of disorder, as follows: 19 samples (63.33%) had other disorders without cognitive or motoric disturbances, 5 samples (16.67%) exhibited cognitive disorders only, without motoric or other disorders, 1 sample (3.33%) had motoric disorders alone, without cognitive or other disorders. There were samples that experienced more than one type of disorder: 5 samples (16.67%) had cognitive, motoric, and other disorders simultaneously.

Table 3.
Statistic Test Gender Differences in the Severity of Covid-19 Symptoms
(Surbakti et al., 2023)

Statistic Test	Severity of Covid-19 Symptoms
Mann-Whitney U	63.500
Wilcoxon W	183.500
Z	-2.136
Asymp.Sig. (2-tailed)	.033
Exact Sig. [2*(1-tailed Sig.)]	.041b

To explore relationships within the data, three statistical tests were conducted. The first test, the Mann-Whitney U Test, examined gender differences in the severity of Covid-19 symptoms. It revealed a significant relationship with a p-value of 0.033, indicating that gender influences the severity of Covid-19 symptoms in this sample. This suggests that male and female participants experienced different levels of symptom severity as it seen on **Tabel 3**.

Table 4.
Statistic Test Gender Disparities in MRI Brain Pathological Findings Post-Covid-19
(Surbakti et al., 2023)

Statistic Test	Pathological Findings Post-Covid-19
Mann-Whitney U	90.000
Wilcoxon W	210.000
Z	-1.175
Asymp.Sig. (2-tailed)	.240
Exact Sig. [2*(1-tailed Sig.)]	.367b

a. Grouping Variable: Gender
b. Not corrected for ties.

Another Mann-Whitney U Test was conducted to explore gender disparities in MRI Brain pathological findings post-Covid-19 as it can be seen on Table 4. However, this test found no significant correlation, with a p-value of 0.240. This suggests that gender does not significantly affect the pathological findings in MRI brain results after recovery from Covid-19, indicating similar brain pathological changes in both male and female participants. The third test, Spearman's Rho Correlation Test, evaluated the relationship between age and the severity of Covid-19 symptoms. Table 5 showed a significant positive correlation with a correlation coefficient of 0.730, indicating that older age correlates with a higher likelihood of experiencing severe Covid-19 symptoms. This suggests that as age increases, the severity of symptoms tends to be higher, highlighting the impact of age on Covid-19 severity.

Table 5.
Statistic Test Relationship Between Age and the Severity of Covid-19 Symptoms
(Surbakti et al., 2023)

			Age	**Severity of Covid-19 Symptoms**
Spearman's Rho	Age	Correlation Coefficient	1.000	.704**
		Sig (2-tailed)	.	<.001
		N	30	30
	Severity of Covid-19 Symptoms	Correlation Coefficient	.704**	1.000
		Sig (2-tailed)	<.001	.
		N	30	30

Four categories were identified based on the range of FA values. In category 1, no samples were included, indicating that no Covid-19 survivors had a high level of anisotropy with FA values above 0.8. This suggests that nerve fibers in Covid-19 survivors are generally not consistently well-organized after viral infection. Category 2 also had no samples included. The FA value range between 0.6 to 0.8 indicates a moderate level of anisotropy, where most nerve fibers remain well-organized. However, in Covid-19 survivor samples, there may be some variations in fiber density or orientation. Category 3 includes samples with FA values below 0.6. This range indicates a low level of anisotropy, which can be caused by damage, structural changes, or disruptions in fiber density or orientation. In this study, there were two samples included in category 3, contributing to approximately 6.7% of the total samples. This indicates that a small number of Covid-19 survivors experienced anisotropy changes leading to fiber damage or disruption. Category 4 is the dominant category, with 28 samples or approximately 93.3% of the total samples in this category. The FA value range below 0.3 indicates a very low level of anisotropy, indicating serious damage to nerve fibers or significant structural loss.

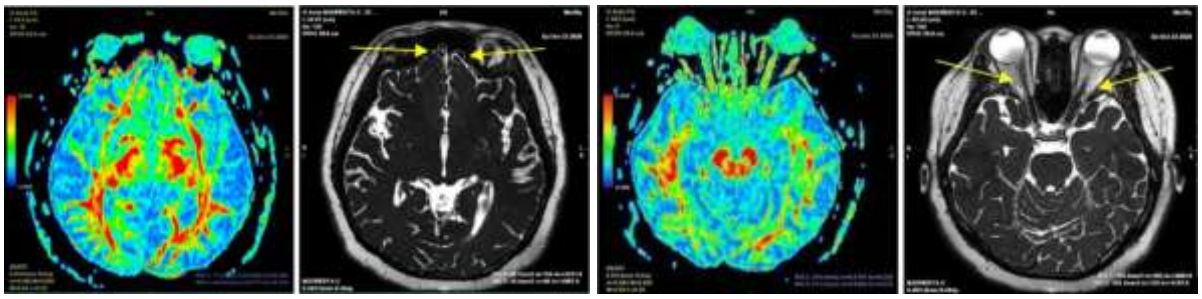

Figure 1. Fractional Anisotropy of CN I, and CN II from samples with FA value range between 0.6 to 0.8 (moderate level of anisotropy), and below 0.6 (low level of anisotropy).
(Surbakti et al., 2023)

By using Fiber Tracking, Infiltrated condition found on Cranial Nerve II (Optic Nerve), Cranial Nerve III (Oculomotor Nerve), Cranial Nerve IV (Trochlear Nerve), Cranial Nerve V (Trigeminal Nerve), Cranial Nerve VI (Abducens Nerve), Cranial Nerves VII and VIII (Facial and Vestibulocochlear Nerves), Cranial Nerves IX, X, and XI (Glossopharyngeal, Vagus, and Accessory Nerves). While both Infiltrated and disrupted condition found on Cranial Nerve I (Olfactory Nerve) and Cranial Nerve XII (Hypoglossal Nerve). These findings underscore the complex and varied neurological manifestations that COVID-19 can have on cranial nerves, affecting sensory and motor functions related to vision, eye movements, facial expressions, auditory perception, and more.

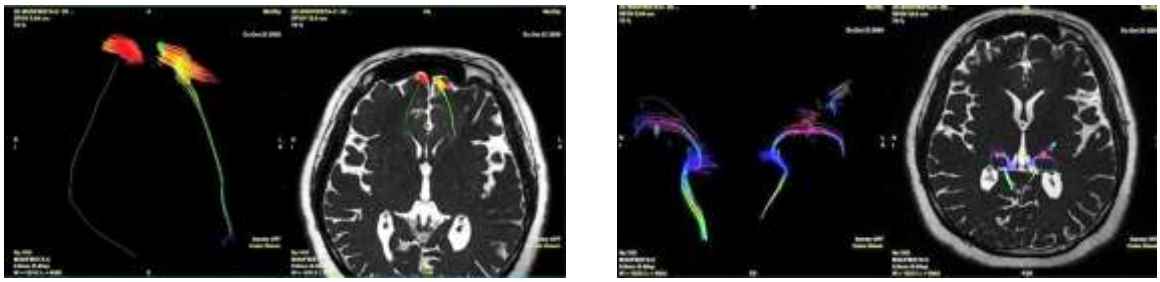

Figure 2. Fiber Tracking CN I (Olfactory) and CN IX, X, and XI (Glossopharyngeal, Vagus, and Accessory) from samples with infiltrated and disrupted condition
(Surbakti et al., 2023)

CONCLUSION

This study provides strong evidence of the impact of Covid-19 on the human brain. Brain MRI results revealed significant pathological findings in Covid-19 patients. Notably, 14% had right-sided brain pathology, 10% had left-sided pathology, and a striking 76% had bilateral brain pathology. Most of these findings (79%) were categorized as circulatory system lesions, while 21% fell into other categories. Fiber Tracking analysis showed disruptions in nerve fiber pathways associated with affected brain areas, including the prefrontal cortex, corpus callosum, and corticospinal tract. This disruption relevant with anosmia (loss of smell) in Covid-19 patients, highlighting changes in brain connectivity and nerve fiber pathways. Fractional Anisotropy analysis indicated reduced FA values in white matter brain tissue, potentially signifying nerve damage or dysfunction in regions related to cognitive and emotional functions. However, it's crucial to note that not all pathological findings directly correspond to neurological symptoms. While the direct relationship between these changes and Covid-19 requires more investigation, these techniques are useful for exploring the virus's neurological effects. Further research is needed to fully understand Covid-19's neurological impact.

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