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New onset tremor in patients with COVID-19: can be a possible link with parkinsonism?

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ABSTRACT

Aims: SARS-CoV-2 is a highly pathogenic member of the coronavirus family. We notice that some patients who were following in outpatient service have a new onset tremor. Our aim to describe these patients and interpreting new onset tremor after COVID-19 that possible link with parkinsonism.

Methods: Forty-two patients with tremor who applied to Alanya Alaaddin Keykubat University Hospital neurology outpatient clinic between the 2021-2022 years were included the study. The data related to demographic characteristics, reasons for application of outpatient neurology clinic, pre-diagnosis and treatment were collected retrospectively.

Results: The patients had a viral infection up to 3 months before the diagnosis of tremor was examined from the hospital system. It was determined that a total of 7 patients had viral infections due to upper respiratory infections and these were confirmed by polymerase chain reaction (PCR). Since two of these patients had concomitant thyroid dysfunction, one had diabetes and one had a history of acute cerebrovascular disorder, they were not included in the study. COVID-19 results were found to be positive wit PCR in 3 patients with a diagnosis of new onset tremor. It was determined in the neurology outpatient clinic notes of the patients that their complaints started after COVID-19.

Conclusion: We haven't enough data about COVID-19 yet but it should be included in the differential diagnosis of patients with new onset neurological symptoms, especially in epidemic situations.. Extensive clinical, neurological, and electrophysiological investigations of the patients may help to understand the virus's role in causing neurological manifestations

Keywords: Tremor, COVID-19, parkinsonism

INTRODUCTION

Since December 2019, the disease called "New Coronavirus Disease (COVID-19)" caused by the new type of coronavirus has spread rapidly from Wuhan province of the People's Republic of China to other provinces and then to the whole world. With this rapidly developing situation that threatens the existence of all humanity, the perspective of today and the future has changed. In this process, new concepts that had never been used before, were also used extensively.

Coronaviruses are approximately 125 nm in diameter, roughly spherical and moderately pleomorphic, single-stranded, positively polarity enveloped RNA viruses with rod-shaped spike protrusions on their surfaces.[1] They are a large family of viruses that are common in humans and animals.[2] Natural reservoir hosts such as wild animals and bats can be played an important role in the transmission of various viruses.[3]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly pathogenic member of the coronavirus family. SARS-CoV-2 is a beta-CoV with a genetic code that is nearly identical to SARS-nCoV.[4] According to recent studies, the virus is 96% similar to a bat coronavirus at the whole-genome stage, indicating that bats are the most likely hosts of the SARS-CoV-2.[5]

Patients with SARS-CoV-2 have a wide variety of clinical symptoms that are ranging from mild to serious. As more information about the SARS-CoV-2 virus has become available, most experts believe that COVID-19 is more than a respiratory disease and that it could affect other human systems. COVID-19's neurological role has been the subject of a growing number of studies recently.[6]

Various neurological symptoms including central nervous system (CNS) involvement, peripheral nervous system (PSS) involvement and skeletal muscle damage have been reported in

more than one third of the patients. Also SARS-CoV-2 nucleic acid component in the cerebrospinal fluid (CSF) of patients and the virus in the brain tissue at autopsies was detected.[7]

As symptoms and diseases that indicate CNS involvement; dizziness, vertigo, sleep disturbance, headache, loss of consciousness, ataxia, seizures, acute cerebrovascular disease, meningitis and encephalitis have been reported.[8,9] The most common complaints in patients with PSS symptoms are taste and smell distortions.[10]

Parkinsonism symptoms such as tremor and bradykinesia have been reported to develop during or after viral infections such as influenza A, HIV, Epstein-Barr virus, hepatitis C virus, varicella zoster, West Nile virus or Japanese encephalitis virus.[11] On the other hand, there are few parkinsonism cases which is possible linked with SARS-CoV-2 in the literature.

We notice that some patients who were following in outpatient service in Alanya Alaaddin Keykubat University Hospital, have a new onset tremor. Their complaints were started during COVID-19 and still going on. Below, you can see three patients who have been following for 3 months because of new onset tremor.

METHODS

This study was approved by Alanya Alaaddin Keykubat University, Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.10.2022, Decision No: 10-04). Forty-two patients with tremor who applied to Alanya Alaaddin Keykubat University Hospital neurology outpatient clinic between the 2021-2022 years were included the study. The data related to demographic characteristics, reasons for application of outpatient neurology clinic, pre-diagnosis and treatment were collected retrospectively. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

RESULTS

Whether the patients had a viral infection up to 3 months before the diagnosis of tremor was examined from the hospital system. It was determined that a total of 7 patients had viral infections due to upper respiratory infections and these were confirmed by polymerase chain reaction (PCR). Since two of these patients had concomitant thyroid dysfunction, one had diabetes and one had a history of acute cerebrovascular disorder, they were not included in the study. COVID-19 results were found to be positive wit PCR in 3 patients with a diagnosis of new onset tremor. It was determined in the neurology outpatient clinic notes of the patients that their complaints started after COVID-19.

Case 1

52 year old woman who have no chronic disease history, was diagnosed with COVID -19 three months ago. Her symptoms started with fever and myalgia, two days after symptoms onset she realized that her right hand was shaking slightly. She was treated by Favipiravir in five days (First day started with 1600 mg two times a day and four days 600 mg two times a day used) without any complication. She had an isolated right hand tremor that was progressively developed. No other abnormal findings were observed during the examination. Brain MRI, serology testing and a comprehensive laboratory analysis including tests for thyroid hormones all yielded a normal result. Her symptoms decreased after rasajilin 1 mg per day started and she can use her hand for daily activities.

Case 2

24 year old woman was diagnosed with COVID -19 four months ago. Her symptoms started wih fever. Before COVID-19 diagnosis, she had no tremor history. She was treated by Favipiravir in five days (First day started with 1600mg two times a day and four days 600 mg two times a day used). She had bilateral tremor that was getting worse day by day after the COVID-19. Brain MRI, serology testing and a comprehensive laboratory analysis were normal. Her symptoms decreased after propranolol 40 mg twice per day started.

Case 3

62 year old man who have diabetes mellitus history almost 2 year. He was diagnosed with COVID -19 three months ago. His symptoms started with dispnea and myalgia, He realized that his right hand was shaking. He was treated by Favipiravir in five days (First day started with 1600 mg two times a day and four days 600 mg two times a day used) without any complication. He had bilateral tremor that was started after COVID-19 treatment and tremor was more prominent in right hand. No other abnormal findings were observed during the examination. His blood sugar was 135 mg/dl and HgbA1C 6.8 mmol/L. Brain MRI, serology testing and a comprehensive laboratory analysis including tests for thyroid hormones all yielded normal. His symptoms decreased after propranolol 40 mg twice per day started and he can use his hand more effectively.

Possible Mechanisms of CNS Invasion of SARS-CoV-2

The coronavirus is thought to reach host cells via angiotensin converting enzyme 2 (ACE2) which is mainly expressed from respiratory tract epithelium, lung alveoli, vascular endothelium, renal cells and small intestine cells.[12] Although the presence of ACE2 in human CNS neurons is not clear, as are particular brain areas or cell types such as neuronal, astrocytes, microglia, immune and vascular cells, SARS-CoV-2 can be spread to the CNS via the ACE 2 receptors.[13,14] Coronavirus may also enter the CNS via the hematogenous or lymphatic system, though this is unlikely in the early stages of the disease.[15]

Blood-brain barrier (BBB) breakdown caused by the cytokine storm associated with peripheral viral infection is one possible mechanism for SARS-CoV-2 RNA presence in the CNS. It is well known that pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 1 beta (IL-1beta), which are associated with inflammation and/or SARS-CoV-2, mediate BBB breakdown.[16]

Aerosol droplets allow coronaviruses to first locate in the infected host's nasal mucosa, then gain access to the CNS via a transcribrial path. After the strong adhesion of SARS-CoV-2, additional axonal transport promotes infection spread to the piriform cortex and other olfactory regions.[17] SARS-CoV-2 broadly diffuse to the CNS within a few days of infection, being detectable in the brains of infected mice or healthy patients.[17,18]

To determine how SARS-CoV-2 infection affects the CNS, researchers will need to conduct detailed neuropathologic studies and sample specific brain regions extensively. Autopsy studies will play a key role in identifying CNS pathology.

DISCUSSION

SARS-CoV-2, like other coronaviruses, has been linked to neurological complications. Such involvement has been observed in more serious cases and could be caused either directly by the virus or indirectly by the systemic effect. We haven't enough data about COVID-19 yet but it should be included in the differential diagnosis of patients with new onset neurological symptoms, especially in epidemic situations.

COVID-19 has a wide range of neurological symptoms from cognitive to cerebrovascular diseases. The most common neurological symptom were headache, myalgia, sleep disturbances and consciousness.[7,8] On the other hand, tremor which is one of the common sign of parkinsonism has only been described in a few COVID-19 related case reports.

Viral Parkinsonism is a neurodegenerative disease caused by a viral infection that causes encephalitis or brain inflammation. Tremor, loss of motor control, stiff movements and loss of balance or difficulty walking are Parkinson's-like symptoms. After viral infections, these symptoms can be appeared in high numbers.[19] The 1918 influenza outbreak and subsequent induction of von Economo's encephalopathy is one of the most well-known and controversial cases of viral parkinsonism.[20] Influenza virus, Coxsackie, Japanese encephalitis B, St. Louis, West Nile and HIV are known to cause parkinsonism.

Many mechanisms of viral parkinsonism remain unknown despite the fact that we know there is a link between viral infections and disease progression decades later. However, some researches have already focused on potential mechanisms between COVID-19 virus and neurodegenerative conditions like Parkinson disease. Some animal studies have shown that coronaviruses can enter the CNS via the nasal cavity and cause neuronal death.[21] Moreover, the presence of antibodies against other coronaviruses that cause the common cold in the CSF of parkinsonism compared to healthy controls suggests that viral infection may play a role in the pathogenesis of the disease.[22]

The mechanism that caused the nigrostriatal dopaminergic nerve terminals to degenerate is unknown, but angiotensin system, which has been linked to COVID-19 pathogenesis, may play a role in the neuroinflammation and neurodegenerative mechanisms seen in Parkinson's disease.[23] Perhaps genetic makeup made patients susceptible to immune-mediated mitochondrial injury and neuronal oxidative stress. Another theory is that the virus causes inflammation by activating microglia, which leads to protein aggregation and neurodegeneration. Another hypothesis is releasing of cytokines may activate immune cells in the CNS and/or allow them from the periphery to infiltrate the CNS and causing brain cell damage. Activated T cells and microglia are such cells that can kill neurons, astrocytes, and vascular cell types.[24]

We present three patients who have new onset tremor in the context of COVID-19. All of them treated with favipiravir. In the literature there is not any side effects like tremor of favipiravir.[25] After stopping the medication, there wasn't any regression in tremor of the patients. This is also supporting that symptoms aren't related with side effect of favipiravir.

More data from cases with similar features is required to determine a causal relationship between SARS-CoV-2 and tremor. In any case, our findings add evidence that is supporting the virus's possible role in the onset of neurological symptoms. Although the serious neurologic complications we've seen are unlikely to be caused by the virus, it's still important to be aware of common neurologic complications so doctors can be prepared, particularly when neurology isn't available.

Limitations

This study has some limitations. Neuroimaging techniques (fMRI, DTI, transcranial Doppler), electrophysiological tests, CSF tests were either not performed or were limited during the outbreak of COVID-19 because of the high risk of cross-infection. Furthermore, we were unable to determine whether these neurologic symptoms are caused directly by the virus or indirectly by another organ damage. Despite these limitations, neurologists should collaborate closely with other specialties through a multidisciplinary approach.

CONCLUSION

We are reaching new information about SARS-Cov-2 which poses a serious threat all over the world. COVID-19 doesn't limit itself to a simple lower respiratory tract infection but can cause serious systemic disease and affect the nervous system. Its neurological effect is mediated by a variety of mechanisms, including direct invasion and a maladaptive inflammatory response. Autopsies of COVID-19 victims, as well as extensive clinical, neurological, and electrophysiological investigations of the patients may help to understand the virus's role in causing neurological manifestations.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Alanya Alaaddin Keykubat University, Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.10.2022, Decision No: 10-04).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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