The Possible Role of COVID-19 in the Triggering of Underlying Mitochondrial Dysfunction in MELAS Syndrome, A Brief Report of three cases

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Abstract

Background: During corona virus pandemic, various neurological complications of COVID-19 have been reported. Recent studies demonstrated different pathophysiology for neurological manifestations of COVID-19 such as mitochondrial dysfunction and damage to cerebral vasculature. In addition, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a mitochondrial disorder with a variety of neurological symptoms. In this study, we aim to assess a potential predisposition in mitochondrial dysfunction of COVID-19, leading to MELAS presentation.

Methods: We studied three previously healthy patients with the first presentation of acute stroke-like symptoms, following COVID-19 infection. We analyzed the patients' clinical data and brain magnetic resonance imaging (MRI) lesions that presented to the neurological center of a university-affiliated hospital in Tehran, Iran, from September 2020 to August 2021.

Results: All cases are characterized by a temporoparietal abnormality in imaging studies and electroencephalogram (EEG). Based on electrodiagnostic tests, three patients were diagnosed with myopathy. In two brothers with relatively the same symptoms, one performed muscle biopsy finding myopathic process, and genetic testing confirmed a 3243A>G point mutation in a heteroplasmic state in one of our patients.

Conclusion: Although MELAS is not a prevalent condition, the recent increase in the number of these patients in our center might indicate the potential role of COVID-19 in triggering the silent pre-existing mitochondrial dysfunction in these patients.

Keywords: COVID-19, MELAS, Stroke-like episode, Mitochondrial dysfunction

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INTRODUCTION

Approximately 25% of infected people with COVID19 have central nervous system (CNS) manifestations. Ischemic stroke is the most common disorder among the cerebrovascular events [1], which is often presenting with large vessel occlusion and may be muti-territorial [2]. Neurological manifestations could be the result of a direct effect of COVID-19 infection or post-infection host immune reaction. Recent studies suggested that mitochondrial dysfunction and damage to cerebral vasculature are related to neurological symptoms of COVID-19 [3]. Mitochondrial encephalo-myopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a mitochondrial disorder with broad manifestations, including seizure, recurrent headaches, stroke-like episodes, cortical vision loss, muscle weakness, and recurrent vomiting [4]. MELAS symptoms could explain by mitochondrial disorder, microvascular angiopathy, and oxidative stress, which is also reported in COVID-19 disease [3,4]. In this study, we collected and summarized the clinical data of 3 patients with symptoms and signs compatible with MELAS syndrome following COVID-19 infection. We propose a hypothesis describing the potential role of COVID-19 in producing processes that aggravate mitochondrial dysfunction and probably be a trigger for MELAS presentation.

MATERIALS AND METHODS

We studied three previously healthy patients with the first episode of acute stroke-like symptoms and concomitant brain magnetic resonance imaging (MRI) lesions that presented to the neurological center university-affiliated hospital in Tehran, Iran, from September 2020 to August 2021. All patients had a history of upper respiratory tract infection (URI) with COVID-19 Polymerase chain reaction (PCR) confirmation test within 20 days before starting symptoms. The clinical data, diagnosis process, and neuroimaging variables of patients were analyzed.

Written informed consent was obtained from all patients, and the ethical committee of Shahid Beheshti University of Medical Sciences has approved the study.

RESULTS

Case Presentations

Case 1

A 27-year-old female patient was brought to the emergency room for a first-time seizure, presenting with head-turning to the right side, right upper extremity flexion with impaired awareness, which lasted for two minutes and was followed by 15 minutes post-ictal confusion. The patient had rhinorrhea, low-grade fever, and mild nonproductive cough for about four days, three weeks ago with a positive RT-PCR test for COVID-19. Her husband claimed that she developed sudden-onset disorientation, confusion, and speaking difficulties six days before the seizure attack. No history of recent trauma or drug/alcohol abuse was reported. She has Suffered from sensory-neural hearing loss (SNHL) since childhood. Moreover, she mentioned a history of hypothyroidism. The psychomotor development was normal.

The neurological examination showed a short stature appearance with bilateral partial ptosis accompanied

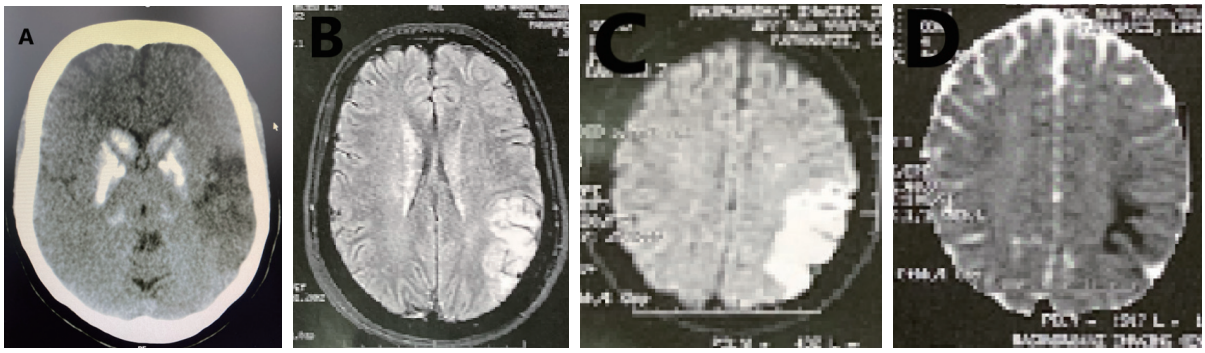

Figure 1. Axial brain CT scan is demonstrating an acute infarction in the left temporoparietal area (A). Brain FLAIR, DWI, and ADC imagings are showing hyperintensity (B), and restricted diffusion (C, D) respectively.

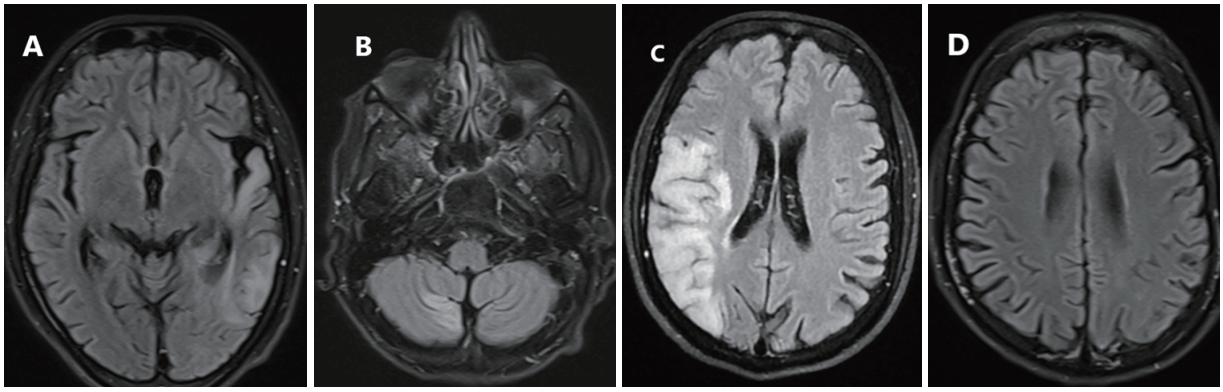

Figure 2. Axial FLAIR brain MRI revealing a left side temporoparietal hyperintensity (A), Axial view of DWI sequence showing right cerebellar restricted diffusion (B), Axial FLAIR imaging demonstrates increased signal on the left temporoparietal region (C), All changes in brain MRI disappear on follow-up imaging of patient 2 (D).

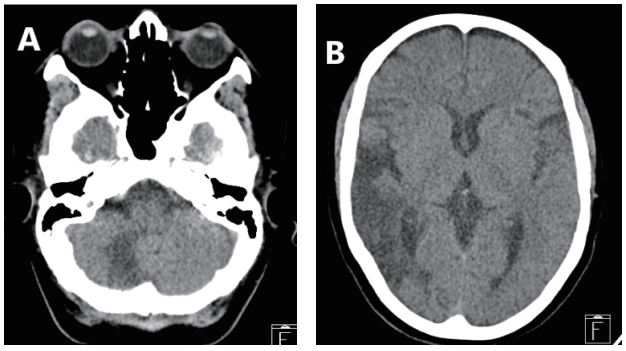

Figure 3. Axial view of brain CT scan without contrast showing a new infarction in right cerebellar hemisphere (A) and a remote hypodensity in the right temporoparietal region (B).

by a normal pupil and eye movement and Wernicke aphasia. Brain computed tomography (CT) scan revealed bilateral symmetric basal ganglia calcification and left side temporoparietal hypodensity (Fig. 1A). Initial laboratory tests showed a calcium level of 6.5 mg/dL and increased serum lactate to 38.3 m/dl (normal range: 4.5-20). Other lab data, including phosphor, parathyroid hormone, vitamin D level, and thyroid function tests (TFT), were within normal limits. Calcium gluconate infusion was given, and the seizure did not repeat at the admission time. EEG showed continuous left temporal focal slowing with no epileptiform discharge. Brain MRI demonstrated left temporoparietal hyperintensity on Fluid-attenuated inversion recovery (FLAIR) and Diffusion-weighted imaging (DWI, ADC) sequences (Fig. 1B, 1C, 1D). Magnetic resonance angiography (MRA), an electrocardiogram (ECG) and trans-thoracic and trans-esophageal echocardiography (TTE, TEE) were unremarkable. Myopathic process was found on the electrodiagnostic study. Finally, the genetic testing showed 3243A>G point mutation in a heteroplasmic state, which is compatible with MELAS syndrome.

Comment: case 2 3 did not check the genetic analysis for mitochondrial mutation (at least check 3243A>G mutation as first case.)

Action/Comment: These cases are presented cognitive impairment, similar to brain fog and characterized with left temporoparietal abnormality in imaging studies and EEG. In addition, both cases developed relatively the same symptoms and case 2 developed a clonic movement. These findings raise the possibility that COVID-19 could be the trigger of

neuropsychiatric presentations of MELAS Syndrome. Also, family history of Short stature, decreased proximal muscle force and Finally, the muscle biopsy that demonstrated non-inflammatory myopathic changes, could be associated with MELAS syndrome.

Case 2 and 3

A 29-year-old male suffered from a sudden-onset right-sided visual field defect accompanied by emotional and behavior disorders. His wife claimed that the patient developed problems with simple mathematics, difficulty in word-finding, and recognizing the faces as well as a more tendency to sleep. He developed right upper extremity clonic movement two days later. His family reported that all the family members experienced fever with chills, headache, and hyposmia compatible with coronavirus infection four weeks before new symptoms, confirmed with RT-PCR, which lasted for ten days. The Mini-Mental State Examination (MMSE) score was 13 at the admission time. Routine lab data, including Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), TFT, antithyroid antibodies, antinuclear antibody, antiphospholipid antibodies, and viral markers were normal. Brain MRI revealed increased T2, FLAIR, and DWI signals involving the left temporoparietal lobe as well as right cerebellar hemisphere (Fig. 2A, 2B). The ECG, TTE, TEE, and brain and cervical CT-angiography (CTA) showed no abnormality. EEG showed left temporal focal slowing with a background of 6 Hz; in addition, routine CSF tests exhibited normal results. Based on history and brain imaging, Acyclovir 10m/kg/dose was started but discontinued following HSV-PCR negative test. The autoimmune neuronal antibodies (anti-Hu, Ri, Yo, NMDA, CV2, and Ma antibodies) were negative in serum and CSF. Spiral chest and abdominopelvic CT scans were unremarkable. All the clonic movement decreased by oral levetiracetam. Because the symptoms were decreased spontaneously, a follow-up visit was considered. After three weeks, his 26-year-old brother is brought to the clinic because of a recently behavioral change. The patient's wife reported that he had developed a memory problem following emotional stress one week ago, so he could not read, write, or calculate correctly. On examination, we noticed that the brothers and other siblings had a short height and proximal muscle force of 4/5. The patient showed short-term memory loss, and the MMSE was 15. T2 and FLAIR hyper signal change were seen in the left temporoparietal on brain MRI (Fig. 2C). Brain and cervical MRA, as well as cardiology evaluation, were unremarkable. All routine blood tests and autoimmune panel antibodies were in normal limits, as was his brother. The serum lactate level was elevated in both brothers (33.9 and 30.4 mg/dl); additionally, they showed non-irritable myopathy in the electrodiagnostic study. Ultimately the muscle biopsy demonstrated non-inflammatory myopathic change; however, the Gomori Thrichrome, SDH and COX staining was not performed in our hospital. Co-enzyme Q10 and L-arginine were administered for the patients, and in follow up all the lesions were disappeared (Fig. 2D).

Comment: Case 4 is not a case of COVID-19 infection, only receive the vaccination only. Maybe not related to COVID-19 infection?

Action/Comment: Case 4 only received COVID-19 vaccination and has not previous history of COVID-19 infection. Case removed from article

DISCUSSION / CONCLUSION

Prior studies discuss the importance of viral-induced mitochondrial dysfunction, leading to changes in the host innate immune responses [5]. Possible mechanisms of viruses for altering mitochondrial function are suggested. The first is that viruses could change the mitochondria dynamics, including autophagy, oxidative phosphorylation, and enzymatic function. In addition, they reduce the contribution of ATP to the mitochondria to provide energy for viral replication, causing cellular stress and mitochondrial damage by generating reactive oxygen species (ROS) [6].

A growing body of evidence revealed that SARS-CoV-2 might functionally target mitochondrial bioenergetics capacity of infected cells to induce viral replication, which could instigate cognitive impairment [7].

Recent studies suggested that mitochondrial dysfunction following COVID-19 could cause neuronal damage. Releasing a large number of inflammatory markers like TNF- alpha and IL-6 prevents mitochondrial oxidative phosphorylation and ATP production, resulting in iron overload and ROS accumulation. These ROS

also could release into the extracellular environment and ultimately result in cell death [7,8]. Moreover, mitochondrial dysfunction of the platelets may potentially increase the risk of coagulopathy and thrombus formation [9].

Stroke-like episodes are a main features of MELAS patients caused by oxidative phosphorylation dysfunction in brain vessels [10]. Since MELAS is not a prevalent condition, the recent increase in the number of these patients in our center might indicate the potential role of COVID-19 in triggering the silent preexisting mitochondrial dysfunction in these patients. Considering COVID-19 pathogenic heterogeneity, longitudinal and standardized studies are needed to determine the possible relationship between these conditions.

Limitation

The present study cannot definitively confirm the link between COVID-19 infection and increased probability of stroke symptoms in MELAS patients.

Statement of Ethics

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients and their families have given their consent for their images and other clinical information to be reported in the article. This study was approved by the Ethic Committees of the Shahid Beheshti University of Medical Sciences.

Conflict of Interest Statement

None of the authors has any conflict of interest to disclose.

Funding Sources

None.

Author Contributions

M. Ram, MM. Rab, Z. Ch was the contributor to writing the manuscript. M. Ram. contributed to the diagnosis and treatment of the patients. M. Ram, L. S contributed to checking the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data used to support the findings this study are included within the article.

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