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Letter to the Editor

There is Evidence that SARS-CoV-2 may be complicated by Stroke and Stroke-like Episodes

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We read with interest the article by Ramezani *et al*. on three patients (patient-1: 27yo female, patient-2: 29yo male, patient-3: 26yo male) with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome in whom SARS-CoV-2 was accused to have triggered a stroke-like episode (SLE) with corresponding stroke-like lesions (SLLs) in classic locations [1]. All patients benefited from coenzyme-Q and L-arginine [1]. In all three patients cerebral lesions resolved spontaneously [1]. The study is compelling but has limitations that should be discussed.

We disagree with the notion that all three index patients were previously healthy [1]. Patient-1 had hearing loss since childhood and hypothyroidism [1]. The patient also was of short stature and had bilateral ptosis on neurologic examination, suggesting that these abnormalities were manifestations of MELAS with an onset long before the actual SLE that lead to admission. Patient-1 additionally had extensive basal ganglia calcification, suggesting that this feature was present already long before the actual admission and manifested clinically. Both, patient-2 and patient-3 had proximal weakness on clinical exam [1], suggesting that it could not be due to the current cerebral lesion and night have been present long before the SARS-CoV-2 infection.

We disagree with the caption of figure 1 classifying the left temporo-parietal lesion as “acute infarction” [1]. Location of the lesion and onset of clinical manifestations (disorientation, confusion, dysarthria) 6 days prior to the seizure suggests a SLL, the hallmark of MELAS.

We also disagree with the description of the ADC lesion as hyperintens [1]. Figure 1 clearly demonstrates that the lesion is hypointense on ADC. Although hyperintensity on DWI and hypointensity on ADC suggests a cytotoxic lesion, it has been shown that SLLs can be hyper- as well hypointense on ADC [2].

A limitation of the study is that the amount of heteroplasmy of the variant m.3243A>G was not mentioned in any of the three index patients [1]. Knowing heteroplasmy rates in clinically affected or unaffected tissues is crucial to assess whether or not clinical severity coincides with the amount of mutated mtDNA, to assess the prognosis of affected patients, and to determine their prospected outcome from the disease.

Another limitation of the study is that only a limited number of stainings was performed with muscle biopsy in patient-2 and patient-3. Missing is immune-histology to demonstrate reduced activity of NADH, overactivity of SDH, and hypoactivity of COX. Missing is also Gomori trichrome staining to eventually demonstrate ragged fibers, a hallmark of MELAS on muscle biopsy. Electron microscopy might show structurally abnormal mitochondria with abnormal deposits of glycogen or lipids.

There is no mention of magnetic resonance spectroscopy (MRS) [1]. MRS usually shows lactate peaks within SLLs on MRI or even outside a SLL [3]. Though it is mentioned that routine cerebrospinal fluid tests were normal, it is not mentioned whether or not CSF lactate was determined. CSF lactate can be elevated even if serum lactate is normal in MELAS patients [4].

The family history of patient-1 was positive for muscle weakness [1]. We should know which family members had proximal muscle weakness and how many of these relative had MELAS as well.

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. SARS-CoV-2 infections may not only be complicated by ischemic stroke but also by SLEs in patients carrying the m.3243A>G variant.

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Keywords: MELAS, mtDNA, m.3243A>G, SARS-CoV-2, COVID-19

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