StroKete-Like Episodes in Mitochondrial Encephalopathy due to MYORG Variants

Abstract:

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LETTER TO THE EDITOR

With interest we read the article by Malaquias et al., (2020) about a family in which three probands manifested with mitochondrial encephalopathy due to the variant NM_020702.4:c.[285_310delinsTTCA];[535_536insC] in MYORG-PFBC (Malaquias, M. J. et al., 2020). Phenotypic manifestations included stroke-like episodes (SLEs), intra-cerebral calcifications, cognitive impairment, dementia, dysarthria, spasticity, Parkinsonism, cerebellar syndrome, dysautonomia (urinary incontinence), and depression (Malaquias, M. J. et al., 2020). It was concluded that MYORG variants can manifest with SLEs and that this observation is novel (Malaquias, M. J. et al., 2020). We have the following comments and concerns.

The study is interesting as SLEs, which manifest as stroke-like lesions (SLLs) on imaging, have not been reported in patients carrying MYORG variants. However, since the pathophysiology of SLEs remains elusive, it is quite surprising that the authors state that “SLEs are due to disconnection of the blood brain barrier (BBB) cells, such as astrocytes, following regional breakdown of mitochondrial energy metabolism” (Malaquias, M. J. et al., 2020). To underscore their statement, the authors cite a recent review about SLEs (Finsterer, J., & Aliyev, R. 2020). In this review we discuss the three main pathophysiological hypotheses, the vascular, epileptogenic, and metabolic hypothesis, to explain the occurrence of a SLE but due to favor an impaired BBB as causative. Though it cannot be excluded that a SLE is due to affection of the BBB, this hypothesis has not been proven yet. A strong argument against BBB disruption as the cause of a SLL is that SLLs are not confined to a vascular territory.

A shortcoming of the study is that none of the three patients with a SLE underwent cerebral MRI during a SLE. SLLs can be best visualised on multimodal MRI. SLLs are characterised by hyperintensity on T2/FLAIR, DWI, and PWI, hypointensity on OEF-MRI (Finsterer, J., & Aliyev, R. 2020), and hypometabolism on PET (Liu, F., et al., 2019). MRS typically shows a lactate peak within the SLL. SLLs are typically not confined to a vascular territory and usually originate from a cortical nucleus to spread subcortically. However, occasionally, SLLs occur exclusively with a subcortical distribution, can be multifocal, and may occur one by one. In a recent study cortical portions of a SLL have been characterised as ischemic in nature and the subcortical as vasogenic (Xu, W., et al., 2018). SLL may resolve spontaneously without a residual lesion but can also end up as white matter lesion, cyst, laminar cortical necrosis, or as toenail sign (Finsterer, J., & Aliyev, R. 2020).

There is no consensus on the treatment of a SLL. A recent consensus statement of experts on MIDs favoured treatment of SLL with anti-seizure drugs (ASDs) disregarding if seizures are reported or not and if the EEG shows epileptiform discharges or not (Ng, Y. S. et al., 2019) but this approach has been challenged (Finsterer, J. 2020). Preliminary data show that SLLs may respond to intravenous application of nitro-oxide (NO) precursors, such as L-arginine or L-citrulline (Ikawa, M., et al., 2020). However, there is no consensus on the beneficality of NO-precursors. We should know which treatment patients II/1, II5, and II/6 received for their recurrent SLEs.

Unclear remains the cause of weakness in patients II/1 and II/5 (Malaquias, M. J. et al., 2020). We should know if weakness was of central origin or due to affection of the peripheral nerves or the muscles. We also should know if...
seizures were excluded as the cause of recurrent hemiparesis. Were EEG recordings truly free of any epileptiform discharges?

Overall, the interesting study has a number of limitations, which should be met before drawing final conclusions. The pathophysiology of SLLs remains elusive, SLLs should be visualised on cerebral MRI, patients with SLEs should receive AEDs and NO-precursors, and the cause of muscle progressive weakness in all three patients should be provided.

REFERENCES

4. Liu, F., Ruan, W., Wang, Y., & Lan, X. (2019). Simultaneous 18F-FDG PET/MRI Assists Diagnosis of a Rare Disease, MELAS. *Clinical Nuclear Medicine, 44*(1), 81-82. doi: 10.1097/RLU.0000000000002344.