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Letter to the Editor

Status Epilepticus and Multifocal Brain Lesions are not Uncommon in m.8993T>G-Related Leigh Syndrome with SARS-CoV-2 Infection

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Letter to the Editor

We reviewed the article by Treitel *et al*. on a 2-month-old boy with Leigh syndrome (LS) due to the homoplasmic variant m.8993T>G in MT-ATP6, which presented with refractory status epilepticus (SE) in the left temporal lobe, hypocitrullinemia, elevated 3-hydroxyisovalerylcarnitine, elevated propionylcarnitine, and excretion of lactate and pyruvate in the urine [1]. Cerebral MRI showed a large region with non-contrast-enhanced signal deviation in the left temporal lobe, which was hyperintense on T2/FLAIR, as well as DWI-hyperintense lesions in the basal ganglia, the right temporal lobe, and punctate foci in the bilateral midbrain [1]. Despite optimal treatment, the patient died five weeks after admission. The study is interesting, but some points should be discussed.

The first point is that we disagree with the view that the index patient exhibited atypical phenotypic features of LS. Refractory epilepsy is a common initial symptom of LS and has been described previously [2]. Hypocortullinemia, elevated 3-hydroxyisovalerylcarnitine, and propionylcarnitine levels have also been described as features of LS patients, particularly in patients with a variant in MT-ATP6 [3]. Why the patient had asymmetric brain lesions is unknown, but it is possible that the existing lesions would have developed into symmetric lesions over time. Since the patient died prematurely, there may not have been enough time for the typical radiological features to develop. It is also conceivable that the brain lesions present were due to the concomitant SARS-CoV-2 infection and were not related to the genetic defect.

The second point is that the index patient did not undergo an autopsy [1]. In order to assess the nature of the brain lesions and determine important genetic characteristics in the mitochondrial DNA of neurons and glial cells, it would have been crucial to examine the clinically and radiologically affected brain tissue. An autopsy can provide a definitive diagnosis of LS by revealing characteristic brain lesions (necrosis, gliosis in the basal ganglia/brain stem) that were overlooked in imaging [4t]. An autopsy can also identify findings in organs other than the brain, such as the heart, gastrointestinal tract, peripheral nervous system, muscles, and endocrine organs [4]. An autopsy can also provide insights into the course of the disease, which is crucial for understanding the mitochondrial basis and choosing treatment, even if the imaging appears clear.

The third point is that the mtDNA copy number was not specified [1]. The mtDNA copy number influences the expression of an mtDNA variant by acting as a buffer or amplifier of an mtDNA variant [5]. Higher copy numbers can compensate for a pathogenic variant and lead to milder symptoms, while lower numbers exacerbate dysfunction and cause a more severe course of disease [5]. This occurs through altered efficiency of oxidative phosphorylation and mitochondrial translation and serves as a compensatory mechanism or biomarker for disease severity [5].

The fourth point is that the mtDNA haplotype has not been described as a modifier of the phenotype [6]. The mtDNA haplotype alters mitochondrial function through interaction with nuclear DNA (nDNA), thereby influencing cellular properties such as energy metabolism, bioenergetics, differentiation, reproduction, fusion, fission, and disease risk. These changes lead to complex traits such as aging, metabolic health, and muscle development [6]. Different haplotypes set different mitochondrial set points for energy production, thereby influencing the cellular stress response. This leads to different gene expression patterns and even changes in DNA methylation in nDNA, which ultimately shapes the phenotype [6].

The fifth point is that SE was described as refractory, but at the same time it is mentioned that the seizures were controlled by the administration of phenobarbital, fosphenytoin, and levetiracetam [1]. This discrepancy should be clarified.

The lactate levels in the CSF, tests for SARS-CoV-2 in the CSF, and the results of CSF cytokines, chemokines, and glial cell factors, which may be elevated in SARS-CoV-related brain disease, are missing. What treatment did the patient receive for the SARS-CoV-2 infection?

Overall, SE and asymmetric cerebral lesions are not an unusual feature of LS. Since the patient was also infected with SARS-CoV-2, it cannot be ruled out that the reported cerebral lesions are due to a complication of the viral infection and are not related to the genetic disorder.

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