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Letter to the Editor

Episodic Sensorimotor Hemisyndrome in Carriers of GJB1 Variants does not Correspond to Stroke-Like Episodes in Mitochondrial Disorders

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Letter to the Editor

We read with interest the article by Zhong *et al*. read about a 37-year-old man with X-linked Charcot-Marie-Tooth disease due to the novel variant c.256_ 257insCCCCATCTCCCATGTGCGGCTGTGGTCCCTGCAGC TCATCCTAGTTTCCA (p.Ala88fsTer13) in GJB1, whose medical history was additionally positive for recurrent stroke-like episodes (SLEs) caused by the visit to high altitudes of maximum 3960 meters [1]. In the last episode, cerebral MRI showed bilaterally symmetrical DWI hyperintense lesions in the periventricular deep white matter and centrum semiovale with corresponding hyperintensity on FLAIR (fluid-attenuated inversion recovery) images [1]. Clinical and imaging abnormalities completely disappeared within one month of onset [1]. The study is interesting, but some points should be discussed.

The first point is that we disagree with the assumption that the index patient actually suffered a SLE [1]. SLEs are a hallmark of mitochondrial disorders (MIDs), particularly mitochondrial encephalopathy, lactic acidosis and stroke-like episode (MELAS) syndrome. SLEs in MIDs are characterized by a cerebral lesion known as stroke-like lesion (SLL), which is characterized by typical location, extent, dynamics, morphology and outcome [2]. SLLs are most often located in the occipito-temporal area, are not limited to one vascular area and initially expand to a maximum and then retract again [2]. On multimodal MRI, SLLs appear as hyperintensity on T2/FLAIR, diffusion-weighted imaging (DWI), and perfusion-weighted imaging (PWI) [2]. They appear as hypointensity on the oxygen extraction fraction (OEF) MRI [2]. On apparent diffusion coefficient (ADC) maps, they can be hyperintense, hypointense or isointense [2]. FDG positron emission tomography (PET) typically shows hypometabolism in the area of the SLL. Magnetic resonance spectroscopy (MRS) typically shows a lactate peak and a reduced N-acetylaspartate (NAA) peak [1]. Magnetic resonance angiography can show compensatory migratory vasodilation [3]. We should know whether all of these modalities were used in the index patient and whether their results corresponded to the characteristics of a SLL. Unless the index patient also carried a pathogenic variant in the mtDNA, it is quite unlikely that he actually suffered four mitochondrial SLEs. A strong argument against mitochondrial SLE in the index patient is also that the imaging findings shown in Figure 2 demonstrate a bilaterally symmetrical lesion. However, the bilateral lesions shown in Figure 2 do not explain the right-sided hemiparesis. A shortcoming of the study is that it did not report how long each previous SLE lasted. SLLs usually last days or weeks and resolve completely or end as focal atrophy, white matter lesion, cyst, laminar cortical necrosis, or the black toenail sign [4].

The second point is that no results from cerebrospinal fluid (CSF) studies have been reported [1]. To rule out infectious or autoimmune encephalitis, it would have been crucial to examine the CSF for cells, glucose, lactate, protein, antibodies associated with autoimmune encephalitis, and neurotropic viruses, including SARS-CoV-2.

The third point is that it was not reported what symptoms the patient developed when he reached the high altitude [1]. Did the patient have symptoms of high altitude pulmonary edema (HAPE) or even high altitude cerebral edema (HACE)? Did hemiparesis develop during ascent to high altitudes or descent? Although not fundamentally ruled out, high altitude illnesses are rare at altitudes below 4000 meters [5].

The fourth point is that it is incomprehensible why the cause of the SLEs was not clarified earlier [1]. The patient reportedly suffered four SLEs within 20 years [1], suggesting that the first SLE occurred at the age of 17 years. What were the clinical, imaging and CSF findings in the last three episodes? Were the imaging findings in the previous episodes the same as in the current episode? Was the hemiparesis always on the right side or did the laterality change?

Overall, recurrent hemisyndrome in GJB1 variant carriers should not be confused with SLEs, which are pathognomonic of

MIDs. An epileptogenic or vascular cause of the hemisyndrome is more likely than a metabolic defect. Complicated migraines should also be ruled out.

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