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Letter to the Editor

Basal Ganglia Calcification Due to Hypoparathyroidism is a not Uncommon Phenotypic Manifestation of Mitochondrial Disorders

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Letter to the Editor

We read with interest the article by Wang *et al*. on a 5-year-old boy with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome) due to the m.3243A>G variant in MT-TL1, which phenotypically manifested as vomiting, seizures, lactic acidosis, hypocalcemia, hypoparathyroidism, and basal ganglia calcification [1]. The patient benefited from treatment of the seizures with midazolam and levetiracetam [1]. The study is interesting, but some points should be discussed.

The first point is that the diagnosis of MELAS is not certain [1]. The phenotypic hallmark of MELAS is a stroke-like episode (SLE) [2], but no SLE was reported in the index patient. Furthermore, the patient does not meet either the Hirano or Japanese criteria for the diagnosis of MELAS [3, 4]. According to the Hirano criteria, MELAS is diagnosed when SLEs occur before the age of 40 and seizures or dementia, lactic acidosis or ragged red fibers, normal early development, recurrent headaches, or recurrent vomiting are present [3]. According to the Japanese criteria, MELAS is diagnosed when there are signs of encephalopathy associated with dementia or epilepsy, SLEs in early life, and biochemical evidence of mitochondrial dysfunction, such as acidosis and the presence of rifted red fibers (RRF) on muscle biopsy [4]. Based on these considerations, the index patient should not be diagnosed with MELAS syndrome, but rather with a non-syndromic mitochondrial disorder (MID) due to the heteroplasmic variant m.3243A>G.

The second point is that, apart from heteroplasmy, no other determinants for the m.3243A>G phenotype have been described [1]. In addition to the heteroplasmy rate, the m.3243A>G phenotype is also determined by the haplotype [5] and the mtDNA copy number [6]. The mtDNA haplotype alters mitochondrial function through interaction with nuclear DNA, thereby influencing cellular properties such as energy metabolism, differentiation, fusion, fission, and disease risk [6]. Different haplotypes set different mitochondrial targets for energy production, resulting in different gene expression patterns and even changes in nDNA methylation, which ultimately shape the phenotype [5]. The mtDNA copy number influences the effect of an mtDNA variant by acting as a buffer or amplifier of an mtDNA mutation [6]. Higher mtDNA copy numbers can compensate for a pathogenic mutation and lead to milder symptoms, while lower numbers exacerbate dysfunction and cause a more severe disease course [6].

The third point is that lactate was not measured in the CSF, either by direct analysis or indirectly by magnetic resonance spectroscopy. MELAS typically manifests not only as lactate acidosis in serum, but also in CSF [7]. It is therefore crucial to test these patients for lactate acidosis in CSF.

The fourth point relates to the right occipital lesion on MRI, which was hyperintense on T2, FLAIR, and DWI [1]. This lesion could be a stroke-like lesion (SLL), the morphological equivalent of an SLE, but several features of an SLL were not reported. If the lesion was also hyperintense on perfusion-weighted imaging, if it was hypointense on oxygen extraction fraction, and if it showed dynamic changes with initial expansion and regression to normal brain tissue or a white matter lesion, cyst, atrophy, laminar cortical necrosis, or toenail sign, it can be classified as an SLL [7, 8].

Overall, carriers of the m.3243A>G mutation require comprehensive investigation to determine whether the phenotype can be classified as syndromic or non-syndromic MID. Basal ganglia calcifications are a common finding in MIDs, and hypoparathyroidism is a common endocrinological abnormality in these patients.

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