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Elevated Body Temperature in Mitochondrial Disorders Results from Uncoupled Oxidative Phosphorylation

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Abstract

In a recently reported patient with Leigh syndrome due to the mt DNA variant m.9176T>C, a unique phenotypic feature, elevated body temperature, was reported for the first time in adult onset Leigh syndrome. Elevated body temperature was most likely not of central origin but due to uncoupling of the oxidative phosphorylation in muscle cells. It is als conceive a bole that an immunological defect due to the underlying metabolic defects, facilitated the development of chronic infections. In this respect we should know the biochemical defect of the oyidative phosphorylation.

Key words: metabolic myopathy, neuropathy, mt DNA, fever, aseptic meningitis,

letter to the Editor

In a recent article, Wei et al. reported about a 26yo male with adult-onset Leigh syndrome (LS) due to the mtDNA variant m.9176T>C in the MT-ATP6 gene [1]. The patient manifested with ataxia, spasticity, nystagmus, hypoacusis, myopathy, neuropathy, lactic acidosis, and elevated body temperature, which was regarded as unique [1]. We have the following comments and concerns.

We do not agree with the explanation that elevated body temperature was of central origin (central fever) [1]. The strongest argument against central fever is that no hypothalamic lesion was described. The patient had bilaterally symmetric lesions of the basal ganglia, the brain stem, and the periaqueductal grey matter in the midbrain but no hypothalamic lesion [1]. The beneficial effect of cooling is no argument for central fever since this effect may be seen also with other causes of fever. The more likely cause of elevated body temperature than central fever

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in the described patient is uncoupling of the oxidative phosphorylation (OXPHOS). Mitochondria are not only responsible for energy production but have a number of other functions as well, such as calcium buffering, apoptosis, ageing, iron handling, hem synthesis, and temperature production by uncoupling the ox hydrogen reaction. An argument against the hypothalamus as the origin of central fever is that lesions of the hypothalamus rather go along with hypothermia than with hyperthermia [2].

Since mitochondrial disorders (MIDs) may also manifest in the cellular immune system [3], it is conceivable that these patients are prone to acquire more frequently infectious disease due to this "genetic immunodeficiency". Particularly viral infections may go along with normal findings on cerebrospinal fluid (CSF) investigations.

To document the pathogeni city of the mt DNA variant, it would be worthwhile to document the presumed biochemical defect of complex-V of the respiratory chain. In case material of the biopsy is still available, it is crucial that biochemical investigations of the muscle homogenate are carried out.

Concerning polyneuropathy, it has to be stressed that it is not an unusual manifestation of a MID [4]. Particularly in patients with NARP, MNGIE, and SANDO due to POLG1 mutations, neuropathy can be a dominant phenotypic feature. More frequently than in specific MIDs, neuropathy occurs as a primary manifestation of non-specific MIDs (mitochondrial multiorgan disorder syndromes (MIMODSs)). Neuropathies can also occur as a secondary complication of primary MID manifestations, such as diabetes, hypothyroidism, hypoparathyroidism, renal insufficiency, or paraneoplastic, since the prevalence of malignancies is increased in MIDs [5].

Table 1 lists 6 patients with normal cerebral MRI and a single patient with mild cerebellar atrophy on MRI. Thus, 7 patients did not fulfil the radiological criteria for LS. Why these 7 patients were nonetheless classified as LS?

Overall, this interesting study could be more meaningful if biochemical investigations, and investigations of the cellular immune system, and MR spectroscopy investigations would have been carried out and if the family history would have been taken carefully. There is also a need to prospectively investigate all MID patients for multisystem involvement at the initial investigation and during follow-up, as MIMODS is the end stage of a MID, if patients survive long enough.

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