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CLARIFYING THE DIAGNOSIS OF EPSTEIN-BARR VIRUS RELATED MYOSITIS IN A GENETICALLY CONFIRMED MITOCHONDRIAL DIABETES PATIENT

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KEYWORDS

Mitochondrial diabetes, MIDD, Epstein-Barr virus, myositis, statins

LETTER TO THE EDITOR

Dear Editor,

We welcome the opportunity to respond to the letter by Dr. Josef Finsterer regarding our article on Epstein–Barr virus (EBV)-related myositis in a patient with maternally inherited diabetes and deafness (MIDD)[1,2]. We are pleased to provide clarification on the points raised.

1. *Lack of genetic confirmation of MIDD:*
   Dr. Finsterer notes that our report did not include confirmation of the underlying MT-TL1 mutation (m.3243A>G). Genetic confirmation of MIDD was already established in a previous publication referenced in our article[3]. The index patient had undergone molecular genetic testing by polymerase chain reaction (PCR) and direct sequencing analysis. This identified the m.3243 A > G mutation at an intermediate heteroplasmy level (30-70%) in peripheral lymphocyte DNA, thereby confirming the diagnosis of MIDD. A detailed family tree covering 5 generations was also provided in the same publication[3].
   To avoid redundancy, we did not duplicate the entirety of that material in the current article, which focused on the acute presentation of EBV-related myositis. Nevertheless, the mitochondrial diagnosis was unequivocally confirmed before the EBV-related event.
2. *Classification as MIDD vs. MIDD-plus:*
   It is mentioned that our patient should have been diagnosed with "MIDD plus". We agree that in addition to diabetes and sensorineural hearing impairment the patient demonstrated multisystem involvement i.e. renal disease and abnormal brain imaging consistent with what has been described by Dr. Finsterer as a "MIDD plus" phenotype - the patient did not have hypertension and hypothyroidism as erroneously mentioned by Dr. Finsterer[4].
   It is well established that MIDD is a heterogeneous disease with various clinical features, as mitochondria are present in every cell of the human body except red blood cells. Hence, any human organ that depends on energy metabolism can be affected (such as central and

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peripheral nervous system, endocrine system, retina, skeletal muscle, heart and kidney)[3,5–7]. Additionally multisystem involvement falls within the spectrum of phenotypic heterogeneity of the m.3243A>G mutation possibly depending on the degree of heteroplasmy and energy requirements of every different tissue[6,8]. The term MIDD-plus has not been widely adopted and in line with the existing literature we have used the term MIDD while acknowledging systemic manifestations.

3. *Evidence for EBV-associated myositis:*

Dr. Finsterer points out that the diagnosis of myositis is not substantiated in our patient given the fact that muscle biopsy was not performed and EBV particles were not identified in muscle fibres.

Although little is known with regard to the mechanisms by which viruses cause muscle injury, proposed mechanisms include not only direct invasion of muscle tissue by the viral agent, but also systemic inflammation associated with cytokine storm as well as autoimmune processes[9–13]. The main histopathologic feature is that of muscle fibre injury rather than invasion of muscle tissue by inflammatory cells or viruses. Muscle biopsy may be entirely normal or may demonstrate varying degrees of necrosis[13–16]. High quality evidence suggests that EBV levels can fluctuate in tissues during the course of the disease or can present in only a small percentage of cells, making it difficult to detect[17]. Thus, excluding myositis when having negative detection can lead to false conclusions. The diagnosis of acute viral myositis in most cases is made on clinical grounds[9]. Nerve conduction studies may be performed to confirm disease localization and muscle imaging, and biopsy are reserved only for special occasions.

The diagnosis of EBV-related myositis in our patient was based on acute-onset diffuse myalgia, modest creatine kinase (CK) elevation, elevation of liver enzymes, EBV IgM positivity, and complete recovery within four weeks. We feel that muscle biopsy would have not influenced management.

Regarding the suggestion of abortive rhabdomyolysis: the absence of significant CK elevation (less than 1000 units/l) or myoglobinuria, the stable renal function, and the lack of electrolyte abnormalities made this diagnosis unlikely.

While no absolute cut-off value for CK elevation is defined, serum CK is usually >5000 units/l with non-exertional rhabdomyolysis and >10,000 units/l with exertional rhabdomyolysis. In a series of 475 hospitalized patients with rhabdomyolysis, the mean peak CKP reported for each of a variety of different causes ranged from approximately 10,000 to 25,000 units/l[18].

4. *Absence of lactate data:*

Lactate levels were not measured during the acute illness as they were not offered in our country at the time. They were well within normal range when measured a few years later. However, the anion gap during the acute episode was normal. This finding argues against lactic acidosis or metabolic decompensation as the cause of myalgia and points towards myalgia caused by myositis given also the rest of the clinical picture.

5. *Use of statins in mitochondrial disease:*

We agree that statins should be used with caution in patients with mitochondrial disease. The patient was commenced on statin therapy (atorvastatin) for hyperlipidaemia before the diagnosis of MIDD was established. After MIDD confirmation, there was no clinical or biochemical evidence of myopathy - his CK levels were within the normal range without myalgias - and therefore continuation of statin therapy with routine monitoring was considered appropriate. This approach is consistent with current clinical practice[19]. Statins may be used cautiously in patients with mitochondrial disease provided there is no baseline myopathy and CK is monitored regularly. Evidence from patients with mitochondrial diseases that used statins for an average of 2 years (equivalent of 20 mg of atorvastatin daily) suggested no obvious statin-induced adverse events in these patients[20].

Statin was temporarily discontinued during the EBV-related episode. After symptom resolution, re-initiation of statin (rosuvastatin) in addition to ezetimibe for more than 8 years now has not caused any CPK elevation, making it unlikely that the myopathy was solely statin-induced. It is possible however that the previous statin use as well as the mitochondrial disease contributed to the EBV induced CPK elevation and myositis.

We thank Dr. Finsterer for his comments. The patient's mitochondrial diagnosis had been genetically established and published prior to the episode of EBV induced myositis. Viral detection in muscle biopsy is not an essential element for the diagnosis of viral myositis. The purpose of our article was to highlight the occurrence of acute EBV-associated myositis in the context of known m.3243A>G disease and statin use. We believe the clinical picture, laboratory data, and complete recovery support this diagnosis.

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