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Mitochondrial Diabetes in MELAS Syndrome

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LETTER TO THE EDITOR

In a recent article, Murakami et al. reported about a study of 14 patients with MELAS due to the m.3243A>G mutation, of which 13 had diabetes [1]. Eight patients developed diabetes prior to the diagnosis of MELAS, 4 concurrently when diagnosing MELAS, and 1 after diagnosing MELAS [1]. Cognitive dysfunction, poor glycemic control, and severe hypoglycemic events were more frequent among the 8 with early onset diabetes compared to those with late onset mitochondrial diabetes [1]. We have the following comments and concerns.

The main disadvantages of this study are the small group size and the single center and retrospective design. These shortcomings may distort all results and may urge for performing better powered, prospective, multi-center studies. Comparing 8 with 6 patients has low statistical power and may give rise to false interpretations and more questions than solutions.

How to explain that cerebrospinal fluid (CSF) lactate was lower among those with early onset diabetes as compared to those with late onset diabetes? Was cerebral involvement more severe among those with late onset diabetes or did these patients more frequently experience seizures or stroke-like episodes than those with early onset diabetes? Was the number of abnormalities on cerebral MRI higher among the late diabetes compared to the early diabetes group?

Occasionally, MELAS patients receive steroids for stabilisation of the metabolic breakdown [2]. In how many of the included patients was diabetes triggered by prior application of steroids? Was there a difference concerning the current medication between the two groups?

Were heteroplasmy rates different between the two groups of patients? Were heteroplasmy rates higher among the eight patients with early onset diabetes compared with late onset diabetes? Were heteroplasmy rates different between muscle, lymphocytes, and urinary epithelium?

Cognitive impairment is a frequent phenotypic feature of mitochondrial disorders [3]. MELAS patients may not only develop cognitive decline because of diabetes or stroke-like episodes but simply because of the metabolic defect also in neurons. This pathomechanism is effective even in the absence of diabetes. To assess if diabetes contributed to the cognitive decline in the presented series of patients it would be interesting to know their individual HbA1c values. In case they were low, diabetic encephalopathy is rather not the key to the pathogenesis of the cognitive decline.

In how many of the 8 patients with early diabetes did delayed diagnosis of MELAS contribute to early progression of the disease? In how many of these 8 patients were mitochondrion-toxic drugs given without being aware of the mitochondrial nature of diabetes? How many of the eight early diabetes patients deteriorated during general anesthesia as has been reported in some of the patients with a mitochondrial disorder [4].

In how many of the 14 patients was the family history positive for diabetes or MELAS? How many of the first degree relatives had MELAS plus diabetes? MELAS is usually a multisystem disease involving the cerebrum, endocrine organs, the gastrointestinal tract, the eyes, ears, peripheral nerves, heart, kidneys, and the muscles [5]. Were the 14 patients systematically screened for multiorgan disorder syndrome (MIMODS)? Which were the clinical manifestations of MIMODS in the 14 reported patients?

Overall, this interesting study could profit from providing more comprehensive data about single patients and their families. To receive more reliable data about differences between early and late onset diabetes in MELAS patients a

prospective and multi-center design with a significantly larger number of patients is warranted.

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