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Letter to the Editor

The Management of Mitochondrial Diabetes Requires Comprehensive Genetic and Phenotypic Information and an Individualised Approach

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Letter to the Editor

We read with interest the article by Oppenheimer *et al*. on a retrospective study involving 15 patients with mitochondrial diabetes [1]. In addition to diabetes, 80% of patients also suffered from hearing loss, and 53% from muscle weakness [1]. The diabetes was treated with insulin and sulfonylureas. Some patients were also prescribed biguanides [1]. Three subjects reported a subjective improvement after taking a mitochondrial cocktails [1]. The study is interesting, but some points should be discussed.

The first point is the retrospective design of the study [1]. Retrospective designs have several disadvantages, such as poor data quality, missing data, the inability to prove causality (only association), susceptibility to memory bias and selection bias, difficulties in controlling for confounding variables, and a generally lower level of evidence compared to prospective studies [2]. Accordingly, the "Methodology" section of the index study stated that not all participants completed the follow-up questionnaire, which led to inconsistencies and inaccuracies in the data collected [1].

The second point is that diabetes in a patient with a mitochondrial disorder (MID) does not necessarily mean that the diabetes is also attributable to the underlying MID. Since four of the 14 patients with the m.3243A>G variant had fathers with diabetes, it should be ruled out that the diabetes in these four patients was transmitted through the paternal line and not through the maternal trait. Did the mothers of these four patients also have diabetes?

The third point is that mitochondrial diabetes can occur not only in syndromic MIDs such as MELAS and MIDD, but also in several other syndromic and non-syndromic MIDs [3]. Since MIDs can be based on mutations in both mtDNA and nDNA genes, it should be borne in mind that MID should be suspected in any patient with an unknown cause of diabetes until it is either confirmed or ruled out.

The fourth point is that "mitochondrial cocktails" have not shown any positive effect in appropriately designed studies on MIDs. Mitochondrial cocktails are usually administered out of desperation because there is no causal therapy for MIDs. It is therefore an unvalidated therapy designed to conceal the helplessness of physicians in the absence of a causal therapy.

The fifth point is that there was no report on how many of the 15 patients had lactic acidosis in their serum or cerebrospinal fluid. In order to assess whether patients with an mtDNA mutation are at risk of developing lactic acidosis when taking metformin or another biguanide, it is important not only to know the determinants of the phenotype, but also to know whether these patients already had lactic acidosis before starting metformin therapy.

The sixth point is that the heteroplasmy rates were not reported in patient 1 [1]. Since heteroplasmy rates in clinically affected tissues are a key determinant of phenotype, along with mtDNA copy number and haplotype, it is essential to determine and report this ratio. High heteroplasmy rates could explain why patient 1 developed a multisystem disease including malignancy [4].

The last point relates to patient 1, who reportedly suffered from weakness, polyuria, and polydipsia at the age of 21 when diabetes was first diagnosed [1]. However, it was not specified what was meant by "weakness" [1]. Do the authors mean muscle weakness, or do they mean fatigue, exercise intolerance, or depression? In order to characterize the phenotype of this patient, it would be essential to describe exactly what type of weakness was meant.

In summary, the index study has limitations that may affect the results and their interpretation. Prospective studies with patients with mitochondrial diabetes are needed to establish a robust genotype-phenotype correlation, provide optimal support for these patients throughout the course of the disease, and offer adequate and informed genetic counseling.

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