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Letter to the Editor

The management of mitochondrial diabetes due to the m.3243A>G variant requires multidimensional considerations

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Letter to the Editor

We read with interest the article by Ng *et al*. on a retrospective study of glucose-insulin secretory response to oral glucose, response to glucose-lowering therapy and heteroplasmy/phenotype correlation in 34 m.3243A>G carriers with diabetes [1]. Seven patients had glucose intolerance or impaired fasting glucose, and all had impaired insulin secretion and sensitivity [1]. One patient was switched from insulin to sulfonylurea, and two patients receiving SGLT2-I and GLP-1 agonists switched to insulin [1]. The study is noteworthy, but some points require further discussion.

The first point is that MIDD may not only be a disorder that manifests with diabetes and deafness, but may have a broader phenotypic spectrum, also referred to as MIDD plus [2]. Organs that may be additionally affected include the brain, eyes, heart, kidneys, peripheral nerves or skeletal muscles. In the brain, MIDD can manifest with leukoencephalopathy, atrophy, basal ganglia calcifications, seizures or cognitive impairment [2]. In the peripheral nervous system, MIDD can manifest not only as neuropathy but also as myopathy. MIDD can also be associated with short stature and lactic acidosis. Therefore, we should know how many of the included patients had other mitochondrial features besides diabetes and deafness. In particular, the 14/34 patients with lactic acidosis and the three patients with cardiomyopathy are expected to have multisystem involvement.

The second issue is that it was not reported whether all mothers of the 27 included patients with diabetes were systematically tested for the presence of the m.3243A>G variant [1]. mtDNA variants are transmitted through the maternal line in 75% of cases [3], suggesting that approximately 20 of the included patients inherited the m.3243A>G variant from their mother. Knowing whether the variant was sporadic or inherited is crucial as it can significantly influence genetic counseling.

The third point is that m.3243A>G carriers with diabetes often have a history of acute or chronic pancreatitis [4]. Therefore, we should know how many of the included patients had a history of pancreatitis and how many of them developed diabetes after pancreatitis.

The fourth point refers to the relationship between heteroplasmy and phenotype [1]. The disadvantage of heteroplasmy determined in blood lymphocytes is that lymphocytes are usually not affected by the underlying m.3243A>G variant. Therefore, the significance of a correlation with the phenotype is limited. The correlation is usually stronger when heteroplasmy is determined in clinically affected tissues. In addition, the phenotypic expression of the m.3243A>G variant may depend not only on the heteroplasmy rate but on several other influencing factors. These include the threshold at which an mtDNA variant becomes symptomatic, the mtDNA copy number, the haplotype and the nuclear background [5]. As long as these additional factors are not included in the establishment of the genotype-phenotype correlation, it may remain weak.

To summarize, the study of interest has limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the study's message and needs to be clarified. The diagnostic and therapeutic management of mitochondrial diabetes due to the m.3243A>G variant requires multidimensional considerations.

Declarations

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