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Letter to the Editor

Before Attributing Mitochondrial Diabetes to the Variant m.7479G>A, it's Pathogenicity must be Proven

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Letter to the Editor

We read with interest the article by Danek *et al*. about a 71-year-old patient with long-standing mitochondrial diabetes mellitus, which was attributed to the m.7479G>A variant in the MT-TL-1 gene with a heteroplasmy rate of 14% in blood lymphocytes [1]. Her blood glucose was controlled with metformin and gliclazide [1]. The article concluded that mtDNA sequencing should be performed in patients with atypical diabetes mellitus and maternal inheritance [1]. The study is noteworthy, but some points warrant discussion.

First, the pathogenicity of the m.7479G>A variant has not been established [1]. There is no evidence that other family members with diabetes also carried this variant, no functional or biochemical validations have been performed to demonstrate a disturbance of cellular energy production, no segregation analysis has been performed, the degree of heteroplasmy was low, higher degrees of heteroplasmy in clinically affected tissues have not been documented, there have been no measurements of respiratory chain complexes and no single fiber analysis was performed [2].

The second point concerns patient screening for multisystem diseases. Since mitochondrial diseases (MIDs) are often progressive, it is conceivable that the index patient may also develop clinical manifestations in organs other than the pancreas or may already have subclinical multisystem disease. Therefore, examination of the brain, spinal cord, ears, eyes, endocrine organs, myocardium, kidneys, and gastrointestinal tract is essential. These are the organs and tissues most frequently affected in carriers of mtDNA variants [3].

The third point concerns the assumption that mucinous pancreatic cancer is not related to the MT-TL1 mutation [1]. There is evidence that neoplasms occur more frequently in carriers of mtDNA mutations than in individuals without these mutations [4]. Both benign and malignant neoplasms are more common in patients with MIDs than in individuals without MIDs [4].

The fourth point is that a patient with a 21-year history of diabetes and poor glycemic control showed no neuropathy [1]. Were all nerve conduction studies (NCS) in this patient truly normal? Diabetic neuropathy is often asymptomatic in the early stages of the disease. It is also conceivable that the patient described developed small-fiber neuropathy, which is usually not detectable in NCS.

Finally, carriers of MT-TL1 mutations frequently exhibit lactic acidosis [5]. Has serum or cerebrospinal fluid (CSF) lactate ever been measured, and was the value elevated or normal? This is relevant because the patient's diabetes was treated with metformin, which poses a risk of lactic acidosis in carriers. CSF lactic acidosis can also be detected by a lactate peak in magnetic resonance spectroscopy. The NAA peak is usually reduced in these cases.

In summary, carriers of newly discovered mtDNA variants should undergo appropriate testing to confirm their pathogenicity. Furthermore, they should be prospectively screened for subclinical or mild multisystem disease.

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