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Letter to the Editor

m.3243A>G Carriers Require Prospective Investigations for Multisystem Involvement and Close Follow-Ups to Avoid Overlooking New Phenotypic Characteristics

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Letter to the Editor

We read with interest the article by Che *et al*. about a 30-year-old man with mitochondrial diabetes due to the m.3243A>G variant in the MT-TL1 gene. Clinically, the disease manifested with ketoacidosis, insulin resistance, diabetic retinopathy, hearing loss, and neuropathy [1]. In addition to the MT-TL1 variant, the patient also carried the c.1336G>A variant in the CEL gene [1]. The m.3243A>G variant was also detected in the patient's sister, but not in his mother [1]. The study is promising, but some points require clarification and should be discussed.

First, it is unlikely that the patient's mother did not carry the m.3243A>G variant. Since the patient's sister also carried the m.3243A>G variant, it is very likely that this mutation was inherited maternally from the mother of both siblings. Were other first-degree relatives clinically affected or did they carry the causative variant? Was the mother actually the mother of the two siblings?

The second point is that the index patient was not prospectively screened for multi-organ involvement [1]. Mitochondrial diseases are characterized by multi-organ involvement, which is either present at the onset of the disease or develops during its course. Of particular interest is whether cardiac and cerebral involvement were present. Cardiac carriers of the m.3243A>G mutation may exhibit hypertrophic or dilated cardiomyopathy or arrhythmias, while cerebral involvement may present with stroke-like episodes, epilepsy, cognitive impairment, migraine, or extrapyramidal disorders [2, 3]. Were these phenotypic features present in the index patient? Was the arterial hypotension due to heart failure, autonomic dysfunction, or simply malnutrition or dehydration?

The third point is that the CEL gene mutation is associated with pancreatitis [4]. Did any of the carriers of the CEL gene mutation have a history of pancreatitis? Was the mother's diabetes due to the CEL gene variant? How was the pathogenicity of the variant demonstrated? Is it conceivable that the CEL variant was not pathogenic and that the mother carried the m.3243A>G variant, but the blood lymphocytes did not?

The fourth point concerns the index patient, who, in addition to diabetes, hearing loss, and neuropathy, also presented with kidney disease, short stature (163 cm), arterial hypotension, and possibly other symptoms. The m.3243A>G mutation can also lead to lactic acidosis, ataxia, myopathy (ptosis, ophthalmoparesis, limb muscle weakness), gastrointestinal dysfunction, exercise intolerance, chronic vomiting, and miscarriages [5].

Fifth, the low body weight was not explained [1]. Did the patient suffer from loss of appetite, chronic diarrhea or chronic vomiting (a possible phenotypic feature of m.3243A>G carriers), malabsorption, a malignant disease, or was the reduced BMI due to the underlying gene defect? What measures were taken to increase and normalize body weight? Sixth, the patient did not undergo cerebral imaging or an EEG [1]. Since the m.3243A>G variant frequently manifests in the brain, cerebral imaging is mandatory. Equally essential is the recording of an EEG to rule out epileptiform discharges.

In summary, carriers of the m.3243A>G mutation require prospective studies for multisystem disease and close follow-up examinations to avoid overlooking the development of new phenotypic characteristics during the course of the disease.

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