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Letter to the Editor

Carriers of the Variant m.14677T>C Require Comprehensive Testing in Order to Adequately Identify Genotypic and Phenotypic Characteristics

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Letter to the Editor

We read with interest the article by Ueda *et al*. about a 44-year-old man who had suffered from bilateral ptosis and ophthalmoplegia since the age of 42, which was attributed to the mtDNA variant m.14677T>C in tRNA (Glu) with varying heteroplasmy in individual muscle fibers [1]. The study is noteworthy, but some ambiguities should be clarified.

The first point is that in a patient with bilateral ptosis and ophthalmoplegia, brain imaging must be performed to rule out a lesion of the brainstem or supratentorial brain as the cause of the eye muscle weakness. A whole-body computed tomography scan is not the appropriate means of determining whether or not there is a lesion of the brain stem. It would also be interesting to know whether the patient had subclinical symptoms in the brain with atrophy, indentations, or lesions of the white matter, as has been previously reported in patients with mitochondrial disorders that manifested as ptosis and ophthalmoplegia [2].

The second point is that ruling out myasthenia requires not only the determination of acetylcholine receptor and muscle-specific tyrosine kinase antibodies, but also electrophysiological tests such as low- and high-frequency repetitive nerve stimulation, needle electromyography, and single-fiber electromyography [1]. In addition, Simpson and Tensilon tests should have been performed to definitively rule out myasthenia [3]. We should also know whether or not the patient had a thymoma. It should also be noted that approximately 10% of patients with myasthenia test negative for myasthenia-associated antibodies.

The third point is that lactate was only measured in serum, but not in cerebrospinal fluid (CSF). Mitochondrial disorders are known to manifest as elevated lactate levels in CSF [4]. Lactate in the brain can be measured either directly in CSF or by magnetic resonance spectroscopy. It is crucial to know whether or not there is an elevated CSF lactate level, as CSF lactate can trigger seizures and greatly influence the outcome for a patient.

The fourth point is that no first-degree relatives were tested for the mtDNA variant that is believed to be responsible for the clinical presentation [1]. Testing other family members is crucial not only to determine whether the variant was inherited from the mother or arose spontaneously, but also to assess the segregation pattern in the family, establish a genotype-phenotype correlation, and provide genetic counseling.

The fifth point is that it is not clear why the patient waited three years before seeing a doctor to investigate the cause of the double vision [1]. Did the double vision occur only sporadically or was it permanent? Was the patient impaired by the double vision or could it be corrected with prism glasses?

The sixth point is that no adequate explanation was given as to why the patient had normal muscle strength on clinical examination but a muscle biopsy revealed metabolic myopathy. Did the patient show muscle wasting, fasciculations, myokymia, or hypotonia, which could be mild signs of involvement of the limb muscles in the disease?

The seventh point is that the patient was not prospectively examined for multisystem involvement [1]. Mitochondrial diseases are known to frequently be associated with multisystem involvement, either at onset or during the course of the disease. Of particular interest is whether the patient had subclinical involvement of the heart, liver, kidneys, and endocrine organs, which are frequently affected in carriers of mtDNA mutations.

In summary, patients with ptosis and ophthalmoplegia require comprehensive individual and family diagnostics to rule out all differential diagnoses, uncover the genetic background, and treat these patients optimally.

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