Asymmetric parietal and temporal lobe atrophy due to the variant m.8363G>A in transfer ribonucleic acid (Lysine)

Josef Finsterer

Department of Neurology, City Hospital Rudolfstiftung, Messerli Institute, Vienna, Austria.

To the Editor: With interest, we read the article by Xu *et al*[1] about a 54-year old man with a multisystem mitochondrial disorder (MID) affecting the brain, ears, and muscle. Clinical manifestations were attributed to the variant m.8363G>A in *tRNA(Lys)*.[1] We have the following comments and concerns.

The patient had mitochondrial myopathy affecting the limb muscles.[1] We should know if also the facial, extraocular, axial, bulbar, or respiratory muscles, frequently affected in MIDs, were involved at diagnosis or became involved during follow-up. Mitochondrial myopathy due to a mitochondrial deoxy-nucleic acid (mtDNA) transfer ribonucleic acid variant usually goes along with combined respiratory chain defects.[2] Thus, we should know the results of biochemical investigations of the muscle biopsy, particularly if there was reduced activity of a single or multiple respiratory chain complexes. Concerning dysarthria, we should know if it was due to the affection of the bulbar muscles or due to the affection of the brain stem. We also should know if nerve conduction studies revealed axonal or demyelinating polyneuropathy, frequently associated with MIDs.[3] Mitochondrial myopathy is frequently associated with elevation of serum lactate either already at rest or during mild exercise (lactate stress test).[4] We would be interested in the serum levels of lactate and if they increased upon mild exercise below the anaerobic threshold.

Since the involvement of the central nervous system is frequently associated with elevated cerebrospinal (CSF) lactate, we should know if magnetic resonance spectroscopy showed an increased lactate-peak or if direct measurement in the CSF revealed cerebral lactic acidosis.

Phenotypic manifestations of mtDNA variants depend on the amount of mutated mtDNA within a mitochondrion or a cell.[5] Thus we should know the heteroplasmy rates in muscle. Since heteroplasmy rates may vary with the degree of organ involvement we should also know heteroplasmy rates from tissues other than the muscle, such as hair follicles, skin fibroblasts, buccal mucosa cells, urinary epithelial cells, or blood lymphocytes.

The family history of the index patient is unclear. Since 75% of the mtDNA variants are inherited from the mother, we should know if the mother of the index case was clinically affected and if she carried the culprit variant as well.

Brain atrophy is a common phenotypic feature of MIDs. Focal atrophy most frequently concerns the cerebellum or the basal ganglia. Focal atrophy maybe is also the end-stage of a stroke-like lesion. We should be informed about the development of focal atrophies, since focal atrophy may become diffuse with the progression of the disease.

Treatment of MIDs with vitamins, lipoic acid, and co-factors is usually ineffective. We should be informed which clinical manifestations in particular improved and if it is conceivable that the improvement was spontaneous, or simply a placebo effect. We also should know if focal cerebral atrophy improved with the improvement of the clinical manifestations.

Since most of the MIDs are multisystem diseases, either already at onset or become a multisystem condition during the course, as in the index case, prospective investigations for sub-clinical or mildly manifesting multisystem involvement should be carried out. This is of relevance as early detection of organ affection in MIDs, particularly of the heart, may improve the outcome of these patients.

Overall, this interesting case could profit from providing a detailed family history, heteroplasmy rates of various tissues, results of prospective multisystem investigations, information which clinical manifestations improved upon therapy, and the results of the biochemical investigations of the muscle homogenate. MID patients with unusual

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Correspondence to: Dr. Josef Finsterer, Department of Neurology, City Hospital Rudolfstiftung, Messerli Institute, Postfach 20, 1180 Vienna, Austria
E-Mail: fifigs1@yahoo.de

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phenotypes require thorough and comprehensive investigations to broaden the knowledge about the phenotypic spectrum of these disorders.

Conflicts of interest

None.

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