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Letter To The Editor

Leigh-Like Mitochondrial Multiorgan Disorder Syndrome Due To an AIFM1 Mutation

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Abstract

In a recent article Morton et al. reported about a new-born female with mitochondrial disorder(MID) due to a mutation in the *AIFM1* gene on chromosome Xq26.1 encoding for a mitochondrial matrix protein with oxidoreductase activity involved in electron transport, apoptosis, ferredoxin metabolism, reactive oxygen species generation, and immune system regulation. The patient obviously manifested also in the lungs with follicular bronchiolitis and hypertrophic walls of pulmonary arteries. Overall, this interesting report could be enriched by genetic investigation of the aunt with multiple sclerosis, a more detailed description of the nerve conduction and electromyographic studies, revision of the cerebral MRIs, prospective investigations of clinically unaffected organs, and by excluding autonomic neuropathy
Keywords: Mitochondrial, Leigh syndrome, nuclear DNA, mutation, cerebral MRI.

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In a recent article Morton et al. reported about a new-born female with mitochondrial disorder(MID) due to a mutation in the *AIFM1* gene on chromosome Xq26.1 encoding for a mitochondrial matrix protein with oxidoreductase activity involved in electron transport, apoptosis, ferredoxin metabolism, reactive oxygen species generation, and immune system regulation [1]. We have the following comments and concerns.

According to the family history a maternal aunt had multiple sclerosis [1]. Was this aunt tested for the *AIFM1* mutation? Since MIDs may mimic or may overlap with multiple sclerosis [2], it is essential that the aunt is tested for the *AIFM1* mutation. This is of particular interest since female carriers of X-linked diseases, such as in the present case, can manifest clinically as well.

The patient was diagnosed with polyneuropathy by electromyography at 4 weeks of age [1]. Do the authors mean electroneurography? Polyneuropathy is usually diagnosed upon nerve conduction studies. Which nerves were tested and to which degree were amplitudes of compound muscle action potentials respectively sensory nerve action potentials reduced? Did needle electromyography show abnormal spontaneous activity? Were motor unit action potentials enlarged or prolonged? Was the interference pattern dense or reduced? Was abdominal distension attributable to involvement of the autonomic nervous system in the polyneuropathy?

Why did the patient receive dichloroacetate? Dichloroacetate is well-known for its mitochondrion-toxicity and contraindicated in MIDs, since it may cause polyneuropathy [3] although this finding has been challenged by more recent studies [4].

Serial MRI investigations of the brain in the index case showed bilateral T2- and DWI-hyperintensities in the anterior-medial thalami, T2-hyperintensities of the head and body of the caudate nucleus bilaterally and the anterior putamina, and bilateral DWI-hyperintensities in basal ganglia, brainstem and occipital lobes [1]. Was there any indication for Leigh or Leigh-like syndrome in this patient?

MIDs usually present as mitochondrial multiorgan disorder syndrome (MIMODS) either already at onset of the disease or with progression of the phenotype during the disease course [5]. The index case manifested obviously in the brain, muscle, nerve, liver, gastrointestinal tract, and lungs. Were any endocrine organs, the heart, kidneys, bone, bone marrow, or the skin additionally affected?

Seizures in the index case were treated with phenobarbital and gabapentine [1]. Particularly from

phenobarbital it is known that it is mitochondrion-toxic and should not be given as first-line treatment for epilepsy in MID patients [6]. Phenobarbital has been shown to induce morphological changes in liver mitochondria [7] and to induce oxidative stress [8]. Was deterioration of the condition attributable to toxicity of phenobarbital?

The patient obviously manifested also in the lungs with follicular bronchiolitis and hypertrophic walls of pulmonary arteries. Did the patient also develop hyaline membrane disease, pulmonary hypertension, interstitial fibrosis, acute lung hemorrhage, restrictive pulmonary insufficiency, asthma, poor ventilator response to hypercapnia, or obstructive sleep apnea, features previously identified as pulmonary manifestations of MIDs? [9].

Overall, this interesting report could be enriched by genetic investigation of the aunt with multiple sclerosis, a more detailed description of the nerve conduction and electromyographic studies, revision of the cerebral MRIs, prospective investigations of clinically unaffected organs, and by excluding autonomic neuropathy.

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