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Letter To The Editor

Mitochondrial ATP6 Mutation Manifesting With Ataxia, Neuropathy, Diabetes, Hypoacusis, and Hypogonadism

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In a recent article, Kytövuori *et al.*, (Kytövuori, L. *et al.*, 2016) reported about two adult siblings with cerebellar ataxia, polyneuropathy, diabetes, mellitus, sensorineural hearing impairment, and hypergonadotropic hypogonadism due to the novel, heteroplasmic mutation m.8561C>G in the overlapping region of the *MT-ATP6 and MT-ATP8* genes respectively (Kytövuori, L. *et al.*, 2016). We have the following comments and concerns.

The two patients were described to have developed polyneuropathy (Kytövuori, L. *et al.*, 2016). Which type of polyneuropathy was diagnosed and was it due to the underlying mutation (mitochondrial neuropathy) or was it secondary due to the diabetes? Which were the HbA1c values in both patients? Which fiber types were affected in patient 1 and was polyneuropathy in patient 1 of the axonal or demyelinating type?

Mitochondrial disorders frequently manifest phenotypically in the heart with hypertrophic or dilative cardiomyopathy, non-compaction, conduction disturbances, arrhythmias, or pulmonary hypertension (Finsterer, J., & Kothari, S. 2014). Were both patients screened for cardiac disease, or was cardiac disease found in any of the first degree relatives?

Pathogenicity of a mtDNA mutation is usually confirmed by application of in-silico computational prediction, by in-vitro biochemical methods, or by in-vivo studies of knock-in transgenic animals in at least 3 generations (Kasahara, T. *et al.*, 2016). Disadvantage of the present investigation is that the mutation was found only in a single generation, that the amount of ATP was normal in both index cases, and that no knock-in transgenic animal studies were carried out.

Mutations in the mtDNA ATP6 gene may also manifest in the skeletal muscle (Mkaouar-Rebai, E. *et al.*, 2016). Did any of the two siblings present with myopathy and was an EMG or muscle MRI carried out to see if there was muscular involvement or not? Did any of the two patients present with ptosis, ophthalmoparesis, or involvement of the axial muscles, including the respiratory muscles?

Mutations in the mitochondrial ATP6 gene have been also associated with Leber's hereditary optic neuropathy (Gao, M. *et al.*, 2015). Did any of the two patients develop visual impairment during the course? Which were the results of funduscopy, visually evoked-potentials, optical coherence tomography, or flourescein-angiography?

In addition to hypergonadotropic hypogonadism ATP6 mutations may manifest with other endocrine abnormalities, such as hypothyroidism (Hao, X. *et al.*, 2015), or breast cancer (Grzybowska-Szatkowska, L. *et al.*, 2014). Were the two index cases or other relatives systematically investigated for endocrinopathy other than hypogonadism?

There are also reports showing that ATP6 mutations may phenotypically manifest as mitochondrial myopathy, lactic acidosis, and sideroblastic anemia

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(MLASA) (Burrage, L. C. *et al.*, 2008).Were the two index cases investigated for haematological disease?

As mentioned by the authors, ATP6 mutations are frequently associated with maternally inherited Leigh syndrome (López-Gallardo, E. *et al.*, 2014). Did cerebral MRI show bilateral necrosis of the striatum, the midbrain, the medulla, or the cerebellum? Which were the results of the EEG examination?

Overall, this interesting report should be broadenend by investigations of systems other than the ones investigated and by strengthening the pathogenicity of the mtDNA variant found in the two presented patients.

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