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Small-fiber neuropathy and the 3243A>G mutation in mitochondrial DNA

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Sirs: The 3243A>G point mutation in mitochondrial DNA (mtDNA) is associated with the MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) syndrome, and sometimes with additional phenotypes like a sensorimotor polyneuropathy [4, 6]. The occurrence of a small-fiber peripheral neuropathy as the presenting clinical manifestation of a 3243A>G point mutation in mtDNA has, according to our knowledge, not been described previously.

A 35 year old man was referred to our neuromuscular clinic with a history of a tingling sensation in the toes of both feet, which has been present for two to three years, as well as a restless feeling in the legs for many years. One year before presentation he developed burning pain in the toes and then fingers bilaterally. He reported no weakness and had no complaints suggestive of an autonomic disturbance. There was no history of alcohol or drug abuse. He was otherwise healthy and used no medication. Previously, his mother was diagnosed with the 3243A>G point mutation in mitochondrial DNA at the age of 51 years after presenting with ptosis, external ophthalmoplegia, limb-girdle weakness and long-standing diabetes mellitus. She had a mtDNA mutation load of 0.8% in leukocytes and 50% in skeletal muscle.

On examination no muscle atrophy or weakness was evident and all tendon reflexes, including the ankle jerks, were normal. All sensory modalities were intact, including vibration sense testing with a Rydel-Seiffer tuning fork. No ataxia was present and the gait was undisturbed. Extensive investigations including vitamins B1, B6, B12, folic acid, serum lactate, creatine kinase, thyroid function tests, fasting serum glucose and HbA1c, serum lipid profile, angiotensin converting enzyme levels and serum protein electrophoresis were normal. Anti-nuclear, anti-SS-A and SS-B, anti-gliadin, anti-endomysial and anti-neutrophil cytoplasmic (cytoplasmic and perinuclear) antibodies as well as cryoglobulins were all negative. Cranial magnetic resonance imaging and electrocardiography were normal. Leukocyte DNA examination revealed the 3243A>G mtDNA point mutation. The percentage of mutated mtDNA in leukocytes was 16%.

Motor and sensory nerve conduction studies and F-responses were performed in the upper and lower limbs and were all normal, as was the Hoffman reflex of the soleus muscle. Concentric needle EMG of distal muscles in the upper and lower limbs was normal. Quantitative sensory threshold testing (CASE IV) of the left foot was performed according to the manufacturer's protocols. Cold thermal threshold and heat pain was evaluated and the results were compared with normative data. For both cold thermal threshold and heat pain the values obtained were above the 99th percentile, indicating hypoesthesia. In addition, cardiovagal autonomic tests assessing sympathetic and parasympathetic responses were normal. After 18 months of follow-up, no progression of symptoms or involvement of large sensory or motor fibers is evident.

We suggest a direct causal relationship between the documented mutation in mtDNA and the small-fiber neuropathy in this patient, as extensive investigations did not reveal another explanation.

The exact prevalence of neuropathies in patients with MELAS and the 3243A>G mutation in mtDNA is unknown, but estimates range from 5 to 97% [1, 4, 5]. Small-fiber involvement, isolated or in combination with large-fiber involvement, is probably underrecognised. Most studies included only patients with abnormalities on nerve conduction studies, thereby effectively excluding patients with isolated small-fiber neuropathies. In patients present-

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ing with sensorimotor neuropathies, small-fiber involvement may be overshadowed by large-fiber involvement and thus go undiagnosed. Furthermore, these studies provide no information regarding the prevalence of neuropathies in mutation carriers without the MELAS syndrome.

Very little is known about the possible mechanism of peripheral nerve involvement in mitochondrial cytopathies. Mitochondrial failure may just be one of a number of upstream events ultimately leading to axonal degeneration via the activation of calpain, a final pathway probably common to many neuropathies [2]. Furthermore, in a study of vinblastine-treated mice mitochondrial dysfunction correlated strongly with and preceded neurite degeneration [3].

In conclusion, we describe a patient with the MELAS 3243A>G point mutation in mtDNA who presented with clinical and electrophysiological findings suggestive of an isolated small-fiber neuropathy. We postulate that mitochondrial cytopathies should be considered in the differential diagnosis of small-fiber neuropathies. Further studies are needed to confirm the relationship between mitochondrial disorders and small-fiber neuropathies.

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