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Case report

An "inflammatory" mitochondrial myopathy. A case report

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Abstract

We describe a case of an adult male patient with progressive external ophthalmoplegia and upper limb weakness, who presented with an episode of sudden respiratory failure. Muscle biopsy showed ragged-red and COX-negative fibers associated with discrete inflammatory infiltrates and necrotizing features. Apart from artificial ventilator support, he was treated with intravenous immunoglobulins and carnitine, with excellent clinical outcome. Mitochondrial DNA analysis revealed the 3251A > G mutation, previously reported in association with rapidly progressive mitochondrial myopathy and respiratory failure. Our case expands the spectrum of this mutation and suggests a therapeutic attempt with immunoglobulins in mitochondrial patients with acute respiratory failure, at least when this mutation and/or muscle inflammation is present. Moreover, this case supports the idea of a pathologic inflammatory response induced by mitochondrial disease; such an abnormal response may be a contributory factor in disease progression or acute exacerbation typical of some mitochondrial diseases, but further studies are needed.

Keywords: CPEO; Inflammation; IVIg; mtDNA; Respiratory failure

1. Introduction

Mitochondrial diseases comprise a heterogeneous group of disorders characterized by primary defects in mitochondrial function [1]. Moreover, recent studies have suggested a role of mitochondrial dysfunction in idiopathic inflammatory myopathies, based on histological, biochemical and molecular studies [2]. So far, data on therapeutic immunomodulatory approaches in mitochondrial myopathies are not available. Here we report the case of a patient harboring a mitochondrial tRNA point mutation who presented with an episode of sudden respiratory failure associated with inflammatory infiltrates on muscle biopsy, successfully treated with immunoglobulin infusion with an excellent outcome.

2. Case report

A 57-year-old Italian man was admitted to our clinic with bilateral ophthalmoplegia, ptosis, upper and lower limb muscle weakness and gait disturbance with hyperlordosis and mild steppage present since age 45. His mother died at age 65 of "early-onset Parkinson disease" (medical records not available). A mathernal niece has mild proximal muscle weakness and exercise intolerance. The remaining family history was negative for neuromuscular or neurodegenerative disorders. The patient had not taken any myotoxic drugs.

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Laboratory exams revealed increased lactate, both basally (65.9 mg/dL; normal <25.5) and after ischemic forearm exercise (peak 124.9 mg/dL). Mild creatine kinase (CK) increment was also observed (282 U/L; normal <170). Rheumatologic antibodies were absent in the patient's serum. Electromyography was consistent with a myopathic process. Electrocardiogram and echocardiogram were normal, whereas the patient showed an impaired pulmonary function with a reduced maximal inspiratory and expiratory pressure.

During the diagnostic work-up, the patient developed an episode of sudden respiratory failure. He was immediately intubated, ventilated with artificial support, and tracheotomy was then performed. The quadriceps muscle biopsy (Fig. 1), performed the first day of artificial ventilation, showed mitochondrial abnormalities with numerous ragged red fibers, focal mild endomysial mainly CD4-positive inflammatory infiltrates, several necrotic fibers and myophagocytosis. Major histocompatibility complex-I (MHC-1) immunohistochemistry did not show reactivity in the sarcolemma of most normal fibers; membrane attack complex (MAC) staining revealed a sarcolemmal and/or cytoplasmatic reaction in necrotic fibers and in rare endomysial capillaries. Immunostaining for dystrophin, laminin, alfa-sarcoglycan, dysferlin and emerin was normal.

Other neuromuscular or cardiopulmonary causes of respiratory failure were ruled out by appropriate examinations, and the patient was promptly treated with intravenous immunoglobulins (0.4 g/kg/day for 5 days) and i.v. L-carnitine (2 g/day), resulting in significant clinical improvement. He was discharged one month after, and the tracheostomy tube was removed few months later.

Mitochondrial DNA (mtDNA) analysis revealed a A → G transition at position 3251 of the mitochondrial tRNALeu(UUR) gene, virtually homoplasmic in muscle and heteroplasmic in blood (Fig. 2), the mathernal niece has the same heteroplasmic mutation in blood and urine.

3. Discussion

The 3251A > G mtDNA mutation was previously reported in patients with rapidly progressive mitochondrial myopathy and respiratory failure. Sweeney and co-workers [3] reported a family with ocular, neck,

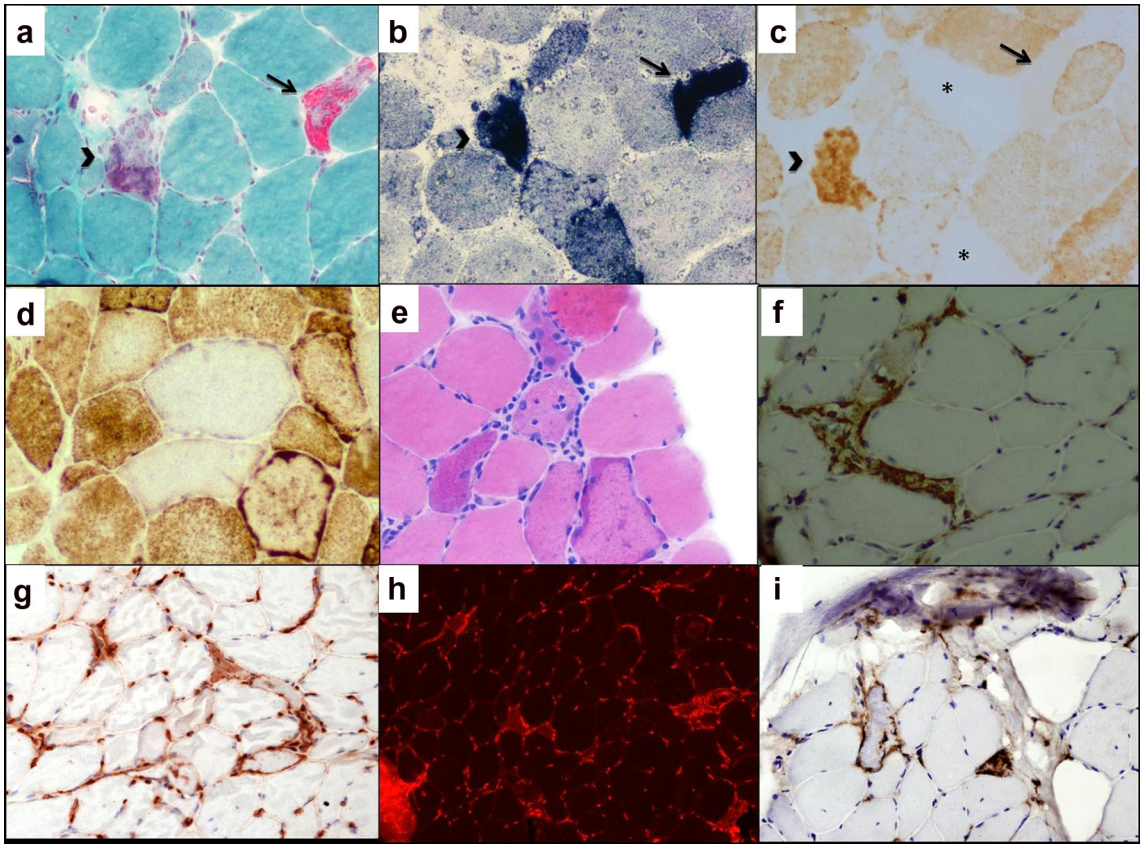

Fig. 1. Muscle biopsy. (a) Modified Gomori's Trichrome staining 20×: two ragged-red fibers, showing (b) intense succinic dehydrogenase (SDH) activity. (c) One of the ragged-red fibers (arrowhead) shows intense cytochrome-c-oxidase (COX) activity, another (arrow) a markedly reduced COX activity; the asterisks signal two COX-negative fibers. (d) COX/SDH-double staining 20× showing COX-negative/SDH-positive fibers. (e) Hematoxylin-eosin staining 20× showing mild focal endomysial inflammatory infiltrate, myophagocytosis, degenerative fibers and a ragged-red fiber. (f) CD4 T-cells immunolabelling 20×. (g) Major histocompatibility complex-I (MHC-1) immunolabelling 20×. (g) Fluorescent MHC-1 immunolabelling 10×: reactivity present in sarcolemma and cytoplasm of degenerative fibers and absent in most of the normal fibers. (h) Membrane attack complex (MAC) immunolabelling 20× revealing a sarcolemmal and/or cytoplasmatic reaction in degenerative fibers and in rare endomisial capillaries.

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