ELSEVIER

Journal of the Neurological Sciences 239 (2005) 21 – 24

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

A case of CPT deficiency, homoplasmic mtDNA mutation and ragged red fibers at muscle biopsy

Monica Sciacco [a,*], Alessandro Prelle [a], Gigliola Fagiolari [a], Andreina Bordoni [a], Marco Crimi [a], Alessio Di Fonzo [a], Patrizia Ciscato [a], Costanza Lamperti [a], Elisabetta D'Adda [a], Stefano Jann [c], Nereo Bresolin [a,b,1], Giacomo P. Comi [a], Maurizio Moggio [a]

[a] *Fondazione IRCCS Ospedale Maggiore-Policlinico Mangiagalli e Regina Elena, Dipartimento di Neuroscienze, Centro Dino Ferrari, Via Francesco Sforza, 35-20122 Milano, Italy*

[b] *Istituto E. Medea IRCCS, La Nostra Famiglia, Bosisio Parini (LC), Italy*

[c] *Divisione di Neurologia, Ospedale Niguarda, Milan, Italy*

Received 28 March 2005; received in revised form 14 July 2005; accepted 15 July 2005
Available online 15 September 2005

Abstract

A 45-year-old male patient had an episode of acute renal failure with myoglobinuria, myalgias, weakness, and markedly increased serum CK levels. Similar episodes had occurred in the past.

Carnitine palmitoyl-transferase II (CPT II) deficiency was documented both biochemically and genetically. Interestingly, muscle biopsy also showed some ragged red fibers (RRF) and complete mitochondrial DNA (mtDNA) sequence disclosed a homoplasmic T3394C point mutation. This mutation is described in Leber's hereditary optic neuropathy (LHON) or in patients with diabetes mellitus.

Keywords: Myoglobinuria; CPT deficiency; Mitochondrial disorder; RRFs

1. Introduction

Recurrent episodes of myoglobinuria are often the main clinical feature of acute "energy" crises caused by defects of muscle metabolism. Disorders of fatty acid oxidation – most frequently carnitine palmitoyl-transferase II (CPT II) deficiency – and of glycogen metabolism are the most common diseases associated with myoglobinuria [1]. More recently, however, recurrent myoglobinuria and rabdomyolisis have been associated with a number of mitochondrial cytopathies sustained by mtDNA mutations [1].

2. Case report

A 45-year-old male patient came to our observation after an episode of acute renal failure due to myoglobinuria, accompanied by intense myalgias and generalized weakness. Symptoms had been triggered by an acute febrile illness for which he had taken non-steroid antiinflammatory medications. Serum CK levels were over 75,000 U/l at onset of symptoms (normal values < 195 U/l) and still around 8000 U/l 1 week later, after he had undergone dialysis (creatinine serum level was 21 mg/100 ml). He completely recovered, with normalization of serum enzymes, in a few weeks. In the past, between the ages of 16 and 30 years, the patient had practiced competitive sports (cycling, athletics, sailing, car rallies) and had presented episodes of myalgias and generalized weakness, often with dark urine, after competitions. Symptoms usually lasted for about 2 days before completely subsiding.

Neurological examination was normal and family history was negative, all family members – parents, 44-year-old

* Corresponding author. Tel.: +39 02 55033851; fax: +39 02 50320430.
E-mail address: maurizio.moggio@unimi.it (M. Sciacco).
[1] Tel.: +39 031 877111.

0022-510X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2005.07.008

brother and 7-year-old daughter–being asymptomatic. Renal function tested by blood routine examination was normal in all family members.

Parents are non consanguineous.

The proband underwent left biceps muscle biopsy, which was normal (including routine histology—histochemistry, histochemical reactions for myoadenilate deaminase, myophosphorilase, phosphofructokinase, and immunohistochemical studies with antibodies against dystrophin and α–γ sarcoglycans) except for the presence of some COX-negative and few COX-positive ragged red fibers (RRF, 2% of total fibers) (Fig. 1).

The clinical picture was highly suggestive for a carnitine palmitoyl-transferase II (CPT II) deficiency, but, given the morphological pattern, we also investigated the possibility of a respiratory chain disorder.

Biochemical carnitine palmitoyl-transferase II (CPT II) assay showed a marked CPT deficiency (isotope 64.5 pmol/min/mg, nv 452±160; forward 147 pmol/min/mg, nv 367±110). CPT2 gene screening [2] revealed that the patient is heterozygous for the common S113L substitution (C338T mutation on exon 3; Fig. 2A, 1st allele). The second mutation is a rare complex heterozygozis (533_534insT; 534_558del) in exon 4. It is an insertion after nucleotide position 533, immediately followed by a 25 nucleotide deletion [4] (Fig. 2A, 2nd allele, and Fig. 2B). CPT mutation study in the patient's family showed that the mother is heterozygous for the common S113L substitution and the father for the rare mutation. Both the brother and the daughter are heterozygous for the common mutation.

Biochemical assay of respiratory chain enzymes only showed a slight decrease of complex IV/cytochrome *c* oxidase (0.248, nv 0.397±0.075).

Mitochondrial DNA (mtDNA) Southern blot analysis excluded the presence of major mtDNA rearrangements.

Complete mtDNA sequence [3] did not reveal any heteroplasmic mtDNA gene mutations, but disclosed a homoplasmic T3394C point mutation. Family screening for this mutation by PCR revealed that it is present in both the mother and the brother, and absent in the father and daughter.

3. Discussion

Skeletal muscle specimens in patients with CPT II deficiency are normal when obtained far from the episodes

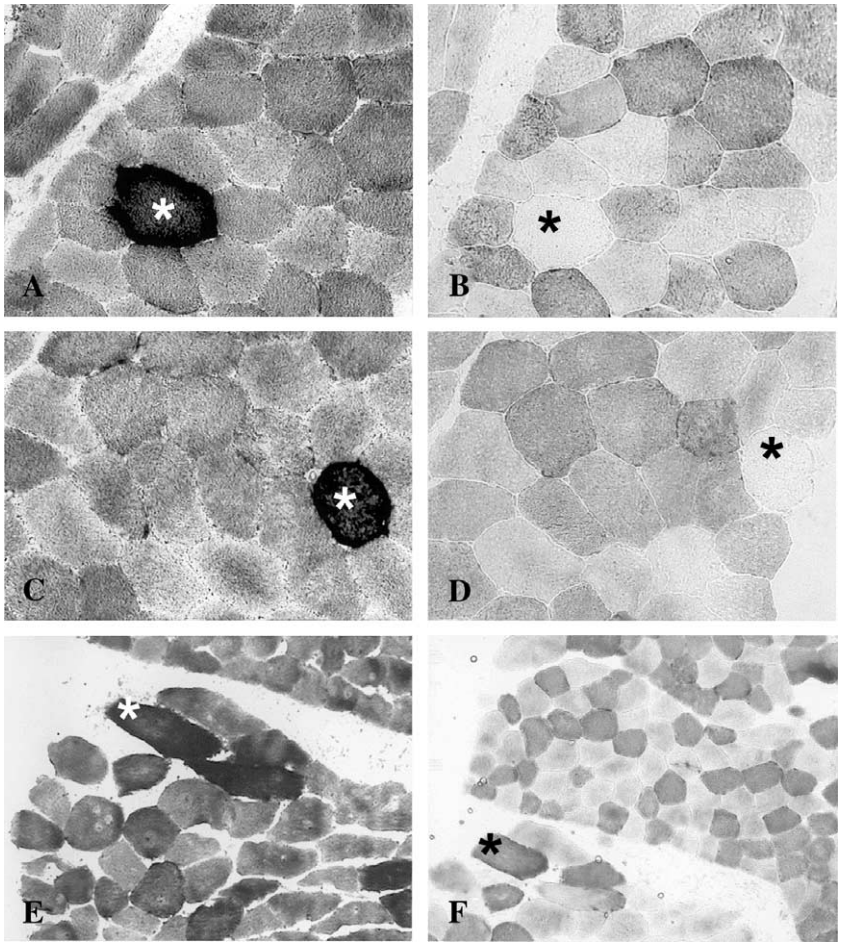

Fig. 1. Histochemical reactions for succinate dehydrogenase (SDH) (A–C–E) and cytochrome *c* oxidase (COX) (B–D–F). RRFs (A–C–E) are both COX-negative (B–D) and COX-positive (F).