Deficit of in vivo mitochondrial ATP production in patients with OPA1-related autosomal dominant optic atrophy. A 31P-MRS study of the skeletal muscle.

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Introduction

Autosomal dominant optic atrophy (ADOA), is the most common form of hereditary optic neuropathy with a disease prevalence ranging from 1:10,000 to 1:50,000 in different populations (1). The disease, clinically characterised by an insidious onset of variable visual loss, is due to a progressive degeneration of retinal ganglion cells (2, 3). In most patients a mutation in the OPA1 gene on the chromosome 3q28 is detected (2, 3). OPA1 encodes a ubiquitously expressed large GTPase related to dynamins, anchored to the mitochondrial inner membrane and implicated in the formation and maintenance of mitochondrial network and morphology (4).

Methods

We studied 6 patients (4 females, 2 males, mean age 43 ± 20, range 18-70) from two Italian families with ADOA. All patients were heterozygotes for the four base deletion c.2708-2711delTTAG in exon 27 of the OPA1 gene. Ophthalmologic examination showed in all patients a pale optic disc with reductions of visual acuity and central vision defect. Informed consent was obtained from each patient and normal volunteer.

The study used a 1.5T General Electrics Medical Systems (Milwaukee, Wisconsin) Signa Horizon LX whole-body scanner. Subjects lay supine with a 6 cm diameter surface coil centred on the maximal circumference of the right calf muscle. Spectra were acquired, with a repletion time of 5 s, at rest (64 FIDs), during an aerobic incremental exercise of plantar flexion (time resolution of 1 min = 12 FIDs per spectrum), and the following recovery. Sixty-four recovery spectra with a time resolution of 10 sec (2 FIDs) were collected. Spectra were post-processed by a time-domain fitting routine AMARES/MRUI (http://carbon.uab.es/mrui) and the concentrations of inorganic phosphate (Pi) and phosphocreatine (PCr) were calculated by assuming a normal ATP concentration of 8 mM. Intracellular pH was calculated from the chemical shift of Pi relative to PCr. The rate of PCr recovery was calculated from the mono-exponential equation best fitting the experimental points, reported as time constants (TCs) as a function of the minimum cytosolic pH (5) and then normalized to pH = 7 (6). Data are presented as mean ± SD. Statistical significance, determined by the Student *t* test for unpaired data, was taken as $p<0.05$.

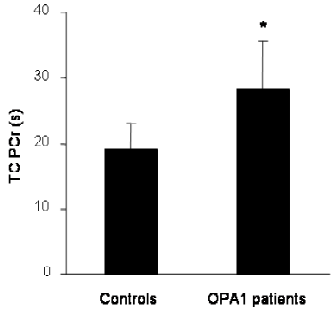

Figure. Phosphocreatine (PCr) post-exercise recovery time constant (TC) in controls and patients with the c.2708-2711delTTAG mutation in exon 27 of OPA1 gene. * $p<0.05$ vs controls.

Results

The resting concentration of phosphocreatine in the OPA1 patients (27.9 ± 2.36) was significantly lower than in controls (31.3 ± 1.53; $p<0.05$), while inorganic phosphate and cytosolic pH were similar in patients and controls (data not shown). In the OPA1 patients the time constant of post-exercise phosphocreatine re-synthesis was significantly higher than in controls (Figure).

Discussion

We show for the first time that the c.2708-2711delTTAG mutation in exon 27 of OPA1 gene induces a reduced rate of mitochondrial ATP synthesis in the skeletal muscle of ADOA patients. Our *in vivo* results support the central role of mitochondrial dysfunction in the physiopathology of ADOA in patients with OPA1 gene mutations. This presents some similarities with Leber's hereditary optic neuropathy (LHON), another mitochondrial disorder due to mtDNA point mutations in complex I, characterised by a deficit of oxidative phosphorylation and retinal ganglion cell degeneration (6). Defective OPA1 may interfere with the assembly and function of the respiratory complexes and ultimately lead to cytocrome *c* release and caspase-dependent apoptotic death of cells (7). A final path of mitochondrial dysfunction in LHON and ADOA may be a common predisposition of neuronal cells to apoptotic death (7, 8).

References

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