CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (CPEO) AND PARKINSONISM ASSOCIATED WITH OPA1 MISSENSE MUTATION AND MUSCLE MTDNA MULTIPLE DELETIONS

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Introduction: The OPA1 protein regulates mitochondrial dynamics by inducing mitochondrial fusion.

Aims: We here describe the first association of parkinsonism and CPEO with a mutation in the OPA1 gene.

Methods: We studied an Italian family with autosomal dominant mitochondrial encephalomyopathy by muscle biopsy, ¹H-cerebral and ³¹P-muscle spectroscopy, DAT-Spect scan and [123]MIBG myocardial scintigraphy. Muscle mtDNA was investigated for rearrangements and the POLG1, POLG2, TWINKLE, ANT1 and OPA1 nuclear genes associated with mtDNA multiple deletions were sequenced.

Results: The clinical phenotype in the proband included CPEO, peripheral neuropathy, sensorineural deafness and late-onset parkinsonism. Ragged red and COX-negative fibers were evident at muscle biopsy. Ophthalmologic investigation disclosed subatrophy of the optic nerve. Cerebral and muscle spectroscopy showed an abnormal ventricular accumulation of lactic acid and defective oxidative phosphorylation. DAT-Spect and [123]MIBG myocardial scintigraphy were congruent with a diagnosis of Parkinson disease. Muscle mtDNA analysis showed mtDNA multiple deletions and sequence of nuclear genes revealed a novel heterozygous missense mutation in the GTPase domain (c.1462A>G; G488R) of the OPA1 gene, which co-segregated with the phenotype.

Conclusions: This family is characterized by CPEO, mtDNA multiple deletions in the skeletal muscle, subclinical optic atrophy and parkinsonism. We found a novel missense mutation in the OPA1 gene, as in other ‘OPA1 plus’ cases. The occurrence of parkinsonism is remarkable, resembling CPEO/parkinsonism with POLG1 and Twinkle mutations. This first case associating parkinsonism with an OPA1 mutation represents an intriguing link between PINK1/PARKIN-related Parkinson diseases and a genetic defect affecting a mitochondrial fusion protein.