Parkinson’s disease associated with impaired oxidative phosphorylation

Abstract Parkinson’s disease may be due to primary or secondary oxidative phosphorylation (OXPHOS) defects. In a 76-year-old man with Parkinson’s disease since 1992, slightly but recurrently elevated creatine phosphokinase, recurrently elevated blood glucose, thickening of the left ventricular myocardium, bifascicular block and hypacusis were found. Cerebral MRI showed atrophy, periventricular demyelination, multiple, disseminated, supra- and infratentorial lacunas, and haemosiderin deposits in both posterior horns. Muscle biopsy showed typical features of an OXPHOS defect. Whether the association of Parkinson’s disease and impaired OXPHOS was causative or coincidental remains unknown. Possibly, the mitochondrial defect acted as an additional risk factor for Parkinson’s disease or the OXPHOS defect worsened the preexisting neurological impairments by a cumulative or synergistic mechanism. In conclusion, this case shows that Parkinson’s disease may be associated with a mitochondrially or nuclearly encoded OXPHOS defect, manifesting as hypacusis, myopathy, axonal polynuropathy, cardiomyopathy and recurrent subclinical ischaemic strokes and haemorrhages.

Keywords Mitochondrial · Neuro muscular · Encephalomyopathy · Extrapyramidal system · Stroke · Lactic acidosis

Introduction Respiratory-chain disorders may be due to mutations in mtDNA or nDNA located genes that encode for subunits of respiratory chain complexes I–V (primary or class I oxidative phosphorylation (OXPHOS) disorders), or due to nDNA mutations in genes that encode for non-OXPHOS mitochondrial proteins, such as the mitochondrial transport and protein assembly system, or may be due to endogenous or exogenous OXPHOS toxins (secondary or class II OXPHOS disorders) [1, 2]. Suspected secondary OXPHOS disorders are Friedreich’s ataxia, hereditary spastic paraparesis, Wilson’s disease, Huntington’s disease, Alzheimer’s disease, epilepsy and Parkinson’s disease [2]. The assumption that there is a relationship between Parkinson’s disease and OXPHOS defects [2, 3, 4, 5, 6], is supported by the following case report.

Case report A 76-year-old man with features typical of Parkinson’s disease such as akinesia, rigidity, resting tremor, asymmetric onset and positive levodopa response, since 1992, was re-admitted for progression of his symptoms. His history was noteworthy for slightly, but recurrently elevated creatine phosphokinase, which had previously remained unrecognised, recurrently elevated blood glucose, cardiomyopathy with bifascicular block, nephrolithiasis and hypacusis. Cerebral CT/MRI scans were normal until 1998, when a few lacunas were reported in the basal ganglia bilaterally. He was under
anti-hypertensive drugs until 1997. He had no history of hyperlipidaemia or hypovolaemia. Besides the anti-Parkinson medication, he was regularly taking only acetylsalicylic acid. Because of being unable to move sufficiently, he was living under continuous care in a nursing home. Clinical neurological examination revealed moderately reduced cognitive functions, prominent frontal release signs (positive snout reflex, positive palmmental reflex, exaggerated glabella reflex), an exaggerated masseter reflex, hypacusis, slight tetraspasticity, diffuse wasting with distal predominance, resting tremor, cog-wheel rigidity, bradydiadochokinesia, ataxia and contractures of the elbows, the knees and the ankles.

Blood chemistry revealed a creatine phosphokinase level of 312 U/l (normal: < 70 U/l), normal serum lactate at rest, normal glucose and glycosylated haemoglobin, and normal clotting-function tests. Because of his physical handicaps, lactate stress testing on a bicycle could not be performed. ECG showed left anterior hemiblock, right bundle branch block and tall R and S waves. Twenty-four-hour ambulatory ECG was assessed as IIIa by the Lown classification. Echocardiography showed concentric thickening of the left ventricular myocardium. A CT scan of the brain showed diffuse atrophy, periventricular demyelination, lacunar state, a recent, left-sided, small basal ganglia haemorrhage and a right-sided cerebellar hyperdensity. An MRI scan of the brain disclosed global atrophy with parieto-temporal predominance, periventricular demyelination, multiple, disseminated, supra- and infratentorial lacunas, mainly in the basal ganglia, the cerebellum and the brain stem and haemosiderin deposits in both posterior horns, being attributed to previous haemorrhages (Fig. 1). HMPAO-SPECT showed strikingly reduced cortical perfusion. FDG-PET scan of the brain disclosed slightly but diffusely reduced cerebral glucose utilisation. Cerebral angiography was normal. Nerve conduction studies were indicative of axonal polyneuropathy. EMG of the right deltoid muscle disclosed increased mean motor unit action potential duration, increased percent polyphasia and reduced interference pattern. Muscle biopsy from the left deltoid muscle revealed typical features of an OXPHOS defect, such as ragged-red fibres, approximately 10% COX-negative muscle fibres, and subsarcolemmal accumulation of abnormally structured mitochondria on electron microscopy (Fig. 2). Biochemical investigation of the muscle homogenate, corrected for citrate synthetase, was normal. Screening for mtDNA mutations in the skeletal muscle and blood lymphocytes was negative. Complete sequencing of the mtDNA genome was not carried out.