

Complex-I defect with minimal manifestations

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Submitted: 10 February 2012

Accepted: 7 April 2012

Arch Med Sci 2014; 10, 1: 200–202

DOI: 10.5114/aoms.2014.40747

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Mitochondrial disorders (MIDs) present with a broad range of clinical manifestations [1] and often with large intra- and interfamilial phenotypic heterogeneity [2], which is why it is often difficult to suspect an MID. In single cases or at onset of the disease, manifestations may be mild and non-specific [3], as in the following case.

The patient is a 56-year-old Caucasian male, with a history of myalgias of the external eye muscles during one month with onset in March 2011 after intake of fluvastatin between December 2010 and January 2011. Afterwards he experienced muscle aching of the thighs, which occasionally had a pulsatile character, with maximal intensity at the left adductor muscles. Since August 2011 he had also noted muscle wasting of the upper arm and thigh muscles. Myalgias were already present after awakening in the morning and generalized to all muscles. Additionally, he complained about easy fatigability, vertigo triggered by head movements, and exertional dyspnea. Years before, he had reacted with “chest pain” to simvastatin. He was working as a controller and described his job as stressful, due to which he had reduced his working hours to 20 h/week. The family history was positive for hyperlipidemia (mother), arterial hypertension (mother), “rheumatological disease” (mother), renal insufficiency (mother), diabetes (grandmother from the mother’s side), pancreatic carcinoma (grandmother from the mother’s side), corpus carcinoma (sister), cerebral tumor (female cousin), and renal carcinoma (uncle).

Clinical neurologic investigation revealed sore neck muscles, generally reduced tendon reflexes, incipient wasting of the left arm and the right thigh, and fasciculations on the right calve. Extensive work-up for neuromuscular disorders revealed leucopenia, cholesterol of 324 mg/dl, triglycerides of 225 mg/dl, reduced folic acid, a positive western blot for myositis antibodies, reduced conduction velocity of the left peroneal nerve attributable to a previous postoperative defect, and a myogenic EMG of the right deltoid muscle. Creatine-kinase and serum lactate were normal whenever tested. Muscle biopsy of the left deltoid muscle revealed slightly increased fiber size variation and scattered COX-negative fibers. Despite this result, rheumatologists prescribed prednisolone (initially 25 mg/day, later tapered down to 6.25 mg) but without effect. Biochemical investigations of the muscle homogenate revealed markedly reduced activity of NADH-CoQ-oxido-reductase per gram of non-collagen protein as well as citrate synthase. Screening for mtDNA deletions, insertions, or depletion is under way. Echocardiography showed mild

thickening of the left ventricular myocardium in the absence of arterial hypertension.

The patient is interesting due to only mild clinical manifestations of a complex-I defect. He had developed myalgias, easy fatigability, and slight muscle wasting and initially his complaints were not taken seriously. Particularly at onset of an MID, but sometimes also over years, mild symptoms of patients with an MID are evident [4] but not taken seriously and are thus often misinterpreted as fibromyalgia or polymyalgia rheumatica. Ignorance towards or underestimation of discrete but indicative abnormalities occurs but needs to be recognized as a major problem, which can be solved by forced education and training and publication of instructive cases. It would also be helpful to study more extensively the clinical course of MID patients and the clinical presentation at onset of such patients. Arguments for an MID in the presented patient are the family history, the individual history, and the clinical neurologic examination. Instrumental findings strengthening the suspicion of an MID include the EMG, the muscle biopsy, and the biochemical investigations.

Myalgia is a frequent symptom of an MID [5, 6] and has been reported in a number of patients with syndromic and non-syndromic MIDs [7]. Myalgias should not be confused with muscle cramps and may occur spontaneously or triggered by exercise or medication. Since myalgias in the presented patient were obviously triggered by a statin, suspicion of a metabolic defect within the myocyte should arise. The suspicion is based on the notion that so-called statin myopathy is regarded as a secondary MID resulting from the mitochondrion-toxic effect of the statin [8] or as a side effect in patients with a primary MID [9–11]. Fatigue may either occur spontaneously or may be triggered by exercise, drugs, heat, food intake, sauna bathing, etc. Fatigue is a frequent manifestation of neuromuscular as well as non-neuromuscular disorders. Exercise-induced fatigue may be caused by central nervous system, cardiac, neoplastic, or neuromuscular disease. The strongest indications for neuromuscular disease in the presented patient were reduced or absent tendon reflexes, the myogenic EMG, and the muscle biopsy findings. Muscle wasting was not convincing but the patient insisted on focal muscle volume reduction for months.

Complex-I of the respiratory chain is composed of at least 45 subunits, of which seven are encoded by genes located on the mitochondrial DNA. Isolated complex-I defects are a frequent cause of MIDs and manifest with broad phenotypic heterogeneity (Table I). Clinical manifestations of isolated complex-I defects are listed in Table I and include migraine, epilepsy, cerebellar signs, spasticity, men-

Table I. Phenotypic manifestations of isolated complex-I defects

Manifestation	Mutated gene	References
Epilepsy	Np	[13, 15]
Migraine	Np	[13]
WMLs	Np	[13]
Cerebellar ataxia	MTND1	[12]
Lactic acidosis	MTND1	[12, 16]
Mental retardation	MTND1, NDUFA1	[12, 14]
Cardiomyopathy	MTND1, NDUFA1	[12, 15]
Spasticity	Np	[15]
Myopathy	Np	[15, 16]
Infantile encephalopathy	ND3	[17]

WMLs – white matter lesions, Np – not provided

tal retardation, cardiomyopathy, encephalopathy, lactic acidosis, and white matter lesions (Table I) [12–17]. Differential diagnoses which should be excluded in a patient with myalgias, fatigability, and mild wasting, before diagnosing an MID, include polymyalgia rheumatica, fatty oxidation defects, glycogenosis, and fibromyalgia.

This case shows that an MID may manifest at onset with only mild symptoms and may be easily missed or misinterpreted. Even complex-I deficiency may present with only myalgia, easy fatigability, or discrete wasting. Those involved in the management of patients with myalgia and fatigue should consider also a complex-I defect as causative.

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