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Adult, isolated respiratory chain complex IV deficiency with minimal manifestations

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Abstract

Objectives: *Isolated complex IV (cytochrome c oxidase) deficiency is one of the most frequent respiratory chain defects in mitochondrial disorders (MIDs) and usually occurs together with severe pediatric or rarely adult multisystem disease. Here we report an adult with isolated complex IV deficiency with unusually mild clinical manifestations.*
Case report: *A 50-year-old man had developed generalized muscle aches and occasional twitching and stiffness of the musculature since age 48 years. He had a previous history of diabetes, acute hearing loss, hyperlipidemia, hyperuricemia, arterial hypertension, polyarthrosis, hypogonadism, and hypothyroidism. The family history was positive for diabetes (mother), CK elevation (brother), myalgias (brother), and proximal weakness of the upper limbs (mother). Work-up revealed hypoacusis, postural tremor and reduced tendon reflexes, recurrent mild hyper-CK-emia, neurogenic needle electromyography, and a muscle biopsy with mild non-specific changes. Biochemical investigations of the muscle homogenate revealed an isolated complex IV defect and reduced amounts of coenzyme Q (CoQ). He profited from CoQ supplementation, low-carbohydrate diet, and gluten-free diet.*
Conclusions: *Isolated complex IV deficiency may present with only mild muscular, endocrine, or cardiac manifestations in adults. Coenzyme Q supplementation, low-carbohydrate diet, and gluten-free diet may have a beneficial effect at least on some of the manifestations.*

Key words: *mitochondrial, myopathy, metabolic, multisystem, complex IV, cytochrome c oxidase, muscle biopsy, creatine kinase.*

Introduction

Primary mitochondrial disorders (MIDs) are due to mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA)-located genes that encode subunits of respiratory chain complexes, assembly factors (ancillary proteins), proteins involved in mtDNA maintenance (intergenomic signaling), in the mitochondrial protein synthesis machinery, in coenzyme Q generation, in the mitochondrial transport machinery, or in apoptosis [7,8]. These mutations may occur together with reduced activity of single or multiple respiratory chain complexes in biochemical investigations [7,8]. Isolated complex IV (cytochrome c oxidase) deficiency is one of the most frequent respiratory chain defects in MIDs and usually occurs together with severe pediatric or rarely adult multisystem disease [20]. Here we report an adult with

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isolated complex IV deficiency with unusually mild clinical manifestations.

Case report

The patient is a 50-year-old Caucasian man, height 172 cm, weight 84 kg, with a history of spontaneous, permanent aching predominantly of the thighs and less intense aching of the lower legs, the neck, and the shoulder girdle muscles since the age of 48 years. Muscle aching could be slightly reduced by initiation of exercise but was markedly intensified after exercise during several days. He reported "heavy legs" after running and occasional twitching and stiffness of the musculature. His previous history was noteworthy for diabetes, acute hearing loss, hyperlipidemia, hyperuricemia, arterial hypertension, which had been well controlled with appropriate medication for 3 years, polyarthrosis, hypogonadism, and hypothyroidism since age 38 years. He also reported a mushy stool for years with slight improvement after changing to a gluten-free diet. The family history was positive for diabetes (mother), CK elevation (brother), myalgias (brother), and proximal weakness of the upper limbs (mother). Clinical neurologic examination at age 50 years revealed slight hypoacusis, mild postural tremor and markedly reduced tendon reflexes. His muscles were generally sore.

Work-up revealed recurrently elevated creatine kinase (CK) values with a maximum value of 1200 U/l (*n*, < 190 U/l) but normal values during several months prior to the last visit in 2/2014. Serum lactate and the forearm ischemic test were normal. Nerve conduction studies of the right femoral nerve, the median and peroneal nerves bilaterally, the left sural nerve and the sensory fibers of the median nerves bilaterally, were all normal. Needle electromyography of two muscles in 6/2011 was normal. Needle electromyography of the right quadriceps femoris muscle in 10/2013 was, in contrast, neurogenic, revealing extensive fibrillations and fasciculations at all recording points, enlarged motor units, and a clear interference pattern. Muscle biopsy from the left lateral vastus muscle in 4/2012 showed two "Ringbinden" (Fig. 1A), one COX-negative fiber (Fig. 1B), and slight type 2 fiber predominance. Ultrastructural examination revealed fibers with subsarcolemmal accumulation of mitochondria and lipid droplets (Fig. 1C), but there was a lack of paracrystalline inclusions or other structural alterations. Biochemical investigations of the muscle homogenate revealed an isolated complex IV defect and reduced amounts of CoQ (Table I). HbA_{1c} was 6.5 (*n*, < 6.0). Echocardiography revealed only mild concentric hypertrophy. Ultrasound of the upper abdomen revealed steatosis hepatis exclusively. Magnetic resonance imagine of the cervical spine was normal. His last medication comprised amlodipine (10 mg/d), L-thyroxine (50 μg/d), CoQ (300 mg/d), and metformin (1000 mg/d). He could accomplish his daily job as an engineer with only progressively stiff neck muscles with increasing duration of his working hours.

Discussion

Isolated complex IV deficiency is one of the most common biochemical abnormalities in MIDs [4,19]. Isolated complex IV deficiency is clinically and genetically extremely heterogeneous (Table II). Clinical manifestations may range from fatal encephalopathy [19], Leigh syndrome (a severe neurodegenerative disorder with characteristic bilateral lesions in the basal ganglia and the brainstem [20]), or epilepsy to myopathy, rhabdomyolysis, or hypertrophic cardiomyopathy (Table II). Genetically, isolated complex IV deficiency may be due to mtDNA mutations or nDNA mutations. mtDNA-located genes associated with isolated complex IV deficiency include genes encoding tRNAs or subunits of complex IV (COX-I, COX-II, COX-III) (Table II). nDNA-located genes associated with isolated complex IV deficiency include an even larger number of genes (Table II). Genes most commonly mutated in isolated complex IV deficiency include SURF1 [20] and SCO2 [3,31].

The reason why such a heterogeneous genetic background leads to the same biochemical defect remains elusive, but it can be speculated that the so far reported genes involved in isolated complex IV deficiency contribute to the composition, assembly, or maintenance of complex IV. Why tRNA mutations cause complex IV deficiency also remains elusive, but these mutations may specifically impair the translation of components of complex IV. Whether hypoacusis, diabetes, arterial hypertension, hyperlipidemia, polyarthralgia, hyperuricemia, hypothyroidism, and hypogonadism have to be regarded as manifestations of the mitochondrial defect remains speculative but previous reports suggest that these manifestations can be occasionally found in patients with MIDs [9]. Since serum CoQ levels were markedly

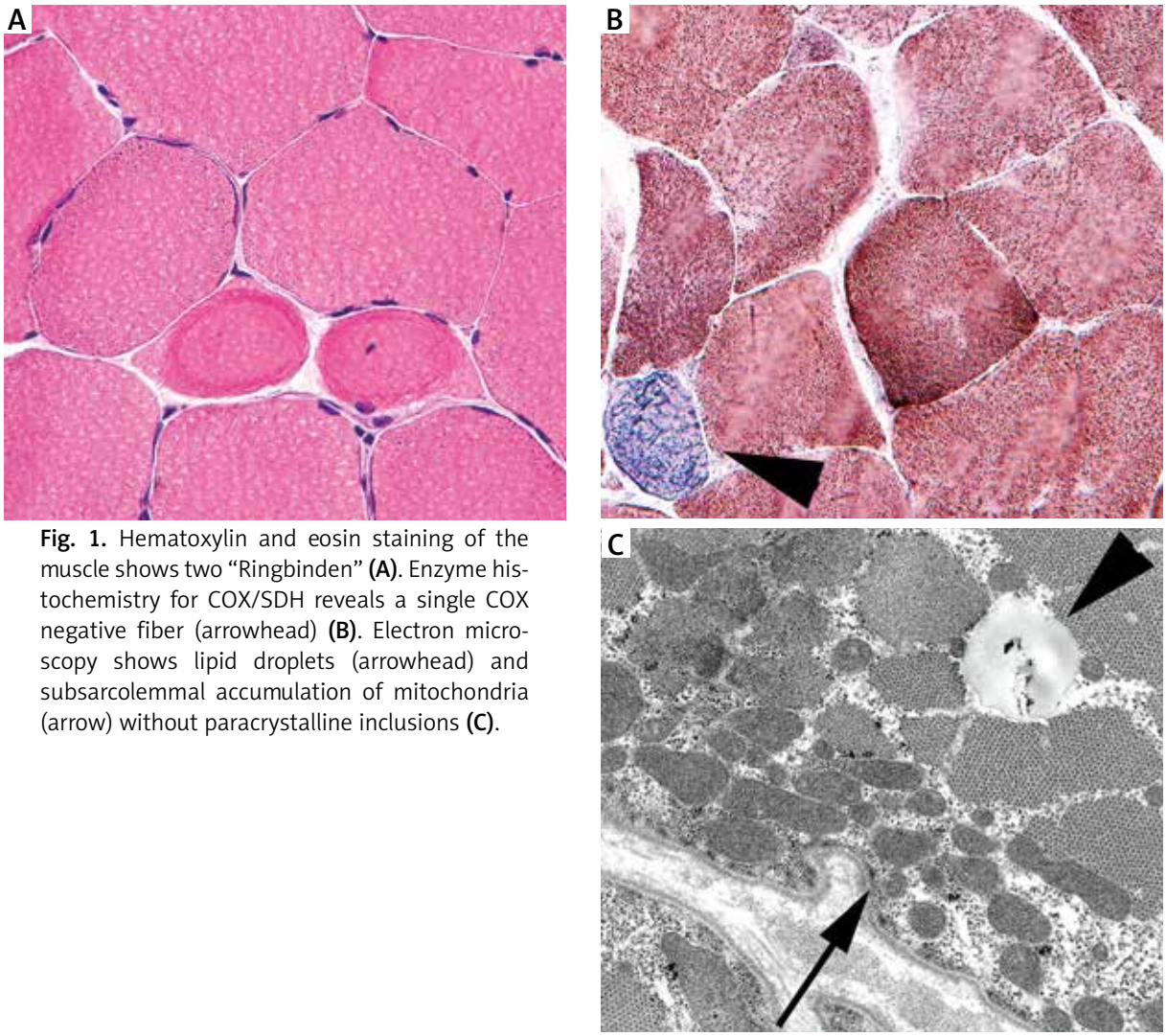

Fig. 1. Hematoxylin and eosin staining of the muscle shows two "Ringbinden" **(A)**. Enzyme histochemistry for COX/SDH reveals a single COX negative fiber (arrowhead) **(B)**. Electron microscopy shows lipid droplets (arrowhead) and subsarcolemmal accumulation of mitochondria (arrow) without paracrystalline inclusions **(C)**.

Table I. Results of biochemical investigations of muscle homogenate in the presented patient

Enzyme activity	Reference limit	Result
Related to non-collagen protein		
Complex I (NADH-CoQ oxidoreductase)	15.8-42.8 U/gNCP	15.6
Complex II/III (succinate cytochrome c oxidoreductase)	6.0-25.0 U/gNCP	9.1
Complex IV (cytochrome c oxidase)	112-351 U/gNCP	46.4
Coenzyme Q	160-1200 mmol/gNCP	111.6
Related to citrate synthetase		
Complex I (NADH-CoQ oxidoreductase)	0.17-0.56 U/U CS	0.26
Complex II/III (succinate cytochrome c oxidoreductase)	0.08-0.45 U/U CS	0.15
Complex IV (cytochrome c oxidase)	1.1-5.0 U/U CS	0.76
Coenzyme Q	2.7-7.0 mmol/U CS	1.8

NCP – non-collagen protein

Table II. Clinical manifestations of and mutated genes in isolated complex IV deficiency

	Mutated gene	Reference
Clinical presentation mtDNA		
Encephalomyopathy	tRNA(Arg)	[24]
Leigh syndrome	tRNA(Leu)	[3]
Leigh syndrome (8344, 8363)	tRNA(Lys)	[3]
Deafness, epilepsy, ataxia	tRNA(Ser)	[29]
Stroke, epilepsy, lactic acidosis	COX-I	[16]
MELAS, encephalomyopathy	COX-II	[15,25]
Myopathy	COX-III	[15]
Myoglobinuria	COX-III	[14]
Encephalomyopathy	COX-III	[13,18]
nDNA		
Leigh syndrome	SURF1	[3,6,20]
Fatal encephalopathy	SCO1	[19]
Cardioencephalomyopathy	SCO2	[3,10,31]
Werdnig-Hoffmann disease	SCO2	[27]
Leigh syndrome, anemia, deafness	COX10	[1,6]
Leigh syndrome	COX15	[5]
Hypertrophic cardiomyopathy	COX15	[2]
Epilepsy	C19orf79	[20]
COX-deficiency	NDUFA4	[23]
Megaconial myopathy	CHKB	[12]
Cognition ↓, dystonia, vision ↓	TACO1	[28]
Encephalomyopathy	FASTKD2	[11]
No mutations described		
Isolated myopathy	n.s.	[17]
Adult Leigh syndrome	n.s.	[22]
Hypertrophic cardiomyopathy	n.s.	[30]
Encephalo-hepatopathy	n.s.	[19,26]
Hypertrophic cardiomyopathy	n.s.	[19,26]
MERRF	n.s.	[21]
Myalgia, diabetes, hypoacusis	n.s.	[Current case]

n.s. – not specified

reduced, a substitution therapy with CoQ 300 mg/d was begun, with some beneficial effect. Low carbohydrate diet enhanced this effect.

This case shows that isolated complex IV deficiency may present with only mild muscular, endocrine, or cardiac manifestations. Coenzyme Q supplementation, low-carbohydrate diet, and gluten-free diet may have a beneficial effect at least on some of the manifestations.

Disclosure

The authors report no conflict of interest.

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