Letter to Editor

Adult-onset, isolated respiratory chain complex-IV deficiency with mild manifestations

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Isolated respiratory chain complex-IV deficiency (ICIVD) usually manifests clinically as an early-onset, severe, multisystem mitochondrial disorder (MID) and only rarely with mild manifestations. Here we present an adult patient with late onset ICIVD with slowly progressive, mild clinical manifestations.
In a 57-years old Caucasian male with exercise-induced myalgia, muscle cramps, ptosis, and recurrent creatine-kinase (CK) elevation, muscle biopsy and biochemical investigations of the left lateral vastus muscle revealed ICIVD. He additionally had developed diabetes, arterial hypertension, hyperlipidemia, retinal detachment, transient hypothyroidism, and a hearing fall. The family history was positive for diabetes, Parkinsonism, and dementia in the mother and myopathy in the brother, suggesting maternal transmission of the MID.
Conclusions: ICIVD may manifest in adulthood with only mild manifestations and may take a slowly progressive course. Patients with mild hyper-CKemia and mild multisystem manifestations, including the muscle, profit from muscle biopsy and biochemical investigations.

Key words: mtDNA, mitochondrial, respiratory chain, multisystem, myopathy.

Introduction

Mitochondrial disorders (MIDs) are most frequently due to mutations in genes encoding respiratory chain complex subunits or assembly factors [1]. Biochemically, isolated or combined complex deficiencies are delineated. The second most frequent type of the isolated respiratory chain complex deficiencies is the isolated respiratory chain complex-IV deficiency (ICIVD) [2, 3]. ICIVD usually manifests clinically as a severe, multisystem mitochondrial disorder (MID) [2, 3, 4] and only rarely with mild manifestations (Table I) [5]. Here we present an adult with late-onset ICIVD with slowly progressive, discrete clinical manifestations.

The patient is a 57-years-old Caucasian male, who developed myalgias of the thighs upon exercise and recurrently elevated creatine-kinase (CK) up to 1000 U/l (n, < 190U/l) since age 48 years. Later on, he additionally developed cramping of the calves. His further history was positive for diabetes treated with alogliptin/metformin and gliclazid, hyperuricemia, hyperlipidemia treated with diet, arterial hypertension, treated with amlodipine, unilateral retinal detachment, transient hypothyroidism, hypogonadism, and an unilateral hearing fall. Diabetes was well controlled with a HbA1c value of 6.7.

Clinical neurologic exam revealed mild, left-sided ptosis, reduced tendon reflexes on the upper limbs, and sore limb muscles. Nerve conduction studies were normal. A first needle electromyography (EMG) showed only non-specific abnormalities. A follow-up EMG showed neurogenic changes. Serum lactate was normal. Muscle biopsy from the left vastus lateralis

Table 1. Patients with ICIVD reported in the literature

Reference	Age (y)	Sex	OS	Clinical manifestations	COX-activity	Mutated gene
[Current case]	57	m	AD	MP, DM, AH, HLP, RA	46.4 (n, 112-351)	nr
[4]	3	m	IF	DD, LE, HY, EP, SS, LA	nr	COX4I1
[4]	11	m	IF	DD, EP, LE, HY	6.5 (n, 24.8-55.8)	COX4I1
[9]	52	f	AD	AT, DA, PNP	nr	MT-CO2
[7]	16	m	CH	SS, VI, PR, OA, MP, EP	4.5 (n, 7.7-21.2)	MT-CO2
[Kotecha 2019]	0	f	IF	Leigh syndrome	nr	LRPPRC
[Otero 2018]	13	f	IF	AT, HY, DA, DT, PNP, TS	normal at age 14y	COX20
[Otero 2018]	32	f	IF	AT, DA, DT, PNP	nr	COX20
[Otero 2018]	28	m	IF	AT, DA, DT, HT, PNP	nr	COX20
[Otero 2018]	7	m	IF	AT, DA, HT, PNP	nr	COX20
[6]	19	f	IF	DD, BK, TS	123 (n, 288-954)	PET117
[6]	8	f	IF	DD, NP, DH, CI	103 (n, 288-954)	PET117
[Baertling 2017]	0.5	f	IF	DD, LA, VO, DY, HY, PH	nr	COX5A/COX4
[Baertling 2017]	1.3	f	IF	LA, PH, HY	169 (n, 288-954)	COX5A/COX4
[Martinet Lyons 2016]	19	f	IF	DD, PNP, LE, TS, AT, CI	nr	COA7
[Ostergaard 2015]	34	f	IF	PNP, SS, EI, OB	65% of lowest co	COA3
[Abdulhag 2015]	2.5	m	IF	LA, CA, BA	undetectable	COX6B1
[Lim 2014]	0.6-27	8m, 3f	IF	Leigh syndrome	10-51% of normal	PET100
[Almalki 2014]	3	m	IF	EP, DD, TS, DY	reduced	FARS2
[Pitceathly 2013]	37	f	IF	MP, PNP, HG, SS, PR, RF	COX/CS ratio: 0.004	COX10
[Leary 2013]	0.5	nr	IF	fatal LE, LA	42% of control	SCO1
[Weraarpachai 2011]	0	f	IF	DY, DD, postnatal death	30-40% of normal	COX14
[8]	35	f	AD	SLE, HA, MI, SS, HG, MP	15% of control	MT-CO1
[Alfadhel 2011]	0	f	IF	CA, neonatal death	decreased	COX15
[Seeger 2010]	20	m	IF	DA, OA, DA, SS, TS	15% residual activity	TACO1
[Seeger 2010]	26	f	CH	SS, DA, DT, TS	nr	TACO1
[Seeger 2010]	12.5	m	IF	DT, TS	nr	TACO1
[Seeger 2010]	15	f	IF	TS	nr	TACO1
[Seeger 2010]	23	f	IF	OA	nr	TACO1
[5]	23	m	AD	SLE, EI, SS, CI, EP, LA	2.9 (n, 105-279)	MT-CO2
[Weraarpachai 2009]	0	f	IF	Leigh syndrome	30-40% of normal	TACO1
[Ghezzi 2008]	14	f	IF	LE	21% of normal	FASTKD2
[Ghezzi 2008]	4	m	IF	LE, HY, EP	reduced	FASTKD2
[Coenen 2006]	nr	nr	nr	Leigh syndrome	13-32% of normal	SURF1, COX10

Table 1. Cont.

Reference	Age (y)	Sex	OS	Clinical manifestations	COX-activity	Mutated gene
[Coenen 2006]	nr	nr	nr	LA, CM, Leigh syndrome	49-80% of normal	nr
[Bugiani 2005]	16	m	IF	Leigh syndrome	42% residual	COX15
[Sacconi 2003]	0.3	m	IF	Leigh syndrome	24% of normal	SURF1
[Sacconi 2003]	0	m	IF	CA	7% of normal	SCO2
[Sacconi 2003]	0-1	14f, 14m	IF	Leigh syndrome, CA, LE	1-30% of normal	nr
[Antonicka 2003a]	0	f	IF	CA	37% of normal	COX15
[Antonicka 2003b]	0.5	m	IF	Leigh syndrome	5% of normal	COX10
[Antonicka 2003b]	0.4	f	IF	CA, LA	18% of normal	COX10

AD – adulthood; AH – arterial hypertension; AT – ataxia; BA – brain atrophy; BK – bradykinesia; CA – cardiomyopathy; CI – cognitive impairment; CH – childhood; DA – dysarthria; DD – developmental delay; DH – diarrhea; DM – diabetes; DT – dystonia; DY – dysmorphism; EI – exercise intolerance; EP – epilepsy; HA – hypoacusis; HG – hypogonadism; HLP – hyperlipidemia; HT – hypothyroidism; HY – muscle hypotonia; IF – infancy; LA – lactic acidosis; LE – leukoencephalopathy; MI. migraine; MP – myopathy; NP – neutropenia; nr – not reported; OA – optic atrophy; OB – obesity; OS – onset; PH – pulmonary hypertension; PNP – polyneuropathy; PR – pigmentary retinopathy; RD – retinal detachment; RF – renal failure; SLE – stroke-like episode; SS – short stature; TS – quadruspasticity; VI – visual impairment; VO – vomiting

muscle revealed mild, non-specific, myopathic changes with scattered atrophic muscle fibers, isolated ring fibers and a single COX-negative muscle fiber (Fig. 1A-E). Normal sarcolemmal immunoreactivity was detected for most muscle dystrophy-relevant proteins. The ultrastructural study by electron microscopy revealed a subsarcolemmal increase of lipopigment and accumulation of slightly enlarged mitochondria with focal, small, electron-dense condensations; typical paracrystalline inclusions were not identified (Fig. 1F-G). Biochemical investigations of the muscle homogenate revealed ICIVD with reduced cytochrome-c oxidase (COX) activity of 46.4 U/g NCP (n, 112-351 U/g NCP). Transthoracic echocardiography at ages 51 years and 56 years revealed mild concentric thickening of the left ventricular myocardium. Cerebral MRI showed non-specific, gliotic spots, in a fronto-parietal distribution. A non-syndromic MID was diagnosed and treatment with coenzyme-Q (CoQ) 400mg/d was begun at age 53 years. His family history was positive for diabetes (mother), Parkinson's disease (mother), dementia (mother), myocloni (brother), hyper-CKemia (brother), and muscle soreness (brother).

ICIVD has been repeatedly reported (Table I) and manifests in the majority of cases with severe clinical manifestations, such as a rapidly progressive, infantile-onset, multiorgan MID, with early death. Syndromic [5] and non-syndromic ICIVD phenotypes [6] have been reported. Contrary to most of the previous descriptions, the index patient manifested with only a mild and slowly progressive phenotype. Myopathy, diabetes, hypothyroidism, hypogonadism, and hypoacusis have been previously reported as manifestations of an ICIVD (Table I) [7, 8]. Particularly myopathy is a common feature of ICIVD (Table I) [2, 7, 9]. Diabetes has been only rarely reported in association with ICIVD (Table I). Hypothyroidism and hypoacusis are common features in MIDs but have been hardly found in patients with ICIVD. Whether hyperlipidemia, arterial hypertension, and retinal detachment are truly attributable to the underlying metabolic defect, remains speculative but it is increasingly recognised that particularly arterial hypertension can be a primary or secondary manifestation of a MID [10]. Additionally, retinal detachment has been recently reported in association with MELAS. The second, neurogenic EMG despite metabolic myopathy is no contradiction and could be explained by muscle fiber hypertrophy, increased dispersion of the motor endplates, and slowed or inhomogeneous propagation of action potentials along the muscle fiber membranes.

The vast majority of patients with ICIVD has an onset at infancy, usually within the first year of life (Table I). Even patients with congenital ICIVD have been reported (Table I). Only few patients have an onset in childhood and even patients with an adult onset have been communicated (Table 1). The genetic cause of ICIVD is heterogeneous and includes mutations in various genes including mtDNA genes (*MT-CO1, MT-CO2, MT-CO3*) and nuclear genes (*COA3, COA7, COX4I1, COX5A, COX6B1, COX10, COX15, COX18, COX20, PET100, PET117, SCO1, SCO2, SURF1, TACO1, FASTKD2, LRPPRC*, and *FARS2*) (Table I).

Assuming that the index patient's condition was inherited from the mother, diabetes, Parkinson's disease, and dementia in the mother were regarded as clinical manifestations of her MID. However, the mother neither underwent clinical nor para-clinical investigations for MID. The brother of the index

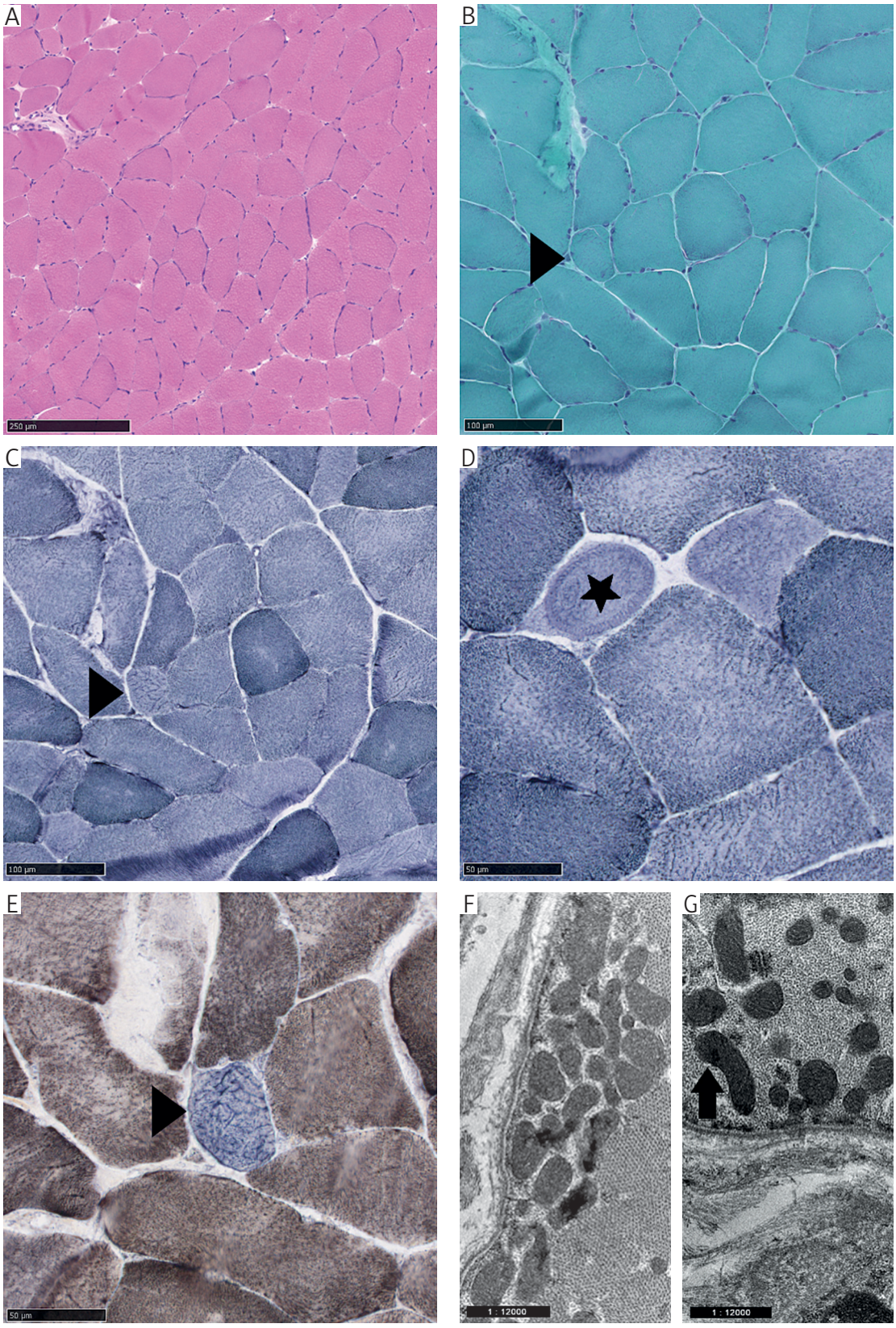

Fig. 1A-E. Histopathology of the left vastus lateralis muscle showing discrete myopathic changes with single atrophic fibers on HE staining (A), absence of ragged-red fibers in the Gomori-trichrome (B) and NADH staining (C, D), a subtle predominance of type II fibers with single ring fibers (D, asterisk), and a solitary COX-negative fiber in the combined COX/SDH histochemical stain (E, arrowheads mark respective fiber). Electron microscopy images illustrate mild ultrastructural changes with a slight subsarcolemmal increase of lipopigment and an accumulation of slightly enlarged mitochondria (F) with focal, small electron-dense condensations (G, arrow) without typical paracrystalline inclusions

patient most likely had inherited the disease as well, given recurrent hyper-CKemia, muscle cramps, muscle soreness, and myocloni. Unfortunately, the brother did not consent to further diagnostic work-up for a MID. Despite these limitations, the family history and the clinical manifestations of the index patient, his mother, and his brother, suggest a maternally transmitted MID.

In conclusion, this case shows that ICIVD may manifest in adulthood with only mild manifestations and may take a slowly progressive course. Patients with mild hyper-CKemia and mild, multisystem manifestations, including muscular symptoms, profit from muscle biopsy and biochemical investigations of the muscle homogenate. In the vast majority of the cases, ICIVD is due to mutations in nuclear genes encoding COX subunits, transcription factors, or assembly factors.

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