MITOCHONDRIAL ELECTRON TRANSPORT CHAIN COMPLEX II AND III DEFICIENCY MYOPATHY: CASE REPORT

ARAYA PUWANANT, M.D.[a], MEDHAT O. HASSAN, M.D.[b], EROBOGHENE E. UBOGU, M.D.[c]

[a]THE NEUROLOGICAL INSTITUTE, UNIVERSITY HOSPITALS CASE MEDICAL CENTER, CLEVELAND, OHIO; [b]PATHOLOGY SERVICE, LOUIS STOKES DEPARTMENT OF VETERANS AFFAIRS MEDICAL CENTER, CLEVELAND, OHIO AND [c]DEPARTMENT OF NEUROLOGY, BAYLOR COLLEGE OF MEDICINE,HOUSTON, TEXAS, UNITED STATES OF AMERICA.

ABSTRACT

INTRODUCTION:

Exercise intolerance, rhabdomyolysis, and myoglobinuria are common complaints that may present as manifestations of metabolic myopathies. Failure to recognize subtle neuromuscular symptoms and signs, or employing the use of nondiagnostic routine muscle biopsies may compromise an accurate clinical diagnosis of mitochondrial myopathy.

CASE REPORT:

A previously active 23-year-old man presented with a history of a severe episode of exertional rhabdomyolysis and myoglobinuria, followed by chronic exercise intolerance and muscle pain. There was no known family history of muscle disease. He was asymptomatic at rest with a normal neuromuscular examination apart from some difficulty arising from a squatting position due to bilateral thigh pain. Resting creatine kinase levels were normal. Electrodiagnostic testing revealed a mild, irritable proximal myopathy. Routine histopathological analysis of a left deltoid muscle biopsy was nondiagnostic. Ultrastructural examination demonstrated a single focus of abnormal subsarcolemmal accumulation of normal appearing mitochondria. Biochemical muscle enzyme analyses revealed markedly reduced mitochondrial electron transport chain complex II and III activities with mildly reduced citrate synthase levels. Coenzyme Q10, total carnitine, free carnitine, and acylcarnitine levels were normal. Fatty acid oxidation enzyme and carnitine palmitoyltransferase activities were also within normal ranges. The patient declined additional testing.

CONCLUSIONS:

This case report further supports the observation that nonspecific exercise intolerance and muscle pain may be due to electron transport chain defects. In addition to careful clinical assessment and specialist neuromuscular evaluation, performing comprehensive muscle biochemical enzyme analyses, genetic testing, or both may be required to accurately diagnose mitochondrial myopathies, especially in the setting of nondiagnostic routine muscle histopathology.

LABORATORY RESULTS

Creatine Kinase: 17,035 U/mL on 05/03/2004 (0-225)

7,477 U/mL on 05/06/2004

240 U/mL on 05/14/2004

188 U/mL on 06/01/2005

220 U/mL on 01/11/2006

171 U/mL on 03/28/2007

Complete blood count, comprehensive metabolic panel, endocrine screen normal.

Declined forearm exercise testing. Lactate/pyruvate testing not performed (patient non-compliance)

ELECTRODIAGNOSTIC STUDY DATA

Nerve / Sites	Lat. 2 ms	Lat. ms	Amp.2-3 µV	Dur. ms	Dist. cm	d Lat. ms	Vel. m/s
R SURAL - Lat Mall							
1. Calf	1.90	1.30	55.4	1.25	10	1.30	76.9
R RADIAL - Snuffbox							
1. Forearm	3.70	2.75	28.6	2.10	14	2.75	50.9

Nerve / Sites	Lat. ms	Amp.1-2 mV	Dur. ms	Area mVms	Dist. cm	d Lat. ms	Vel. m/s
R MEDIAN - APB							
1. WRIST	3.30	12.9	4.45	34.2	7		
2. ELBOW	7.25	12.5	5.05	33.2	25.5	3.95	64.6
R COMMON PERONEAL - EDB							
1. Ankle	3.50	6.3	4.15	13.0	9		
2. Fib Head	9.70	5.9	4.50	13.1	33	6.20	53.2
3. Knee	10.75	5.7	4.65	12.9	6	1.05	57.1

Nerve	Fmin ms
R MEDIAN	24.05
R COMMON PERONEAL	42.50

EMG Summary Table									
	Spontaneous					MUAP			Recruitment
	IA	Fib	PSW	Fasc.	Other	Amp	Dur.	PPP	Pattern
R. TIBIALIS ANTERIOR	N	N	N	N	N	N	N	N	N
R. GASTROCNEMIUS (MEDIAL)	N	N	N	N	N	N	N	N	N
R. VASTUS LATERALIS	Incr.	1+	1+	N	N	1-	1-	N	Mild Incr.
R. ILIOPSOAS	N	N	N	N	N	1-	1-	N	Mild Incr.
R. GLUTEUS MEDIUS	Incr.	N/1+	1+	N	N	1-	1-	1+	Mild Incr.
R. FIRST DORSAL INTEROSSEOUS	N	N	N	N	N	N	N	N	N
R. EXTENSOR INDICIS PROPIUS	N	N	N	N	N	N	N	N	N
R. FLEXOR CARPI RADIALIS	N	N	N	N	N	1-	1-	N	Mod Incr.
R. TRICEPS	N	N	N	N	N	1-	1-	N	Mild Incr.
R. DELTOID	Incr.	N/1+	1+	N	N	1-	1-	1+	Mild Incr.
R. INFRASPINATUS	N	N	N	N	N	1-	1-	N	Mild Incr.

Total and free carnitine and acylcarnitine contents are normal.

Short-, medium- and long-chain acyl-coA dehydrogenase activities are normal.

Carnitine palmitoyltransferase-I and –II activities are normal.

Serum coenzyme Q10 levels are normal (0.9 mg/L; range 0.5-1.0 mg/L)

MUSCLE HISTOCHEMISTRY :

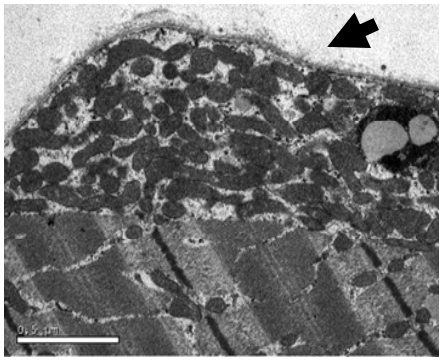
A standard battery test of enzyme histochemical analyses was performed on the frozen muscle specimens, including myofibrillary adenosine triphosphatase (pH 4.3 and 10.4), nicotinamide adenine dinucleotide (NADH)-tetrazolium reductase, alkaline phosphatase, non-specific esterase, modified Gomori trichrome, periodic acid Schiff, and adenylase deaminase, as well as hematoxylin and eosin (H&E) stain.

Additional sections were stained to detect glycolytic enzymes myophosphorylase and phosphofructokinase, and the mitochondrial enzymes succinate dehydrogenase (SDH) and COX. Oil-red O was also performed to assess lipid stores.

Formalin-fixed tissue was processed in paraffin and sections stained with H&E and Masson's trichrome.

For electron microscopy (EM), sections were fixed in buffered formalin and embedded in epoxy resin to generate semithin (1 µm) and ultrathin sections.

ELECTRON MICROGRAPH OF SKELETAL MUSCLE



Enzyme	ETC Complexes	Patient's value (I)*	Patient's value (II)*	Normal Range*	Control Mean ± SD (n=49)*	% Patient's value/ Mean
NADH-ferricyanide reductase	I	11.8	12.3	11.5-60.1	29.9 ± 12.9	39.5, 41.1
NADH-cytochrome c reductase (roteonone sensitive)	I, III	**-0.09**	**-0.18**	0.2-4.7	1.2 ± 1.1	**-7.9, -15.4**
Succinate dehydrogenase	II	0.24	N/A	0.1-2.0	0.8 ± 0.4	30.3
Succinate-cytochrome c reductase (antimycin A sensitive)	II, III	**0.31**	**0.33**	0.4-4.9	2.1 ± 1.2	**14.6, 15.5**
Succinate Q reductase (TTFA-sensitive)	II	N/A	**0.12**	0.5-1.5	0.9 ± 0.3	**13.5**
Succinate Q reductase (TTFA-sensitive) + duroquinone (coenzyme Q_{10})	II	N/A	0.31	0.3-2.1	1.1 ± 0.6	28.5
Decylubiquinol-cytochrome c reductase (antimycin A sensitive)	III	**5.1**	**3.6**	6.8-35.2	15.2 ± 6.8	**33.6, 23.7**
Cytochrome c oxidase	IV	64.7	N/A	57.3-373.0	148.9 ± 67.2	43.4
Citrate synthase		**6.2**	**7.1**	9.4-30.0	18.6 ± 4.7	**33.3, 38.2**

* Enzyme activities in µmol/min/g net weight. Numbers in bold indicate abnormal values. NADH: nicotinamide adenine dinucleotide, TTFA: thenoyl-trifluoroacetone.