

Mitochondrial Disease in Adult and Pediatric Patients with Fatigue and Myalgias [P09-094]

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Background/Methods

Fatigue, and myalgias are commonly encountered symptoms of mitochondrial disease and may be the only symptoms in adults or children. These symptoms can be caused by nuclear DNA or mitochondrial DNA (mtDNA) mutations. Given the complex mechanisms producing mitochondrial disease, a multifaceted approach must be used for diagnosis. OXPHOS enzymology alone is insufficient for diagnosis of mitochondrial disease. A retrospective analysis of evaluations performed on 62 patients was performed.

36 adults (>19 years) (11 male; 25 female)

Mean age \pm SD = 39.2 \pm 9.2 years; Median = 39.5 years; Range 20-60 years

21 children (<18 years) (11 males; 10 females)

Mean age \pm SD = 10.5 \pm 4.5 years; Median = 11 years; Range 3-18 years

Mitochondrial disease diagnosed by published criteria (reviewed in 1). Data for Pediatric and Adult patients for the following categories of testing were reviewed. **Metabolic testing:** Organic acids, amino acids, blood lactate and pyruvate. **Muscle biopsy:** Histology, OXPHOS enzymology, Quantitative Western blot of selected OXPHOS enzyme subunits (Complexes I-V), muscle CoQ10 levels, mtDNA copy number determination, mtDNA analysis (sequencing, deletion/duplication testing), Glycolytic enzymes. **Fibroblast culture:** Fatty acid oxidation testing.

Summary

- Mitochondrial disease is an important cause of fatigue and myalgias, which can be the only symptoms in adult and pediatric patients. A multi-faceted diagnostic approach is essential for proper diagnosis. OXPHOS enzymology alone is NOT sufficient for patient diagnosis (see diagnostic criteria reviewed in reference 1).
- In children, the most significant lab abnormalities were identified when fatigue was accompanied by myalgias and cramps. Rhabdomyolysis was not observed. None harbored defects in fatty acid oxidation (100% tested) or in glycogen metabolism (48% (10/21) tested). CPK is increased in 24% (5/21) (300-500 IU/L up to 3000 IU/L). Patients with increased CPK did not harbor defects in dystrophin, sarcoglycans ($\alpha, \beta, \gamma, \delta$), dysferlin, calpain3 (CAPN3), or caveolin (CAV3). Muscle histology was non-diagnostic in 85.7% (18/21). Mitochondrial myopathy was observed in 9.5% (2/21) and myopathic changes in 4.8% (1/21). One child had a deficiency in CoQ10 which is a treatable abnormality. Pathogenic mtDNA mutations were identified in 22% (2/9).
- In adults, the most significant lab abnormalities were identified when fatigue was accompanied by myalgias and cramps. Rhabdomyolysis was observed in 25%. Evaluation for defects of glycogen metabolism and fatty acid oxidation were negative. CPK was increased in 17%. Muscle Coenzyme Q10 deficiency (a treatable defect) was present in 41% (7/17). A decreased mtDNA copy number was present in 7% (2/27). Pathogenic mtDNA mutations were identified in 8% (2/26). MtDNA mutations with significant evolutionary conservation were observed in 27% (7/26).

References

- Shoffner JM. Mitochondrial Diseases. In: Gilman S, ed. MedLink Neurology. San Diego: MedLink Corporation, 2008

PEDIATRIC	Fatigue Only	Fatigue, Myalgias	Fatigue, Myalgias, Cramps	TOTALS (All Groups)
RESULTS	33% (7/21)	43% (9/21)	24% (5/21)	
Weakness	0% (0/7)	0% (0/9)	40% (2/5)	9.5% (2/21)
Increased CPK	0% (0/7)	22% (2/9)	60% (3/5)	24% (5/21)
Rhabdomyolysis	0% (0/7)	0% (0/9)	0% (0/5)	0% (0/21)
Abnormal Metabolic Testing	14% (1/7)	22% (2/9)	80% (4/5)	33% (7/21)
Abnormal OXPHOS Enzymology	57% (4/7)	89% (8/9)	60% (3/5)	71% (15/21)
Abnormal OXPHOS Western Blot	0% (0/7)	67% (4/6)	75% (3/4)	41% (7/17)
Abnormal Muscle CoQ10	0% (0/7)	33% (1/3)	0% (0/4)	7% (1/14)
Abnormal mtDNA Copy Number	0% (0/7)	33% (1/3) Increased	25% (1/4) Increased	14% (2/14)
Heteroplasmic Pathogenic mtDNA mutations	0% (0/3)	33% (1/3) Cytochrome b Deletion: 15319_15327delCCTAGCAAC	33% (1/3) tRNA ^{Leucine(UR)} 3280A>G	22% (2/9)
ADULT	Fatigue Only	Fatigue, Myalgias	Fatigue, Myalgias, Cramps	TOTALS (All Groups)
RESULTS	(11/36)	(16/36)	(9/36)	
Weakness	18% (2/11)	13% (2/16)	22% (2/9)	17% (6/36)
Increased CPK	0% (0/11)	25% (4/16)	22% (2/9)	17% (6/36)
Rhabdomyolysis	0% (0/11)	25% (4/16)	11% (1/9)	14% (5/36)
Abnormal Metabolic Testing	27% (3/11)	19% (3/16)	44% (4/9)	28% (10/36)
Abnormal OXPHOS Enzymology	73% (8/11)	94% (15/16)	78% (7/9)	83% (30/36)
Abnormal OXPHOS Western Blot	71% (5/7)	38% (5/13)	44% (4/9)	48% (14/29)
Abnormal Muscle CoQ10	40% (2/5)	75% (3/4)	25% (2/8)	41% (7/17)
Abnormal mtDNA Copy Number	25% (2/8) Decreased	0% (0/10)	0% (0/9)	7% (2/27)
Pathogenic mtDNA mutations	14% (1/7) ATP6: 8999T>C Val158Ala Homoplasmic	8% (1/13) ND5: 13246T>C Phe304 Leu Heteroplasmic	0% (0/6)	8% (2/26)
Provisionally Pathogenic mtDNA mutation	43% (3/7) Homoplasmic	15% (2/13) Homoplasmic	33% (2/6) Homoplasmic	27% (7/26)