Case Report

MITOCHONDRIAL DYSFUNCTION PRESENTING AS MYASTHENIC SYNDROME

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ABSTRACT
Mitochondria, present in almost every cell of human body, are required for incessant supply of atps needed for optimal functioning of cells. Mitochondria are found in neuromuscular junctions (nmj) and in skeletal muscle fibers, hence their dysfunction may present with fluctuating muscle strength on exertion, mimicking myasthenia gravis (mg). We present four cases presenting with myasthenic symptoms but had mitochondrial dysfunction.

Keywords: Mitochondrial Disease, Neuromuscular Junction, Myasthenia, Forearm Exercise Test, Redragged Fibers

INTRODUCTION
Mitochondria are powerhouse of cell and are required for utilization of oxygen by tissue on minute to minute basis (Pieczenik, 2007). Skeletal muscles are the highest consumer of oxygen in the body, furthermore, mitochondrial oxidative phosphorylation is found to increase up to 100 fold from rest to exercise in healthy muscles (Jensen, 2002). Expectedly, therefore, mitochondrial diseases (mtdx) affecting skeletal muscles commonly present with exercise intolerance, but occasional presentation with muscle weakness is not unknown (Olsen, 2003). Merrf and Kearns-Sayre syndrome are the classical skeletal muscle disorders caused by mitochondrial cytopathies with demonstrable ragged red fibers (rrf) in muscle tissue but not all patient with mtdx show histological abnormalities (Adriana, 2007). Therefore screening of mtdx cannot solely depend on muscle biopsy for it might result in significant under diagnosis.

In quest to find alternate ways to diagnose mitochondrial dysfunction Jensen et al., (2002) studied oxygen saturation, in venous blood, at rest and during exercise in 12 cases of known mtdx and underpinned the inability of the exercising muscle to extract oxygen from blood. They found that aerobic forearm exercise test (afet) could be a reliable tool to screen for mtdx. Utility of afet in diagnosing mtdx has been convincingly validated by others (Taivassalot, 2002; Meulemans, 2007). In normal subjects the venous oxygen saturation (vpao2) falls rapidly, soon after the initiation of exercise, followed by rapid recovery after cessation of the exercise. Patients of mtdx show rising levels of vpao2 during exercise (pseudo-arterialisation), suggesting failure of the exercising muscle to extract o2 effectively (Jensen, 2002).

Further, in skeletal muscles mitochondria are found in abundance in subsarcolemmal and intermyofibrillar region (Ferreira, 2010; Stadhouders, 1987) and are also closely related to neuromuscular junction (nmj). Effective response of acetylcholine receptors (achr) and various ions channels, related to nmj, depends upon satisfactory mitochondrial functions (Rash, 1974). Patients with skeletal muscle weakness induced or exacerbated by exercise are usually considered to suffer due to acquired or congenital neuromuscular junction (nmj) dysfunction like myasthenia gravis (mg), lems, channelopathies or acetylcholine (ach) deficiency etc (Pieczenik, 2007). Myasthenic syndrome (ms) hardly gets a mention in the list of diseases caused by mitochondrial dysfunction (Anthony, 2006).

To best of our knowledge only four cases of mtdx presenting as ms are on record in English literature. Jason et al., (2002) described a case of sixty three year old male with asymmetric ptosis, diplopia with weak orbicularis oculi without any decrement on repetitive stimulation (rns) of facial nerve. Patient was initially treated as mg with prednisone for a month without significant improvement (Barton, 2010). They performed a muscle biopsy which showed rrf and subsarcolemmal accumulation of mitochondria.

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Raed et al., described a case of twenty five year old man who presented with bilateral ptosis, fatigable weakness and markedly raised achr antibody levels. They found neuromuscular transmission defect on single fiber electromyography but the patient responded neither to neostigmine nor to corticosteroid. The histopathological examination of orbicularis oculi showed abnormal mitochondrias (Behbehani, 2007).

Paulo et al., (1989) reported a case of eleven year old boy, symptomatic for four years, with external ophthalmoplegia, bilateral ptosis and quadriparesis. The patient showed a decremental response of 26% on rns and was treated with anti acetylcholinesterase (antiache) medication with moderate improvement. The therapeutic response to medication was thought to be suboptimal leading to muscle biopsy, later revealed granulous material at sub-sarcolemmal region and increased number of mitochondria. Joseph finsterer has described a case of sixty nine year old patient who presented with bilateral, edrophonium responsive, ptosis of fifteen year duration. This patient had abnormal decremental response on rns and mildly elevated achr antibodies, but did not respond to prolonged therapy with immunomodulators (Finstererj, 2010).

We report four patients who were, at presentation, suspected to have mg but failed to show either adequate response to pharmacotherapy or had atypical results on rns, raising suspicion of alternate diagnosis thus leading to screening for mtdx deploying afet and muscle biopsy.

CASES

Between March, 2010 and July, 2014 we saw four patients, who at presentation were thought to have mg based on their clinical symptoms (table 1). Two of them (case 1 and 2) were siblings born out of non-consanguous marriage, they and case 3 had symptoms in pre-adolescent age, while in case 4 became symptomatic in late age.

Thyroid profile, creatine phosphokinase (cpk) and antibodies against achr were checked. Rns was performed using surface recording electrodes and supra-mamal repetitive with five successive 3hz, 0.1 msec stimuli, decrement of 10% or more between first and third response was taken as significant. Afet was performed with slight modification of previously described protocol (Ferreira et al., 2010), using a hand dynamometer with patient seating in a chair. At the outset the maximum grip strength was ascertained and then mean of three maximum voluntary contractions (mvc) was calculated. The patient then was allowed to rest for 20 minutes after inserting a large bore venous canula in antecubital vein. For the test the patient was required to exert 40% of mvc, for 3 minutes with alternating grip-release cycle each lasting for one second. Following exercise the limb was kept immobile for 10 minutes. Blood samples were drawn at 0 and 3 minutes. Third sample was drawn at 10th minute after completion of the exercise. Samples send to the laboratory, wrapped in ice packs, and were processed within 20 minutes on a blood a gas analyzer (cobas b 121 systems, roche diagnostics, Germany). Moderately affected deltoid muscle was biopsied, one piece was saline soaked another was preserved in glutaryldehide and sent for analysis.

All four cases consented for afet and rns, three agreed for muscle biopsy while one (case 2) declined it.

DISCUSSION

Summary of the results of biochemistry, rns and muscle histology are provided in table-2. Afet showed had rise in vpaO2 saturation with initiation of exercise, and it continued to rise even after the stopping of the exercise after 3 minutes in case 2 and 4. Post exercise rest phase vpaO2 levels showed a reducing trend in other two patients failed to return to initial level even after rest of 10 minutes (figure 1). Review of the reported cases suggests mtdx presenting as ms have two clinically distinct patterns, one which mimics mg (mtdxmg) and other with exercise induced weakness of girdle muscles (mtdxgd) but normal rns. Mtdxmg Patients showed decremental response on rns and varying degree of improvement in weakness with anti ache drugs (pyridostigmine) as seen in our cases (case 1 and 2) and cases of Paulo et al., (1989) and Joseph (2010). Two of our cases 3 and 4, despite having exercise induced girdle weakness, neither showed significant abnormality on rns nor any improvement with antiache medication, mimicking the case of Jason et al., (2010).
a closer look at the ultra structure of nmj and muscle fibers might offer an explanation to this phenomenon. Nmj consists of presynaptic nerve terminal and a postsynaptic membrane with intervening cleft and mitochondria are present in high numbers in post-synaptic membranes as well as pre-synaptic nerve terminal of nmj (Wood, 2001; Rash, 1974). During exercise the role of presynaptic nerve terminal, is more or less, limited to seeding the post synaptic membrane with appropriate number of ach quanta sufficient to initiate an action potential. Presynaptic nerve terminal has active zones, where ach containing vesicles are found in cluster and get released in response to nerve stimulation. From the active zone of presynaptic nerve terminals far more quanta of ach are released than required to initiate an action potential in post synaptic membrane. It is estimated that for a single nerve impulse ach vesicles are released only from 10% of active zones, thus leaving a huge potential for augmentation in times of high demand like exercise. It is, therefore, more likely for mtdx to show electrophysiological features suggestive of postsynaptic nmj dysfunction (Wood, 2001).

The post synaptic membrane is a complex structure studded with deep folds and crests, where crests are the places where ach are found in high numbers, as against this the voltage gated sodium channels (vgsc), required for generation of propagated action potential, are located deep in the folds of synaptic membranes. At post-synaptic membrane mitochondria are closely related to junctional clefts and are required for the normal functioning of the ionic channels located in neuromuscular junction (Pieczenik, 2007). Dupuis et al have studied nmj morphology in mice and described that muscle mitochondria uncoupling results into malfunctioning of acetylcholine clustering and significant deterioration of nmj architecture with age (Dupuis, 2009). The postsynaptic response to neurotransmitter depends on activation of achr and vgsc. A reduction in the numbers of any one of them results in reduction of safety factor of nmj, resulting in inefficient neuromuscular transmission (Dupuis, 2009).

Furthermore, in skeletal muscles, mitochondria are present not only in nmj but also throughout the muscle fiber, particularly in close relation to sarcoplasmic reticulum and t-tubules (Volkers, 2010) and they are functionally and structurally distinct with differing cytochrome content (Floeter, 2010). It is known that power generated by the skeletal muscle is dependent on actin and myosin (Shorten, 2009), atps, required for this energy guzzling process, are provided by the sarcoplasmic mitochondria. In mt_gd (patient 3,4), failure to contract efficiently during exercise, therefore, might result in fatigable skeletal muscles, a weakness which is not expected to respond to pyridostigmine.

Tissue diagnosis and genetic testing are often used to diagnose mtdx but many patients with mtdx may not have histo-pathologically discernible abnormalities (Olsen, 2003). Furthermore, facilities and expertise to perform these tests is scarce. Increasing number of critical units across the country has made blood gas analyzers available practically in every town, thus afet can be used to screen patients with ms who are suspected to have mtdx.

<table>
<thead>
<tr>
<th>Table 1: Clinical feature of the cases</th>
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<tbody>
<tr>
<td>Age (in years)/Gender</td>
</tr>
<tr>
<td>Age at Onset (years)</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>External History</td>
</tr>
<tr>
<td>External Ophthalmoplegia</td>
</tr>
<tr>
<td>Exercise induced muscle weakness</td>
</tr>
<tr>
<td>Weak eye closure</td>
</tr>
<tr>
<td>Ptosis</td>
</tr>
<tr>
<td>Response to Pyridostigmine</td>
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</tbody>
</table>

✓ = Present; X = Absent

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Table 2: Investigations of the patients

<table>
<thead>
<tr>
<th>Case</th>
<th>CPK</th>
<th>Thyroid profile</th>
<th>AchR Antibodies</th>
<th>RNS§</th>
<th>Muscle Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>ND*</td>
<td>Subsarcolemmal aggregation of large number of mitochondria with altered cristae pattern suggestive of mitochondrial disorder</td>
</tr>
<tr>
<td>2</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>NORMAL</td>
<td>ND*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>Raised</td>
<td>NORMAL</td>
<td>ND</td>
<td>RRF-10%, rimmed vacuole 2% RBF and 15-20% Cox deficient fibers RBF‡</td>
<td></td>
</tr>
</tbody>
</table>

*ND-not done; †RRF- Ragged Red Fibres; ‡RBF- Ragged Blue fibers; §RNS- Repetitive Nerve Stimulation

Figure 1: Graph showing paradoxical rise in saturation during exercise (pseudoarterialisation)

REFERENCES
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