Adult-Onset Mitochondrial Myopathies with Dyspnea as the Main Manifestation: A Case Report and Literature Review

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Abstract

Background: The mitochondrial myopathies are inherited metabolic diseases caused by disorders of oxidative phosphorylation at the mitochondrial respiratory chain level. The phenotype of mitochondrial myopathies is heterogeneous.

Methods: Here, we report a case of a patient who presented with exertional dyspnea and sought medical consultation at respiratory department. We also review the characteristics of the patients published previously.

Results: A heterozygous A3243G mutation was found in mitochondrial tRNA Leu (MT-TL1) gene from total DNA extracted from the peripheral blood specimen of the patient. Abnormal mitochondria were found under electron microscopy, and a few ragged-red fibers were found under MGT staining with muscle biopsy. Twenty four cases of adult-onset mitochondrial myopathy with dyspnea as the main manifestation were reported. Restrictive pulmonary ventilation dysfunction and decreased maximum inspiratory pressure were the typical manifestation of pulmonary function tests in these patients. A3243G mutation within MT-TL1 gene was the most common mutation in mtDNA.

Conclusion: Adult-onset mitochondrial myopathy with dyspnea as the main manifestation was a rare phenotype of mitochondrial myopathies. Mitochondrial myopathies should be considered in the differential diagnosis of unexplained exertional breathlessness.

Keywords: Mitochondrial myopathies; Mitochondrial diseases; Dyspnea; Mitochondrial DNA

Introduction

The mitochondrial myopathies are inherited metabolic diseases caused by disorders of oxidative phosphorylation at the mitochondrial respiratory chain level [1]. The common clinical manifestations of mitochondrial myopathies include myalgia, muscle weakness and fatigue. Adult-onset mitochondrial myopathy with exertional dyspnea as the main manifestation without obvious muscle weakness was an uncommon phenotype. Here, we report a case of a patient who presented with exertional dyspnea and sought medical consultation at respiratory department. We also review the characteristics of the patients published previously.

Patients and Literature Review

Case histories

A 59-year-old male patient was admitted to this hospital on 01 November 2018 at respiratory department. The patient complained of 10 years of exertional dyspnea and one month of exacerbation. The patient also reported palpitation, weakness of lower limbs, myalgia and occasional abdominal distension. Prior to hospitalization, the patient experienced a weight loss of about 5 kg in the past year. The patient had a history of hypertension for 2 years. The patient had 10 years history of smoking 10 cigarettes per day. The family history for neuromuscular diseases was not remarkable. Upon examination, the patient's temperature was 36.1°C, the patient's blood pressure was 112/74 mmHg, the patient's pulse was 100 beats per minute, the patient's respiratory rate was 20 breaths per minute, and the patient's oxygen saturation was 97% while the patient was breathing ambient air. Physical examinations showed crackles on auscultation in the right lower lobe of the lung. Examination of muscle strength of limbs and nerve reflex was not remarkable.

Laboratory and supplementary examinations

Laboratory tests of the peripheral blood, CT, Pulmonary Angiography, Echocardiography, Electromyography (EMG) and peripheral nerve conduction velocity, lung function test, and magnetic resonance imaging of the brain was performed under standard procedure.

Muscle biopsy

Muscle biopsy was performed on the left quadriceps femoris. The serial enzyme staining was done with Haematoxylin and Eosin (HE), Cytochrome C Oxidase (COX), Modified Gomori Trichrome (MGT), Nicotinamide Adenine Dinucleotide (NADH), Succinate Dehydrogenase (SDH) and COX/SDH. Electron microscopic examination was performed by standard techniques.
**Genetic analysis of the peripheral blood**

Total DNA was extracted from blood using the centrifugal column method. Mitochondrial DNA and nuclear DNA were analyzed by next-generation sequencing technology. Point mutations and large fragment deletion mutations in mitochondria DNA were analyzed with NC_012920.1 as the reference sequence. Hg19 was used as the reference sequence of nuclear gene to analyze point mutations and Copy Number Variation (CNV).

**Literature review**

A literature search was performed up to 03 April 2022 using the electronic databases PubMed and CNKI. The searches were limited to the literature published in English and Chinese. "Mitochondrial myopathy" was searched in the title and/or abstract field.

**Study approval**

Approval of ethics committee about this study was authorized by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University, with a waiver of informed consent.

**Results**

**The patient's laboratory and supplementary examinations**

Laboratory tests of the peripheral blood revealed decreased lymphocyte count (0.98 × 10⁹ per liter, reference range 1.1-3.2 × 10⁹ per liter). The level of phosphocreatine kinase (CK, 455 U per liter, reference range 26-174 U per liter), lactate dehydrogenase (LDH, 277 U per liter, reference range 108-252 U per liter), aspartate aminotransferase (45 U per liter, reference range 15-40 U per liter), n-terminal pro-brain natriuretic peptide (1.97Kpa, % pred 18.8%). Results of magnetic resonance imaging of the brain were noncontributory.

**Histopathologic studies of muscle biopsy**

Observation under electron microscopy showed that the mitochondria between myofibrils were increased, enlarged and clustered, with the inner cristae disoriented and broken. The inner cristae were concentrated and stacked in some mitochondria. Small vacuoles were seen in some mitochondria (Figure 1A-E). HE staining on light microscopy showed that the muscle fibers of skeletal muscle tissue were mildly variable in fiber size, and some muscle fibers were mildly atrophic (Figure 2A). MGT staining revealed a few Ragged-Red Fibers (RRFs). Rimmed Vacuoles (RVs) and tubular aggregates were not seen on MGT staining (Figure 2B). NADH staining showed that the activity of enzymes under sarcolemma was increased in a few muscle fibers (Figure 2C). SDH/COX staining revealed individual blue fibers (Figure 2D). The enzyme activity neither increased nor decreased on COX staining (Figure 2E). SDH staining revealed individual Ragged-Blue Fibers (RBF) (Figure 2F).

**Genetic analysis of the peripheral blood**

Genetic analysis of the peripheral blood from the patient indicated that a heterozygous A3243G mutation was found in MT-TL1 gene (encoding mt-tRNALeu (UUR)) from total DNA extracted from the peripheral blood specimen. The mutation load was 86%.

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**Figure 1**: Manifestations of muscle biopsy under electron microscopy. A) The mitochondria between myofibrils were increased, enlarged and clustered (red arrow), and the inner cristae were disoriented and broken (blue arrow). The inner cristae were concentrated and stacked in some mitochondria (25000X). B) The sarcolemma shrinks (red arrow), the mitochondria under the sarcolemma were increased, enlarged and gathered (blue arrow), the inner cristae were disoriented and broken (black arrow), and the inner cristae were concentrated and stacked in some mitochondria (20000X). C) The mitochondria under the sarcolemma were increased, enlarged and clustered, and the internal cristae were disoriented and broken. The internal cristae of some mitochondria were concentrated and lumpy stacked (red arrow), and the electron density was increased (60000X). D) The sarcolemma shrinks like comb teeth (red arrow), and the mitochondria under the sarcolemma were increased, enlarged and clustered (blue arrow). Small vacuoles were seen in some mitochondria. The inner cristae were disoriented and broken. The inner cristae of some mitochondria were concentrated and lumpy stacked (25000X). E) Small vacuoles were seen in some mitochondria. The inner cristae were disoriented and broken. The inner cristae of some mitochondria were concentrated and lumpy stacked (red arrow) (40000X).
clinical characteristics of adult-onset mitochondrial myopathy with dyspnea as the main manifestation

Twenty-three cases of adult-onset mitochondrial myopathies with dyspnea as the main manifestation were reported in the literature [2-13]. Adding to the case we reported, a total of 24 cases were reported. The clinical and demographic characteristics of the patients are described in Table 1. The age of diagnosis was between 19-70 years (median age 44). The age of onset of the symptoms was between 19-70 years (median age 34). Fifteen patients were male (15/24). The main manifestations were dyspnea, exercise intolerance and respiratory failure. The Phosphocreatine Kinase (CK) was detected in 16 patients, of which CK was increased in 12 patients (12/16). Pulmonary function tests were performed in 12 patients, among which, 7 patients showed restrictive pulmonary ventilation dysfunction (7/12). Four patients showed normal pulmonary ventilation function (4/12). One patient showed decreased FEV1 (1/12). Maximum inspiratory pressure (PImax) was measured in 3 patients, among which, 2 patients showed a significant decrease in the PImax (2/3). Electromyography was performed in 8 patients, of which, 6 patients showed myopathic changes. Muscle biopsy was performed in 18 patients, among which, Ragged Red Fibers (RRF) were found in 16 patients. A total of 17 patients completed mitochondrial gene mutation detection. A3243G mutation within MT-TL1 gene was found in 8 patients (8/17), which was the most common mutation. T3250C mutation within MT-LL1 gene was found in one patient (1/17). A8344G mutation within MT-TK gene (encoding mt-tRNALys) was detected in 3 patients (3/17). T5543C mutation within mitochondrial tRNASp gene was detected in one patient (1/17). G14846A mutation within the mtDNA cytochrome b gene was detected in one patient (1/17). Iron-Sulfur Cluster Scaffold Protein (ISCU) Mutation within the nuclear DNA (nDNA) was detected in 2 patients (2/17).

For treatment of these patients, 8 patients (8/24) received mechanical ventilation or Non-Invasive Ventilation (NIV). Eight patients (8/24) received coenzyme Q10. Seven patients (7/24) received vitamin-B or vitamin-C. Five patients (5/24) received L-carnitine, and 2 patients (2/24) received idebenone. For prognosis of these patients, 10 patients (10/24) were clinically improved, and 2 patients (2/24) were clinically stable. Two patients (2/24) were clinically worsened, and 2 patients died of respiratory failure.

Discussion

In this article, we reported a patient of adult-onset mitochondrial myopathy with dyspnea as the main manifestation. The clinical manifestations of mitochondrial myopathies vary and include myalgia, fatigue and muscle weakness [14]. Pure exertional dyspnea with adult-onset was a very rare phenotype of patients with mitochondrial myopathy.

Three pathophysiologic mechanisms could cause exertional dyspnea in patients with mitochondrial myopathy: dysfunction of the respiratory centers which caused abnormality of the respiratory drive, weakness of the respiratory muscles, or increased ventilatory drive caused by lactic acidosis [2,3,15]. Significant decreased PImax in this patient showed that the respiratory muscle weakness could be the main reason for exertional dyspnea.

Pulmonary function test is a basic examination for the differential diagnosis of dyspnea. In this study, we analyzed the results of pulmonary function tests in the patients. Restrictive pulmonary ventilation dysfunction was the most common abnormality found in the patients. PImax was significantly decreased in most patients, which represents the weakness of the respiratory muscles.

EMG is utilized in the diagnostic evaluation of neuromuscular disorders, however the patient had unremarkable changes on EMG test. In a study reported by Moloney et al., the percentage of definite concordance between EMG and muscle biopsy findings was 76.6%. In the study, seventeen patients had a normal EMG and an abnormal muscle biopsy, of which 6 had histopathological findings consistent with mitochondrial myopathy, central core myopathy or glycogen storage disorder [16]. The reason of unremarkable changes on EMG test of the patient may be the imperfection of EMG for the diagnosis
Table 1: All Reported Literature Cases of adult-onset mitochondrial myopathies with dyspnea as the main manifestation.

<table>
<thead>
<tr>
<th>Case (Age/ gender)</th>
<th>Reported by</th>
<th>Family history of neuromuscular disease</th>
<th>Time of onset of disorder (years old)</th>
<th>Gene analysis</th>
<th>Muscle biopsy</th>
<th>Electromyography</th>
<th>CK (reference range 18–198U/L)</th>
<th>Pulmonary function tests</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (22/M)</td>
<td>[2]</td>
<td>NO</td>
<td>19</td>
<td>NA</td>
<td>RRFs</td>
<td>Myopathic changes</td>
<td>Normal</td>
<td>NA</td>
<td>NA</td>
<td>Discharged against advice on the 8th hospital day and expired a few days later</td>
</tr>
<tr>
<td>2 (56/M)</td>
<td>[3]</td>
<td>NO</td>
<td>41</td>
<td>NA</td>
<td>RRFs</td>
<td>NA</td>
<td>Elevated (1ULR–2ULR)</td>
<td>NA</td>
<td>Mechanical ventilation</td>
<td>Died 5 months later</td>
</tr>
<tr>
<td>3 (70/F)</td>
<td>[3]</td>
<td>NA</td>
<td>70</td>
<td>NA</td>
<td>Subsarcolemmal accumulation of cosinophilic material in most muscle fibers</td>
<td>Normal</td>
<td>Normal</td>
<td>Mechanical ventilation</td>
<td>Respiratory function improved gradually</td>
<td></td>
</tr>
<tr>
<td>4 (43/M)</td>
<td>[4]</td>
<td>NO</td>
<td>30</td>
<td>Deletion of 24 bp within the cytochrome b gene (mtDNA)</td>
<td>Cytochrome oxidase-positive RRFs</td>
<td>Myopathic changes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>5 (32/M)</td>
<td>[5]</td>
<td>Yes</td>
<td>30</td>
<td>A3243G mutation within MT-TL1 gene (mtDNA)</td>
<td>a few RRFs</td>
<td>Normal</td>
<td>Elevated (2 ULR)</td>
<td>Restrictive ventilatory impairment, decreased PImax (20% of predicted values)</td>
<td>NIV</td>
<td>Clinically improved</td>
</tr>
<tr>
<td>6 (34/F)</td>
<td>[6]</td>
<td>NA</td>
<td>34</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Marked restrictive ventilatory impairment, decreased PImax (50 cm H2O)</td>
<td>Nocturnal NIV</td>
<td>Clinically stable</td>
<td></td>
</tr>
<tr>
<td>7 (47/F)</td>
<td>[7]</td>
<td>Yes</td>
<td>45</td>
<td>NA</td>
<td>RRFs</td>
<td>Myopathic changes</td>
<td>Elevated (1ULR–2ULR)</td>
<td>Mild restrictive ventilatory impairment</td>
<td>Nocturnal NIV, coenzyme Q10, Vitamin-B</td>
<td>Clinically improved</td>
</tr>
<tr>
<td>8 (19/F)</td>
<td>[8]</td>
<td>NA</td>
<td>NA</td>
<td>A3243G mutation within MT-TL1 gene (mtDNA)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Mild restrictive ventilatory impairment</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>9 (57/F)</td>
<td>[8]</td>
<td>NA</td>
<td>NA</td>
<td>G1486A mutation within cytochrome b gene (mtDNA)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>10 (60/M)</td>
<td>[8]</td>
<td>NA</td>
<td>NA</td>
<td>F5543C mutation within tRNAThr gene (mtDNA)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
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</tr>
<tr>
<td>11</td>
<td>(37/M)</td>
<td>[8]</td>
<td>NA</td>
<td>NA</td>
<td>Iron-Sulfur Cluster Scaffold Protein mutation (nDNA)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>(38/M)</td>
<td>[8]</td>
<td>NA</td>
<td>NA</td>
<td>Iron-Sulfur Cluster Scaffold Protein mutation (nDNA)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Mild restrictive ventilatory impairment</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>(30/M)</td>
<td>[9]</td>
<td>NO</td>
<td>30</td>
<td>A3243G mutation within MTT-L1 gene (mtDNA)</td>
<td>RRFs</td>
<td>Dramatic decreases in the patient's motor and sensory amplitude with normal nerve conduction</td>
<td>Elevated (6ULR~7ULR)</td>
<td>NA</td>
<td>Coenzyme Q10, L-carnitine, vitamin-B2,</td>
</tr>
<tr>
<td>14</td>
<td>(45/F)</td>
<td>[10]</td>
<td>YES</td>
<td>32</td>
<td>A3243G mutation within MTT-L1 gene (mtDNA)</td>
<td>RRFs</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
<td>Coenzyme Q10, L-carnitine, multi-vitamins</td>
</tr>
<tr>
<td>15</td>
<td>(52/M)</td>
<td>[10]</td>
<td>NO</td>
<td>49</td>
<td>A8344G mutation within MT-TK gene (mtDNA)</td>
<td>RRFs</td>
<td>NA</td>
<td>Elevated (5ULR~6ULR)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>16</td>
<td>(66/M)</td>
<td>[10]</td>
<td>NO</td>
<td>51</td>
<td>A8344G mutation within MT-TK gene (mtDNA)</td>
<td>RRFs</td>
<td>NA</td>
<td>Elevated (10ULR~11ULR)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>17</td>
<td>(33/M)</td>
<td>[10]</td>
<td>YES</td>
<td>27</td>
<td>A8344G mutation within MT-TK gene (mtDNA)</td>
<td>RRFs</td>
<td>NA</td>
<td>Elevated (4ULR~5ULR)</td>
<td>NA</td>
<td>Coenzyme Q10, L-carnitine, multi-vitamins</td>
</tr>
<tr>
<td>18</td>
<td>(37/F)</td>
<td>[10]</td>
<td>YES</td>
<td>27</td>
<td>T3250C mutation within MTT-L1 gene (mtDNA)</td>
<td>RRFs</td>
<td>NA</td>
<td>Elevated (6ULR~7ULR)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>19</td>
<td>(30/M)</td>
<td>[10]</td>
<td>NO</td>
<td>19</td>
<td>NA</td>
<td>RRFs</td>
<td>NA</td>
<td>Elevated (10ULR~11ULR)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>20</td>
<td>(46/M)</td>
<td>[10]</td>
<td>YES</td>
<td>30</td>
<td>NA</td>
<td>RRFs</td>
<td>NA</td>
<td>Elevated (1ULR~2ULR)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>21</td>
<td>(52/M)</td>
<td>[11]</td>
<td>NO</td>
<td>52</td>
<td>A3243G mutation within MTT-L1 gene (mtDNA)</td>
<td>RRFs</td>
<td>Myopathic changes</td>
<td>Normal</td>
<td>Moderate restrictive ventilatory impairment</td>
<td>NIV, Vitamin-C, vitamin-B1, riboflavin, coenzyme Q10, cobamamide, L-carnitine</td>
</tr>
<tr>
<td>22</td>
<td>(35/F)</td>
<td>[12]</td>
<td>NO</td>
<td>35</td>
<td>A3243G mutation within MTT-L1 gene (mtDNA)</td>
<td>A large number of vacuoles in muscle fibers</td>
<td>NA</td>
<td>Elevated (19ULR~20ULR)</td>
<td>Decreased FEV1 (FEV1&lt;80% pred, FEV1/FVC&lt;70%)</td>
<td>NIV, Vitamin-B, Vitamin-C, coenzyme Q10</td>
</tr>
</tbody>
</table>
oxidative capacity of patients with mitochondrial myopathies [22]. Exercise training could improve muscle strength and be effective to relieve the symptoms of mitochondrial myopathies [20,21]. Case series studies showed that coenzyme Q10 and idebenone may be effective to relieve the symptoms of mitochondrial myopathies [19]. Case reports and differential diagnosis.

excluding the above etiology, especially with muscle weakness, fatigue, disease, cardiac disease, or pulmonary vascular disease. For patients with dyspnea as the chief complaint, lung function test, echocardiography, and CT pulmonary angiography will be prescribed to determine whether the patients have pulmonary disease, cardiac disease, or pulmonary vascular disease. For patients excluding the above etiology, especially with muscle weakness, fatigue, elevated phosphocreatine kinase, or lactic acidosis, neuromuscular diseases include mitochondrial myopathy should be considered as the differential diagnosis.

Conclusions

In conclusion, adult-onset mitochondrial myopathy is a rare cause of exertional breathlessness who seeks medical advice in the department of respiratory. Our data confirmed that mitochondrial myopathies should be considered in the differential diagnosis of unexplained exertional breathlessness.

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References


