# Case Report

# Fulminant Respiratory Muscle Paralysis, an Expanding Clinical Spectrum of Mitochondrial A3243G tRNALeu Mutation

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*Mitochondrial disease is a group of rare disorders, caused by mitochondrial dysfunction. They are usually the result of mutations of either mitochondrial DNA or nuclear DNA. A3243G transition in the tRNALeu is one the most frequent mutations of the mitochondrial DNA. Phenotypic expression of this mutation varies. The most well-recognized phenotype is Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. Isolated myopathy with respiratory muscle weakness in this mutation has been rarely documented. The authors reported a 20-year-old Asian female presenting with a fulminant hypoventilatory respiratory failure with mild weakness of the limbs. Electrophysiologic study showed evidences of myopathy. Restrictive physiology of the lungs was demonstrated by pulmonary function test. Subsarcolemmal accumulation of mitochondria was demonstrated by Gomori trichrome and succinate dehydrogenase stains. Genetic study revealed the A3243G mutation in mitochondrial DNA in peripheral blood. Isolated mitochondrial myopathy severely affecting respiratory muscles may be considered as an uncommon clinical spectrum of A3243G mitochondrial disease.*

**Keywords:** *Mitochondrial disease, A3243G mutation, Neuromuscular respiratory failure, Bilateral diaphragmatic weakness, Myopathy*

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Mitochondrial disease, caused by mitochondrial dysfunction resulting in inadequately intracellular energy production, is a group of rare disorders. Their clinical presentation and genetic determination are heterogeneous. Common manifestations are varieties of neurological symptoms, such as seizure, myoclonus, migrainous-like headache, stroke-like phenomenon, and muscle weakness. Mitochondrial disorders are usually result from mutations of either mitochondrial DNA or nuclear DNA. A3243G transition in the tRNALeu is the most frequent mutation of the mitochondrial DNA. Phenotypic expression of this mutation varies; however, it could be categorized into syndromic and non-syndromic manifestations[1].

The most well-recognized syndromic phenotype of this mutation is mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. Other well-defined syndromes include myoclonic epilepsy and ragged-red fibers (MERRF) syndrome, chronic progressive external ophthalmoplegia (CPEO), Kearns-Sayre syndrome, Leigh syndrome, and maternal inherited diabetes and deafness. The non-syndromic manifestations, for instance, hypertrophic cardiomyopathy and isolated myopathy, are diagnostical challenges. Isolated myopathy with predominant respiratory muscle weakness in mitochondrial A3243G mutation has been rarely reported. To the best of our knowledge, only four cases had been described[2-5]. The authors reported a young Asian female presenting with fulminant respiratory

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muscle paralysis, and mild weakness of the limbs, harboring the A3243G mutation in mitochondrial DNA.

**Case Report**

A 20-year-old Asian female experiencing orthopnea for three months, presented to a local general hospital with hypoventilatory respiratory failure accompanying with cardiac arrest. Three months prior to the admission, she developed mild degree of shortness of breath every time lying flat. The onset of each orthopnea was rather rapid and happened within few minutes when lying down. A few weeks later, the symptom increased in severity to the extent that she was unable to breathe upon lying down and had to stay upright throughout the night. Nevertheless, she was able to maintain her daily activities and still went to school as usual. She had no complaint of daytime dyspnea or sleepiness. The patient was evaluated but the cause of orthopnea was not defined. On the day of admission, she had severe dyspnea while riding bicycle back home and was sent to the emergency room. At the hospital, the patient developed cardiac arrest with electrocardiogram showing asystole. Resuscitation was done and the patient regained normal consciousness. Investigations showed no evidences of primary cardiac, lung parenchymal, or systemic disorders. Attempt weaning off ventilator was unsuccessful because of carbon dioxide retentions, causing acute deterioration of her consciousness. For their presumptive diagnosis of myasthenic crisis, she received one cycle of intravenous immunoglobulin and pyridostigmine without any improvement. Tracheostomy was then performed. The patient was able to eat, sit, and be mobile but required assisted ventilation at all times. She remained at the local hospital for almost two months before being referred to our hospital.

The patient's past medical history was striking with decreased exercise tolerance, becoming evident in physical education classes. However, she retained normal daily activity and was able to climb up to the fifth floor at school. She has had normal intelligence. Her perinatal history as well as growth and development records were unremarkable. She had no history of airway and lung diseases. Her family history was negative for neuromuscular and genetic disorders.

On examination, the patient was fully conscious and able to follow commands. Apart from being on tracheostomy tube with artificial ventilatory support, other general examinations were normal. Tachypnea and rapid, shallow breathing with abdominal paradoxical respiration were observed when she lay supine and was discontinued from the ventilator. Neurological examination showed normal cranial musculature. Neck flexor muscles and bilateral upper trapezius, deltoids, biceps brachii, triceps brachii, and iliopsoas were weak of grade IV/V according to Medical Research Council (MRC) grading criterion. Other muscular tests were of normal strength. Sensation and deep tendon reflexes were normal. Other neurological examinations were unremarkable. No deformity of the spines was observed.

Laboratory investigations found a remarkably elevated venous lactate level of 9.1 mmol/L (normal value 0.5-2.2 mmol/L). Complete blood count, fasting blood sugar, kidney function test, liver function test, thyroid function test, serum electrolytes, serum creatine phosphokinase, and lactate dehydrogenase were normal. Chest radiographic study was normal. However, the diaphragms were slightly elevated bilaterally. Echocardiogram was normal. Audiogram and complete eye examination were also normal. Due to the severity of disease at the beginning, the patient was unable to effectively undergo the pulmonary function test. Subsequent pulmonary function test, performed months later, clearly revealed a restrictive lung physiology: Forced vital capacity (FVC) of 1.24 (36% of predicted), FEV1 (Forced expiratory volume 1) of 1.10 (35% of predicted) and FEV1/FVC of 88%. At supine position, a 30% drop of FVC was detected. Magnetic resonance imaging (MRI) of the brain was unremarkable.

Electrodiagnostic study was carried out by using the CareFusion Nicolet EDX System with Viking Software. Sensory and motor nerve conduction studies were normal. Repetitive nerve stimulation test of five nerve-muscle pairs was normal. Concentric needle electromyogram (CNE) showed mild degree of positive sharp waves at the mid cervical paraspinal muscles. No spontaneous activity was demonstrated elsewhere. Motor unit action potentials of left deltoid and left upper trapezius muscles were of small duration, low amplitude, and polyphasia but showed a normal recruitment pattern. CNE of biceps brachii, triceps brachii, iliopsoas, vastus medialis, hip adductors, and other distal muscles on the left side was normal. These findings were indicative of a non-irritable myopathy.

Muscle biopsy of the right deltoid was performed. Haematoxylin and eosin stain showed some slightly basophilic and granular fibers. There was

no evidence of inflammation. The Gomori trichrome and succinate dehydrogenase histochemistry stains demonstrated the subsarcolemmal accumulation of mitochondria, as the classic ragged red and ragged blue fibers, respectively. They mostly affected type I muscle fibers. Staining for glycogen was normal. Mild degree of lipid deposition was seen in some muscle fibers. Screening for common point mutation by next generation sequencing revealed an A3243G mutation of the mitochondrial DNA in peripheral blood specimen.

Diagnosis of A3243G mitochondrial DNA mutation was made. She was managed symptomatically and supportively. Coenzyme Q10, vitamin E, and vitamin C were given. A month later, she was discontinued from full mechanical ventilator support, nevertheless requiring bilevel positive airway pressure (BiPAP) via tracheostomy during the night. This patient was evaluated one year later. She was able to perform normal daily activities such as riding motorcycle. Nocturnal BiPAP had been well tolerated. Neck and limb muscles were of normal strength. Concentric needle EMG still showed evidences of myopathy. Restrictive lung physiology, in slightly lesser degree, could still be demonstrated by the pulmonary function test.

**Discussion**

Mitochondrial disease has been increasingly recognized in clinical practices for decades especially in the field of neurology. Mitochondria is the main resource of energy production of the cells, thus, mitochondrial dysfunction typically influences functions of the organs and tissues with high-energy requirement. The most commonly affected organs include brain, nerves, and muscles. Other possible targets are endocrine and renal systems. Mitochondrial disease classically presents with multi-system dysfunction and has high variety of clinical manifestation[6]. Overlap of clinical presentations among different mitochondrial syndromes is common.

Skeletal muscle contraction requires high energy, thus it is a vulnerable organ in mitochondrial disease. "Isolated mitochondrial myopathy" is referred to mitochondrial disease presenting with isolated skeletal myopathy[7]. These patients may present with muscle weakness as well as exercise intolerance. Axial and proximal limb muscles are predominantly involved, with variable onset and severity. In such circumstance, it may not be easy to distinguish isolated mitochondrial myopathy from other types of myopathy. Respiratory muscles are group of skeletal muscles needed for an inspiration. Diaphragm, external intercostal, and accessory muscles are the main inspiratory muscles, with diaphragm playing the most important role[8].

Acute respiratory failure is an emergency and life-threatening condition. Prompt diagnosis and proper treatment are very crucial. Acute respiratory failure may be classified into two major types, a hypoxic failure and a hypoventilatory failure[9]. Weakness of the respiratory muscles, abnormality of respiratory drive and some primary pulmonary disorders are among the causes of hypoventilatory failure. Hypoventilatory failure due to respiratory muscle weakness is a critical feature of some neuromuscular diseases, such as Guillain-Barre syndrome and myasthenia gravis. The symptom usually develops when weakness of limbs is marked. If such is not a case, the discovery for the cause of respiratory failure becomes more difficult. As a rule, myopathy presents itself with symmetrical weakness of the proximal limb muscles. However, certain metabolic myopathy, such as late onset Pompe myopathy, a glycogen storage disease, frequently has a prominent respiratory muscle weakness, disproportionately to the degree of limb weakness[10].

Predominant respiratory muscle weakness in mitochondrial myopathy is not common and a small number of cases have been documented[2-5,11-15]. The diagnosis of mitochondrial disease of those cases was mostly based on muscle histopathology. Identification of mutation in those cases had not been much investigated. To date, five cases (including the presented case) with A3243G mutation presenting with hypoventilatory respiratory failure had been reported.

Kamakura K et al, in 1995, first reported a 57-year-old man with two episodes of respiratory failure occurred within one year[2]. The diagnosis of A3243G mutation was made during the first episode when he had subacute severe weakness of limbs and bulbar muscles accompanied respiratory muscle paralysis. The weakness had gradually resolved before he developed the second episode of an isolated respiratory muscle paralysis. Yang CC et al reported a 55-year-old woman presenting with mild degree of limb weakness and decreased exercise tolerance for one year and subsequently developed repeated episodes of transient respiratory hypoventilation[3]. Chang KC et al also reported a middle-aged man presenting with acute respiratory hypoventilation[4].

This patient suffered from a mild degree of chronic progressive generalized muscle weakness over two years. He also had intermittent diarrhea and weight loss. A3243G mutation was found in both muscle and blood specimens. Saneto RP et al reported an 11-year-old boy with subacute respiratory compromise and hypercarbia[5]. Investigation revealed abnormal mitochondrial structure in the muscle and heteroplasmic A3243G mutation. For the prognosis, three adult patients required nocturnal non-invasive ventilation. Duration of follow-up ranged from few months to three years. The teen-age patient was weaned off ventilator several months after diagnosis.

A3243G mutation is one of the most common mutations in mitochondrial DNA. Clinical phenotype varies among cases. This variability is principally explained by distinctive characteristic of mitochondrial genetics, for instance, mitotic segregation, heteroplasmy, and threshold effect, which could result in a variation of abnormal mitochondrial loads in different organs[6]. Some authors hypothesized that cases with predominant respiratory muscle weakness might have increased numbers of abnormal mitochondria in the diaphragm[2]. However, this hypothesis has not been verified.

Two possible mechanisms leading to respiratory hypoventilation in mitochondrial diseases have been postulated[2,11,16]. Kamakura K et al demonstrated limitation of diaphragmatic movement by fluoroscopy and suggested a mechanism of primary weakness of the respiratory muscles[2]. Others had found a reduction of respiratory drive to hypoxia and hypercarbia in the setting of mild degree of respiratory muscle weakness in their cases and postulated that dysregulation of the respiratory center in the brainstem could lead to respiratory hypoventilation[11]. However, an absence of abnormal brainstem signs might argue against this conclusion. In the presented case, respiratory muscle weakness, due to mitochondrial myopathy, was thought to be the major mechanism contributing to hypoventilatory respiratory failure. Our assumption was based on the patient's unique clinical presentation and findings of the pulmonary function test. Severe orthopnea and abdominal paradox, which abruptly occur during lying supine, is a clinical clue for bilateral diaphragmatic paresis[8,17]. Paradoxical breathing is a sign of bilateral diaphragmatic weakness that is more pronounced in the supine position. Upon inspiration, the inspiratory muscles contract allowing the thoracic cage to rise and the intrathoracic pressure to drop. The weakened diaphragm fails to contract, moves in the cephalad direction from the fall in the intrathoracic pressure causing the intraabdominal organs to be displaced. The displacement of the intraabdominal organ in the cephalad direction causes the appearance of the abdominal walls moving inwards while the chest wall rises during inspiration which is the hallmark of paradoxical breathing. Clearly, this unique clinical phenomenon was repeatedly demonstrated in the presented case. In addition, severe restrictive physiology of the lungs with an absence of primary lung disease was obviously shown by the accompanying pulmonary function test. These findings indicated the severe weakness of the respiratory muscles. Moreover, reduction of upright to supine FVC of 30% or over also suggests the weakness of bilateral diaphragms[17]. However, other than a normal MRI of the brain, any other physiological test to exclude another mechanism was not performed. Because mitochondrial disease can affect different organs, the underlying mechanism of hypoventilation might be different among cases and combination of more than one mechanism is possible.

**Conclusion**

Isolated mitochondrial myopathy predominantly affecting respiratory muscles is an uncommon clinical presentation of A3243G mitochondrial disease. The presented case has value to expand the clinical spectrum of this disorder. Isolated mitochondrial myopathy should be added into the differential diagnoses of neuromuscular respiratory failure. In addition, severe respiratory muscle weakness due to mitochondrial myopathy contributing to a respiratory failure was revealed in the presented case.

**What is already known on this topic?**

A3243G mitochondrial disease has variety of clinical manifestation but usually presents with MELAS syndrome. Manifestation with hypoventilatory respiratory failure is very uncommon. Only four cases have been described in the literatures. Underlying mechanism is still uncertain.

**What this study adds?**

Fulminant respiratory muscle paralysis in a patient with A3243G mutation was firstly reported in a Thai patient. The presented case had expanded the clinical spectrum of mitochondrial A3243G mutation. Primary respiratory muscle weakness is a mechanism

leading to hypoventilatory respiratory failure in A3243G mitochondrial disease.

**Potential conflicts of interest**

None.

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## *ภาวะกล้ามเนื้อหายใจอ่อนแรงรุนแรง ขยายลักษณะทางเวชกรรมคลินิกของการกลายพันธุ์ชนิด A3243G ในดีเอ็นเอของไมโทคอนเดรีย*

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*โรคของไมโทคอนเดรียเป็นกลุ่มโรคหายากที่เกิดจากไมโทคอนเดรียทำหน้าที่ผิดปกติ ซึ่งเป็นผลจากการกลายพันธุ์ของดีเอ็นเอของไมโทคอนเดรีย หรือ ดีเอ็นเอของนิวเคลียส การกลายพันธุ์ชนิด A3243G เป็นการกลายพันธุ์ของดีเอ็นเอของไมโทคอนเดรียที่พบได้บ่อยที่สุดชนิดหนึ่ง ผู้ป่วยที่มีการกลายพันธุ์ชนิดนี้มักเกิดกลุ่มอาการ "มีลาส" ภาวะกล้ามเนื้ออ่อนแรง และกล้ามเนื้อหายใจอ่อนแรงเป็นอาการที่มีรายงานน้อยมากในการกลายพันธุ์ชนิดนี้ ผู้นิพนธ์รายงานผู้ป่วยหญิงชาวเอเชียอายุ 20 ปี มีกล้ามเนื้อหายใจอ่อนแรงรุนแรงมาก ร่วมกับอาการอ่อนแรงเพียงเล็กน้อยของกล้ามเนื้อแขน ขา การตรวจไฟฟ้าสรีรวิทยาแสดงหลักฐานของโรคกล้ามเนื้อ การทดสอบหน้าที่ปอดพบการขยายตัวของปอดจำกัด การตรวจพยาธิวิทยากล้ามเนื้อด้วยการย้อมพิเศษพบการสะสมของไมโทคอนเดรียในบริเวณซับซาร์โคเลมมัลของกล้ามเนื้อ การตรวจวิเคราะห์พันธุกรรมพบการกลายพันธุ์ชนิด A3243G ในดีเอ็นเอของไมโทคอนเดรียในเลือดผู้ป่วย ภาวะกล้ามเนื้อหายใจอ่อนแรงอย่างรุนแรง อาจจัดเป็นลักษณะเวชกรรมคลินิกที่พบได้ไม่บ่อยอย่างหนึ่ง ในโรคของไมโทคอนเดรียที่มีการกลายพันธุ์ชนิดนี้*