KC Chang 鄭國釗 YF Mak 麥婉芬 WC Yu 余衛祖 KK Lau 劉國光 WW Yan 殷榮華 TC Chow 周達倉

Respiratory insufficiency in a Chinese adult with mitochondrial myopathy

患線粒體肌病成年華人的呼吸困難

Mitochondrial myopathy is an important but uncommon cause of respiratory insufficiency in adults. We report the first case of respiratory insufficiency associated with adult-onset mitochondrial myopathy seen in a Chinese adult in Hong Kong. The patient presented with peripheral oedema and shortness of breath over 2 to 3 days. There was a history of gradual progressive limb weakness over approximately 2 years, hypertrophic cardiomyopathy, intermittent diarrhoea, and weight loss. The diagnosis was made by skeletal muscle biopsy and molecular study, which revealed the A3243G point mutation.

線粒體肌病雖然是成人呼吸困難的一個重要原因,但很少見。我們發現了一宗因線 粒體肌病而導致呼吸困難的病例,這亦是首宗在香港成年華人中報告的個案。患者 出現外圍水腫和呼吸短促二至三天。患者肢體逐漸虛弱大約有兩年,患有心肌肥大 症、間歇性腹瀉、及體重減輕。診斷是由骨骼肌活組織檢查和分子研究作出的,檢 查研究顯示有 A3243G 點突變。

Introduction

Mitochondrial disorders are rare, heterogeneous, and predominantly neurological in manifestation. Classical syndromes include Kearns-Sayre syndrome, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibres (MERRF), chronic progressive external ophthalmoplegia (PEO), Leber hereditary optic neuropathy, and neurogenic weakness ataxia with retinitis pigmentosa. Mitochondrial myopathy is a form of metabolic myopathy. A Medline search identified five non-English articles and five English articles reporting the association of mitochondrial myopathy and respiratory insufficiency in adults.¹⁻⁵ We report the first case of such an association in a Chinese adult in Hong Kong.

Case report

A 32-year-old man presented with bilateral ankle oedema and severe shortness of breath of a few days' duration. There were no other chest symptoms. The patient reported the insidious onset of generalised and progressive limb weakness associated with deterioration in exercise tolerance over approximately 2 years. Other history of note included review by a private cardiologist 1 year previously for an abnormal electrocardiogram (ECG); echocardiography also revealed abnormalities. The patient had had intermittent diarrhoea for approximately 6 months. No abnormalities had been detected on colonoscopy examination. He had a family history of neuromuscular disease. Of his three siblings (one brother and two sisters), one of his elder sisters had ocular myasthenia gravis associated with thymic hyperplasia. The patient's father had thyrotoxicosis. The patient did not smoke or drink alcohol. Drug history was unremarkable. He was employed as an airport technician.

On presentation, the patient was noted to be thin with bilateral ankle oedema. Examination of the respiratory and cardiovascular systems was normal, apart from evident tachypnoea and tachycardia. Abdominal examination was unremarkable. Examination of the neurological system showed mild wasting of

Key words:

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Yaumatei Chest Clinic, Yaumatei Jockey Club Polyclinic, 145 Battery Street, Kowloon, Hong Kong KC Chang, MSc, MRCP Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Hong Kong: Department of Pathology YF Mak, FRCPA, FHKAM (Pathology) TC Chow, MPhil Department of Medicine and Geriatrics WC Yu, FRCP (Edin), FHKAM (Medicine) KK Lau, MRCP, FHKAM (Medicine) Intensive Care Unit WW Yan, FRCP (Edin), FHKAM (Medicine)

Correspondence to: Dr KC Chang

the shoulder girdle muscles and 'winging' of the scapulae. The sternomastoid muscles were weakened. Limb power was grade four, both proximally and distally. The remainder of the neurological examination, which included assessment of gait, tendon reflexes, plantar responses, examination of the cranial nerves, cerebellar function, and fundoscopy, showed no significant abnormalities.

Chest radiography showed no significant findings. Arterial blood gas analysis was consistent with type II respiratory failure. The patient had a mild macrocytic anaemia. Creatine kinase, lactate dehydrogenase, and levels of the cardiac isoenzyme of creatine kinase were all increased approximately two-fold. Alanine transferase and alkaline phosphatase levels were mildly elevated. Renal biochemistry and blood glucose were normal.

Electrocardiography showed sinus tachycardia, right axis deviation, tall P waves in lead II, right bundle branch block, and deep S waves in leads V3 and V4. Serial ECG showed no evidence of acute myocardial infarction. Echocardiography showed concentric left ventricular and apical hypertrophy, but no evidence of pulmonary hypertension.

The patient's ECG and echocardiography recorded 1 year previously were located for comparison. The earlier ECG also showed sinus tachycardia, right axis deviation, right bundle branch block, tall P waves in lead II, deep S waves in V3 and V4, as well as 'high take-off' ST segment elevation in leads V2 to V5, and left ventricular hypertrophy on voltage criteria. The earlier echocardiogram showed right ventricular wall thickening, marked thickening of the left ventricular wall and papillary muscles with the exception of the inferior portion of the interventricular septum, normal left ventricular systolic and diastolic function, normal valves, mild tricuspid regurgitation, and the absence of outflow tract obstruction.

The patient subsequently required mechanical ventilation for respiratory failure. Ventilator use was discontinued gradually over 4 days and supported by non-invasive positive pressure ventilation (NIPPV). After further stabilisation, the patient could be supported by nocturnal NIPPV alone, without supplemental oxygen. Electrocardiography showed normalisation of the P wave, disappearance of the right bundle branch block, similar S waves in V3 and V4, and left ventricular hypertrophy on voltage criteria. Arterial blood gas analysis showed compensated chronic type II respiratory failure. Lung function tests indicated a restrictive lung disorder, with marked reduction of the forced expiratory volume in 1 second and forced vital capacity. Maximum inspiratory pressure and maximum expiratory pressure were both markedly reduced to approximately 20% of predicted values.

Serial biochemical tests showed gradual normalisation of muscle enzymes over 3 weeks. Viral studies for myocarditis were normal. The patient's anaemia gradually improved as his diarrhoea subsided. Investigation with regard to the macrocytic anaemia showed a normal reticulocyte count, a normal but low level of vitamin B12, a normal level of red cell folate, and normal thyroid function tests. Iron stores were normal.

A neuromuscular cause for the respiratory failure was considered. Edrophium (Tensilon) testing showed no abnormality. Nerve conduction studies and needle electromyography (EMG) were normal. Assays for antinuclear factor, rheumatoid factor, and anti-acetylcholine receptor antibody were normal. Magnetic resonance imaging of the brainstem and cervical spinal cord showed no significant findings. In view of the family history of neuromuscular disease, abnormal levels of muscle enzymes, and multisystem involvement, mitochondrial myopathy was suspected.

Muscle biopsy of the deltoid was performed. Myopathic changes were seen but there was no evidence of significant inflammation. Staining for glycogen was unremarkable. The Gomori trichrome stain revealed a few ragged red fibres (Fig 1) and there was an increase in oxidative enzyme activity appearing as subsarcolemmal crescents. Ultrastructural examination of the muscle fibres showed an increase in the number of mitochondria, with prominent mitochondrial abnormalities evident including circular and stack cristae as well as paracrystalline inclusions (Fig 2). Screening for common point mutations by polymerase chain reaction (PCR) showed an A3243G MELAS mutation in both the muscle biopsy specimen and the peripheral blood specimen.

The patient was reviewed a few months later. Nocturnal non-invasive ventilation was well tolerated. He had gained weight and exercise tolerance had improved. Electrocardiography showed sinus rhythm, a heart rate of 90 to 100 beats per minute, right axis deviation, normal P waves, right bundle branch block, and deep S waves in leads V3 and V4. Reassessment by needle EMG of different muscle groups showed chronic myopathic changes.



Fig 1. Histological examination of the muscle biopsy showing ragged red fibres (Gomeri trichrome stain x200)



Fig 2. Electron microscopy of muscle fibre showing an increased number of abnormal mitochondria (x13000)

Discussion

Mitochondria are double-membrane cytoplasmic organelles devoted to energy production. Oxidative phosphorylation takes place in the mitochondria and the process involves respiratory chain complexes I to V. These complexes consist of protein subunits, which are encoded by the nuclear genome and the mitochondrial genome. Mitochondrial disorders occur as a result of one of the following defects: mutations of the mitochondrial DNA (mtDNA), mutations of nuclear DNA, or defects in the intercommunication between nuclear DNA and mtDNA.⁶

The hallmark of mitochondrial diseases is their clinical and genetic variability.7 There are three main types of pathological mtDNA mutations: deletion, duplication, and point mutation. While mtDNA deletions are not transmitted, the other two types of mtDNA defects are transmissible from the mother to the offspring by maternal inheritance. The diverse clinical variability of mitochondrial diseases is partly attributed to heteroplasmy, which refers to the presence of a mixture of mutated and wild type molecules. The proportion of pathogenic mutated mtDNA (mutation load) at the cellular level determines the phenotypic expression, which may also vary according to the different requirements for oxidative phosphorylation by different organs, and environmental factors.8 When the mutation load exceeds a critical threshold (typically 85%), the deleterious effects of the mutation will be manifested clinically as a disease syndrome. The level of heteroplasmy or mutation load for a certain pathogenic mtDNA mutation varies among different hosts as well as between the different tissues and organs of the same host. The mutation load can also increase or decrease with time.

In general, patients with mitochondrial disorders present with one of three main clinical patterns: a classical clinical syndrome, a non-syndromal constellation of suggestive clinical features, or unexplained symptoms and signs.⁷ The group of patients with unexplained symptoms and signs often have non-neurological clinical manifestations and multisystem involvement, which was a clue to the patient's diagnosis in this case.

The absence of demonstrable myopathic changes in the initial assessment by needle EMG in this patient suggests that mitochondrial myopathy cannot be excluded by a single normal EMG assessment. Muscle biopsy is the cornerstone of investigation of mitochondrial myopathy. Although the presence of ragged red fibres-corresponding to subsarcolemmal accumulations of mitochondria-is the pathological hallmark of mitochondrial myopathy, it is not a specific finding.9 Similarly, the demonstration of abnormal mitochondria with paracrystalline inclusions on electron microscopy is also relatively non-specific.¹⁰ Specific biochemical tests that pinpoint mitochondrial dysfunction include the demonstration of cytochrome c oxidase deficient fibres, and evident deficiency on respiratory chain complex assays. The pattern of abnormalities seen in these biochemical tests guides additional analysis. A molecular diagnosis of mitochondrial disease is straightforward when screening for common point mutations by PCR is positive, as seen in this case.

The A3243G point mutation accounts for approximately 80% of the MELAS cases.¹¹ It refers to an A-to-G mutation at position 3243 of the tRNA^{Leucine(UUR)} gene. The genotype-phenotype correlation of this mutation is rather loose, and it has been detected in patients with maternally inherited PEO, isolated myopathy, cardiomyopathy, and gastrointestinal dysmotility.^{12,13} This patient provides another example of the loose genotype-phenotype correlation. While he does not have MELAS syndrome, the clinical features of myopathy, cardiomyopathy and gastrointestinal dysmotility, which are all associated with A3243G point mutation, are seen. The patient's diarrhoea is likely to be a manifestation of visceral myopathy or myenteric plexus neuropathy.

Patients with the A3243G MELAS mutation often demonstrate a low mutation load in blood analysis,⁷ although this patient showed the contrary. The positive blood test in this case supplemented the muscle biopsy findings. It has been shown that the frequency of major neurological features for patients with A3243G MELAS mutation is related to the level of mutation load in the patient's muscle but not to that in blood.¹⁴ Given the high level of mutation load in this patient's muscle, his prognosis is reasonably poor, but it is noteworthy that the level of mutation load in muscle may also decrease with time.¹⁵ In this case, there was no conclusive evidence of disease in the patient's mother and the patient's three siblings. Screening of the mother's blood for A3243G point mutation was negative. This is consistent with the observation that the level of A3243G MELAS mutation load in the mother's blood is related to the frequency of affected offspring.¹⁶

Nonetheless, one of this patient's sisters had findings suggestive of maternally inherited chronic PEO, which is also associated with A3243G point mutation. This sibling presented with ptosis and external ophthalmoplegia. The tensilon test was positive but the assay for anti-acetylcholine receptor antibody was normal. Screening for A3243G MELAS point mutation in her blood was negative and she refused muscle biopsy.

Cardiac involvement in mitochondrial diseases is variable. It has been suggested that a deletion of mtDNA may produce cardiac conduction disturbances, while point mutation may cause left ventricular hypertrophy and wall motion abnormalities.¹⁷ Kearns-Sayre syndrome results from deletion of mtDNA and various cardiac conduction disturbances,7,18 such as prolonged intraventricular conduction time, bundle branch block, bifascicular block, and complete atrioventricular block have been reported. Myoclonic epilepsy with ragged red fibres and MELAS are both caused by point mutation. Reported cardiac involvement in MERRF includes dilated cardiomyopathy,^{17,19} and hypertrophic cardiomyopathy with diffuse hypokinesia.17 Cardiac involvement in MELAS includes hypertrophic cardiomyopathy,^{20,21} Wolff-Parkinson-White syndrome,²¹ ischaemic heart disease,²² and left ventricular hypertrophy.^{17,23,24} Left ventricular hypertrophy is a characteristic clinical feature in MELAS, which may be associated with dilation of the left ventricle²³ and normal wall motion or diffuse hypokinesia.¹⁷ The patient in this case shares the A3243G point mutation of MELAS, and demonstrated cardiac findings of hypertrophic cardiomyopathy with normal ventricular size, normal wall motion, absence of outflow tract obstruction, and variable occurrence of right bundle branch block.

Conclusions

We report the first case in Hong Kong of an association between adult-onset mitochondrial myopathy and respiratory insufficiency. Although mitochondrial myopathy is rare, it should be considered in the context of respiratory failure due to neuromuscular causes, especially when there is multisystem involvement.

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