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## Rehabilitation of Patients with MELAS Syndrome: A casereport

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## Case Report

# Rehabilitation of Patients with MELAS Syndrome: A Case Report

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MELAS (mitochondrial encephalomyopathy, lactic acidosis, and recurrent stroke-like episodes) syndrome is a mitochondrial disorder. Patients with mitochondrial myopathies typically have exercise-induced symptoms. Thus, patients are often advised to avoid exercise, which leads to deconditioning. Currently, the concept of aerobic exercise training as therapy for mitochondrial disease is not well established. We report the case of a patient with adult-onset MELAS, who responded positively to a low intensity rehabilitation program. Low intensity training was safe and significantly improved our patient's physical fitness. During the 20-month follow-up period, there was no significant reduction in muscle strength and function. Therefore, short-term endurance training was very useful in our patient. Given this result, studies with a proper aerobic exercise protocol and long-term follow-up are warranted. (Tw J Phys Med Rehabil 2006; 34(3): 183 - 188 )

**Key words:** aerobic exercise, MELAS syndrome, mitochondrial myopathy, rehabilitation

## INTRODUCTION

MELAS (mitochondrial encephalomyopathy, lactic acidosis, and recurrent stroke-like episodes) syndrome is a mitochondrial disorder. Patients with MELAS generally have a poor prognosis and outcome, as effective therapies for MELAS syndrome have not been established. The clinical management of individuals is largely supportive and includes exercise training.<sup>[1]</sup> In recent studies, exercise has been shown to be of possible benefit to patients with mitochondrial disease as it prevents deconditioning, which can exacerbate pre-existing exercise intolerance and fatigability.<sup>[2,3]</sup> Aerobic training enhances aerobic

capacity, muscle oxidative metabolism, and ATP production, decreases lactate levels, and improves quality of life in patients with mitochondrial disease.<sup>[4]</sup> A regular low intensity regimen can improve muscle endurance and cardiopulmonary function.

## CASE REPORT

The patient, a thin 45-year-old woman, was admitted to our hospital due to an episode involving visual hallucinations, migraine-like headaches, seizure, vomiting, loss of consciousness, and relative left limbs weakness. None of her family members or relatives had MELAS. Her speech was fluent with normal comprehension and

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repetition. She had grade 4 muscle power of her left arm and left leg. She had intact, symmetrical deep tendon reflexes and absent Babinski response bilaterally. The Functional Independence Measure (FIM) score was 74. On day 2 of her hospitalization, her visual hallucinations, headache, and vomiting completely resolved. Using a cane, she could walk a maximal distance of 15 meters; she had a wide-based, slightly ataxic gait as well.

Laboratory data included a serum lactate of 2.4 mmol/L (normal < 2.1 mmol/L). Magnetic resonance imaging (MRI) studies showed infarcts in the brain (Figure). Nerve conduction velocities (NCV) of both lower limbs were normal, but, on electromyography (EMG), myopathic changes were seen in both lower limbs. On echocardiography, the resting ejection fraction was >50%. A muscle biopsy was taken from the rectus femoris muscle and ragged red fibers were noted on examination. Genetic testing revealed a point mutation at nt 3243 of the mitochondrial tRNA gene, confirming the diagnosis of MELAS.

In the third week of her hospitalization, the patient's neurologist consulted us for a rehabilitation program. In general, the main goal of rehabilitation is to improve physical work capacity, endurance, activities of daily living (ADL), and independence. The rehabilitation program prescribed for the patient included aerobic training (treadmill and stationary bicycle) and ADL practice (Table). The patient pedaled a cycle ergometer with a very low constant workload of 30 watts for 15

minutes and walked on a treadmill for 15 minutes at a speed from 1.0-2.0 mph (0% grade). The rehabilitation training program was done 5 days a week for 6 weeks while the patient was hospitalized. After 8 weeks of hospitalization, the patient was discharged in stable condition. At the time of discharge, she showed improvements in muscle power, balance, endurance, and her gait speed. Her left extremity muscle power improved from grade 4 to grade 5; the FIM score was 126 (the highest level of independence); her gait speed was 0.77 m/s during the 10-Meter Walk Test; and the total distance covered during the 6-Minute Walk Test (6MWT) was 190 m.

After discharge, the rehabilitation program prescribed for the patient emphasized instrumental ADL and home aerobic exercise (Table). She began using a stationary bicycle at home for 15 min, 5 times per week. She also walked in her community 15-20 min daily. She could do household tasks, including housecleaning, laundering, washing dishes, and changing bed linens without difficulty. At 16 weeks, the patient's 6MWT increased to 220 meters, and her gait speed was 0.85 m/s during the 10-Meter Walk Test. At the 20-month follow-up visit, the patient's clinical outcome was encouraging, and her physical function had not significantly deconditioned.

## DISCUSSION

Given our experience with this patient, we found that a rehabilitation program did indeed improve our patient's

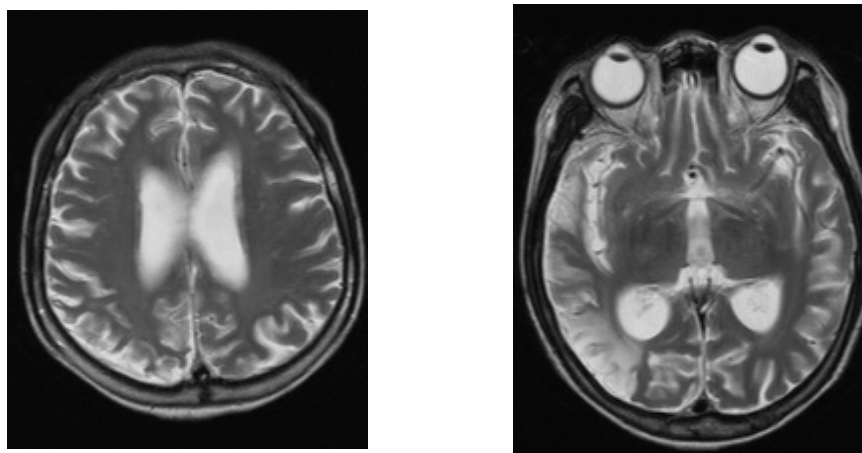


Figure. Magnetic resonance imaging study of the brain shows hyperintense T2 lesions predominantly in the gray and subcortical white matter in the right temporal, parietal, and occipital lobes.

Table. The rehabilitation program protocol designed for our MELAS patient from the initial stage to the maintenance stage

	Mode	Intensity (RPE)	Duration	Frequency
Aerobic exercise (in initial and improvement stages)	1. Stationary bicycle (25 watts) 2. Treadmill (speed 1- 2 mph; 0 % grade)	< 10	10-15 min/day	5 days/week
Home aerobic exercise (in maintenance stage)	Stationary bike	10-11	15 min/day	5 days/week
Self-care (ADL)	Eating, grooming, dressing	<10	15 min/day	5-7 days/week
Instrumental ADL	1. Community activities, such as shopping and socializing 2. Housekeeping skills, such as cooking and cleaning	10-11	15-30 min/day	5-7 days/week

RPE, the rate of perceived exertion; ADL, activity of daily living

muscle strength, gait speed, physical function, and quality of life. The recovery was possible due to the muscle adaptation that occurs with exercise training, which may improve aerobic capacity, muscle oxidative metabolism, the mitochondrial respiratory chain, and decrease secondary physical deconditioning.<sup>[5,6]</sup> The patient's ataxic gait pattern resolved, and she was able to walk with a normal gait due to improved muscle strength and decreased muscle fatigability. The patient progressed greatly in her ADL functional skills. The FIM on admission was 74, but had increased to 126 at the time of discharge. After discharge, the patient was prescribed a low level exercise program as part of her outpatient phase. The goal of our ADL training is to minimize dependence and give the patient the ability to perform daily skill tasks. We evaluated the needs of the treatment phase based on the patient's physical status and provided an effective rehabilitation program. In general, patients needs to have adequate ROM and good coordination and muscle strength in order to perform feeding, dressing, and grooming skills, as well as to hold tools. The ability to perform key ADL also requires gross motor and fine motor coordination. The functional score is associated with an improvement in the patient's progress. During the maintenance stage, the patient's improvement was limited, but sustained home aerobic exercise could maintain her fitness level. Generally, aerobic exercise training effects last only a few weeks if physical activity ceases; therefore, home exer-

cise rehabilitation is an important alternative type of outpatient exercise program. Home aerobic exercise with minimal resistance can prevent fatigue and cardiopulmonary dysfunction. All of these results have been reported to be related to improvement of skeletal muscle oxidative capacity by extraction of available oxygen and enhancement of oxygen utilization by muscle.<sup>[7]</sup>

The treatment of mitochondrial disease has traditionally involved diets or drugs, such as coenzyme Q, cytochrome C, nicotinamide, dichloroacetate, and succinate; however, their effects are controversial. Rehabilitation in the form of aerobic training is another approach to the treatment of mitochondrial disease. In one of the latest review articles about mitochondrial myopathy, Taivassalo et al. stated that myopathic patients typically are exercise intolerant because their capacity for oxygen utilization (systemic a-vO<sub>2</sub> difference) is markedly low.<sup>[6]</sup> It is thought that the capacity for oxygen extraction is directly correlated with the degree of impaired muscle O<sub>2</sub> extraction, and that capillary density and mitochondrial oxidative capacity increase in skeletal muscle if adequate training is given.<sup>[6]</sup> The reported benefits of endurance training in patients with mitochondrial myopathy include notable improvement in work and oxidative capacity. Thus, muscle mitochondrial adaptations can improve the systemic a-vO<sub>2</sub> difference, increase the extraction of oxygen during exercise, and may also allow patients to tolerate submaximal exercise.<sup>[6]</sup>

When a rehabilitation program is prescribed for patients with mitochondrial myopathy, the exercise intensity should be such as to avoid further muscle damage due to overload exertion. The exercise prescription should consider what will benefit the patient most. The decision to increase training depends on the patient's tolerance of current training and the patient's functional capacity. Exercise prescriptions for individuals should consider their physical status when designing suitable modes of exercise, as well as their intensity, duration, frequency, and rate of progression. Training progression should follow three stages: the initial stage, the improvement stage, and the maintenance stage. In the initial and improvement stages, dramatic progress is not easy, but low-intensity training has beneficial effects. In the maintenance stage, the purpose is to maintain the training effects, since the  $\text{VO}_{2\text{max}}$  has been confirmed to decrease significantly within 3 weeks of stopping intense endurance training.<sup>[8]</sup>

We used the rate of perceived exertion (RPE) to monitor training intensity and the degree of exertion. Intensity is the most important part of an exercise prescription. All the training intensities prescribed for our patient were lower than Borg RPE scale 12 (light and very light). Low impact exercise, such as walking and cycling, was designed to decrease injury and increase cardiopulmonary function. The ergometer bicycle exercise was done at a very low workload and maintained at 25 watts for 10-15 min. With the very low intensity, training is safe and does not cause fatigue.<sup>[9]</sup> Deborah et al. found that treadmill training using a sub-maximal protocol is good for patients with mitochondrial disease and increased aerobic capacity.<sup>[10]</sup> In our patient, the intensity of the treadmill during training progression was set around 1-2 mph (0%) for 15 min. We estimated that the functional capacity of our patient was 4-6METs, based on the approximate energy requirements in METs while on the bicycle ergometer.<sup>[11]</sup> This means that our patient could perform many moderate ADL (4-6METs) and could also tolerate the rehabilitation program. Our patient had no complications caused by treadmill and ergometer training. The effect of rehabilitation on this patient's physical performance has been encouraging.

The clinical course of mitochondrial diseases is progressive and unpredictable; therefore, the early diag-

nosis of mitochondrial disease is important. Once a patient is diagnosed with MELAS, treatment should be started to relieve symptoms and, perhaps, to delay the progression of the disease. MELAS patients need to continue aerobic exercise as long as there is improvement in their physical status. Patients with mitochondrial disease typically have variable degrees of exercise intolerance. Exercise should not be avoided, as this may cause physical fitness deconditioning. Although there have been few reported studies dealing with the clinical training response, exercise therapy appears to be an alternative treatment for mitochondrial disease.

A proper exercise prescription seems to benefit MELAS patients, with improvements in physical function and potential psychological effects. Short-term endurance training in mitochondrial disease improves functional aerobic capacity and increases ATP production, while it decreases blood lactate levels and heart rate during resting and exercise. It still remains to be determined whether rehabilitation programs could benefit all MELAS patients. Given our results with this patient, low workload aerobic training may be a potential treatment for MELAS patients. Thus, aerobic exercise training can be recommended as one of the therapies for mitochondrial disease. Nevertheless, designing a safe and efficient exercise protocol remains a major challenge. Future research should focus on long-term efficacy, identification of safe endurance training programs, and the improvement of mitochondrial oxidative capacity. ADL maintenance and long-term follow up of MELAS patients is required.

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## MELAS 症候群病人之復健：病例報告

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粒線體肌肉腦病變乳酸中毒暨類中風樣發作症候群(mitochondrial encephalomyopathy, lacticacidosis, and recurrent stroke-like episodes, MELAS syndrome)是一複雜且多系統的粒線體疾病，在臨床上並不常見。粒線體肌肉腦病變乳酸中毒暨類中風樣發作症候群病患常有肌肉無力的症狀，病患也常被要求避免運動，因而造成病患體力更加衰退。過去有關於粒線體的疾病的復健治療觀念尚未普遍接受。本文報告一位四十五歲女性，經神經科醫師診斷為粒線體肌肉腦病變乳酸中毒暨類中風樣發作症候群，該病患在病情穩定後，開始接受復健治療，本個案經低強度的復健有氧運動訓練後，有正面的效果及極佳的功能恢復。經二十個月之長期追蹤，病患仍維持在一定的肌力而功能也未變差。短期耐力訓練對該病患是有幫助的，長期追蹤及適當的運動是未來努力的重點。（台灣復健醫誌 2006；34(3)：183 - 188）

**關鍵詞：** 有氧運動(aerobic exercise)，粒線體肌肉腦病變乳酸中毒暨類中風樣發作症候(MELAS syndrome)，粒線體肌肉病變(mitochondrial myopathy)，復健(rehabilitation)