

Fatigue and exercise intolerance in mitochondrial diseases. Literature revision and experience of the Italian Network of mitochondrial diseases

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Abstract

Fatigue and exercise intolerance are common symptoms of mitochondrial diseases, but difficult to be clinically assessed. New methods to quantify these rather common complaints are strongly needed in the clinical practice. Coenzyme Q10 administration and aerobic exercise may improve exercise intolerance, but more definite studies are still pending. Herein, we have revised "how to measure" and "how to treat" these symptoms of mitochondrial patients. Subsequently, we reviewed the clinical data of the 1164 confirmed mitochondrial patients present in the Italian nation-wide database of mitochondrial disease, with special regard to exercise intolerance. We observed that more of 20% of mitochondrial patients complain of exercise intolerance. This symptom seems to be frequently associated with specific patient groups and/or genotypes. Ragged red fibers and COX-negative fibers are more often present in subjects with exercise intolerance, whereas lactate levels could not predict this symptom. Multicenter efforts are strongly needed for rare disorders such as mitochondrial diseases, and may represent the basis for more rigorous longitudinal studies.

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1. Introduction

The most crucial task of the mitochondrion is the generation of energy as adenosine triphosphate, by means of the electron transport chain [1]. This pathway is under control

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of both nuclear and mitochondrial (mtDNA) genomes. Mitochondrial diseases are a group of disorders caused by impairment of the respiratory chain. They are one of the commonest inherited neuromuscular diseases, with an estimated prevalence of 1–2 in 10,000. The genetic classification distinguishes the disorders due to defects in mtDNA from those due to defects in nuclear DNA. The effects of mutations which affect the respiratory chain may be multi-systemic, with possible involvement of visual and auditory pathways, heart, central nervous system, and skeletal muscle [1]. The “red flags” of mitochondrial diseases are myopathic signs and symptoms (including fatigue and exercise intolerance), eyelid ptosis, ophthalmoparesis, axonal multifocal neuropathy, sensorineural hearing loss, pigmentary retinopathy, optic neuropathy, diabetes mellitus, hypertrophic cardiomyopathy, migraine, short stature [2].

Experienced fatigue may be defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion. More specifically, muscle fatigue with exercise intolerance is a multifactorial process characterized by failure to maintain an expected level of force during sustained or repeated muscle contraction, and is considered a common symptom of mitochondrial diseases. It is putatively due to an increased skeletal muscle dependence on anaerobic metabolism, with increased lactate and free radical generation, phosphocreatine (PCr) depletion, reduced oxygen extraction. At the whole body level, this is characterized by a reduction in maximal oxygen consumption (VO_2) with excessive carbon dioxide production (VCO_2), increased rating of perceived exertion and hyperdynamic circulatory response at a given exercise intensity [3].

2. How to measure fatigue and exercise intolerance in mitochondrial patients?

Exercise intolerance is difficult to be clinically assessed and quantified. Classically, the characterization of exercise intolerance is performed using cycloergometry with measurements of VO_2 , VCO_2 , respiratory exchange ratio, heart rate, minute ventilation, rating of perceived exertion, and cardiac output [3]. Taivassalo and co-workers [4] evaluated oxidative capacity and circulatory and ventilatory responses to maximal cycle exercise in 40 patients with biochemically and/or molecularly defined mitochondrial myopathies associated with variable degrees of exercise tolerance, comparing those responses with healthy sedentary individuals results. In mitochondrial patients, mean peak work capacity and VO_2 were significantly lower than in controls, but the range was quite broad [4]. Oxidative capacity in patients was limited by the ability of muscle to extract available oxygen from blood, as indicated by a linear correlation between peak VO_2 and peak systemic arteriovenous O_2 difference. In the patients group, the increase in cardiac output relative to VO_2 and ventilation was increased compared to controls. In patients with heteroplasmic mtDNA mutations, an inverse relationship between the proportion of skeletal muscle mutant mtDNA

and peak extraction of available O_2 during exercise was observed [4]. Another study [5] showed that the severity of oxidative impairment (as assessed during cycloergometer exercise) closely correlated with venous O_2 levels during forearm exercise, which resulted paradoxically increased in these patients. This may reflect a blunted ability of working muscle to extract O_2 , resulting in high O_2 delivery relative to use, high tissue O_2 content, and elevated O_2 levels in venous effluent [5].

From a biochemical perspective, in patients with suspected mitochondrial disease, lactate increase after effort is commonly measured and has diagnostic use [2]. However, the role of lactate in the development of exercise intolerance in these patients is unclear. In a double-blinded, placebo-controlled, crossover study in seven patients with mitochondrial myopathy, lowering of lactate with dichloroacetate could not improve exercise tolerance and oxidative capacity, suggesting that lactate is not the primary cause of exercise intolerance [6]. A biochemical study could not demonstrate any difference between healthy controls and mitochondrial patients; consecutive 60-min microdialysis samples were taken from the tibialis anterior muscle in eleven healthy subjects and four patients with mitochondrial myopathy, before and after sustained isometric foot dorsi-flexions [5]. Before exercise, mean concentrations of lactate, pyruvate, hypoxanthine, urate, aspartate, and glutamate did not differ between controls and patients. After exercise, both groups showed increased concentrations of lactate, pyruvate, and urate, decreased hypoxanthine, and no change in aspartate and glutamate [5]. Exercise-induced increase in integrated electromyogram amplitude and rated subjective fatigue were correlated to increased post-exercise lactate concentrations, with no differences between the two groups. This experimental apparatus could allow the detection and monitoring of biochemical changes in the interstitial space, but larger studies should be performed [5]. Oxidative stress may also have a role [7], but further studies are needed.

Another approach to measure fatigue is the use of magnetic resonance spectroscopy (MRS), a frequency analysis of the MR signal that allows an evaluation of brain and muscle metabolism in vivo [2]. Phosphorous (31P) MRS measures PCr and inorganic phosphate (Pi) fluctuations during muscle exercise, thus monitoring oxidative metabolism. The most useful indicators of mitochondrial disease are combined low PCr/Pi ratio at rest and low post-exercise recovery, and delay in post exercise adenosine diphosphate (ADP) recovery. Nevertheless, 31P MRS of skeletal muscle does not seem to be a sensitive diagnostic test for mitochondrial myopathy [2]. In a study of seven patients with single large-scale deletion, nine with mtDNA point mutations and 14 healthy subjects, PCr/Pi and ATP production after exercise was similar in patients and healthy subjects [8]. For these reasons, muscular 31P MRS is still experimental in clinical practice, but could potentially be a useful tool for monitoring the response to therapies.

3. How to treat fatigue and exercise intolerance in mitochondrial diseases?

The treatment of mitochondrial diseases is still inadequate, despite great progress in the molecular understanding of these disorders. Therapies that have been attempted include respiratory chain cofactors and other metabolites and antioxidants, but their role in the treatment of the majority of these patients remains unclear. However, a randomized trial reported that 60 days of coenzyme Q10 (1200 mg/day) treatment had minor but significant positive effects on cycle exercise aerobic capacity (with significant increase in VO_2) and post-exercise lactate, even though it did not affect other clinically relevant variables such as strength or resting lactate [9].

Several studies have found that supervised aerobic activity can improve exercise capacity, reduce lactate and improve ADP recovery kinetics using MRS [3]. The effect of 12 weeks cycle training on exercise capacity, quality of life and underlying molecular and cellular events have been studied in 20 mitochondrial patients and 13 healthy subjects [10]. After the training, maximum VO_2 and muscle citrate synthase increased in patients and healthy controls, while mtDNA quantity in muscle only increased in the patient group. Therefore, aerobic training could efficiently improve oxidative capacity in patients with mitochondrial myopathy, and regular aerobic exercise may be recommended in these subjects [10].

4. The experience of the Italian Mitochondrial Registry Network

Based on the database of the “Nation-wide Italian Collaborative Network of Mitochondrial Diseases”, we preliminarily reviewed the clinical data of the 1164 histologically, biochemically and/or molecularly defined patients present in our database (June 18th, 2012) and followed in the different Centers, with special regard to exercise intolerance.

The database establishment (and its use for scientific purposes) was permitted by the local Ethical Committees of the single Centers, which obtained the patients’ written consent, and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. It has been supported by a Telethon Grant (GUP09004).

Data were expressed as means \pm standard deviation. Comparisons of proportions have been performed by Chi-square test. A P value <0.05 was considered as significant. Data analysis was carried out using MedCalc® Version 7.3.0.1.

The clinical picture was fully available for 1100 patients (mean age at onset 24.4 ± 20.5 years; age at last evaluation 39.8 ± 22.3 years; females 51.0%; childhood onset [before age 16-yrs] 43.8%). Exercise intolerance was part of the clinical picture in 222/1100 patients (20.2%), being the fourth clinical manifestation in term of frequency in

these patients after ptosis/ophthalmoparesis, muscle weakness and hearing loss. In 108 of them, exercise intolerance was one of the presenting symptoms at the onset of the disease.

In order to understand if the presence (or absence) of exercise intolerance was linked with specific molecular or pathological features, the patients of the Registry have been divided in two groups, with and without exercise intolerance. Age at onset, age at last evaluation and gender ratio did not significantly differ between the two groups.

From a genotype-based approach (Table 1), the common mtDNA *A3243G* mutation associated with MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) and other clinical phenotypes, was less present in the group without than one with exercise intolerance ($P < 0.0005$). Exercise intolerance was reported in 33/95 (34.7%) of the *A3243G* patients of our database.

The other common mtDNA change, the *A8344G* “MERRF” (myoclonic epilepsy with ragged red fibers) mutation, showed the same frequency in the two groups. From the opposite perspective, 9/36 (25.0%) *A8344G* patients complained of exercise intolerance.

The mtDNA *T8993C* mutation, associated with NARP (neuropathy, ataxia, retinitis pigmentosa) and with maternally-inherited Leigh syndrome, was more common in the group without than with exercise intolerance, but the difference did not reach statistical significance. Only 1/20 of the *T8993A* patients complained of exercise intolerance. As expected, patients with genetically-confirmed Leber hereditary optic neuropathy (LHON) were far more common in the group without than with intolerance ($P < 0.0001$). The same was observed for *OPA1* gene mutations, the most common cause of autosomal dominant optic atrophy (ADOA). *POLG* gene mutations had the same frequency in the two groups; 8/41 (19.8%) *POLG* patients complained of exercise intolerance.

From a phenotype-based approach, patients with PEO phenotype were more common in the group with exercise intolerance (87/222 [39.2%] versus 247/878 [28.1%], $P < 0.002$); 87/334 (26.0%) of patients with PEO reported exercise intolerance. Leigh syndrome was more common in the group without exercise intolerance (72/878 [8.2%] versus 5/222 [2.3%], $P < 0.005$). Probably, in these young

Table 1

Genotype-based approach. The patients have been divided in two groups, with and without exercise intolerance. For more details, see text. n.s., not significant difference. LHON: Leber hereditary optic neuropathy.

	Exercise intolerance: No ($n = 878$)	Exercise intolerance: Yes (222)	P
mtDNA <i>A3243G</i> mutation	62 (7.1%)	33 (14.9%)	<0.0005
mtDNA <i>A8344G</i> mutation	27 (3.1%)	9 (4.1%)	n.s.
mtDNA <i>T8993C</i>	19 (2.2%)	1 (0.5%)	n.s.
mtDNA LHON mutations	98 (11.2%)	1 (0.5%)	<0.0001
<i>OPA1</i> mutations	85 (9.7%)	1 (0.5%)	<0.0001
<i>POLG</i> mutations	33 (3.8%)	8 (3.6%)	n.s.

patients, the subtle symptom “exercise intolerance” is hidden by the devastating neurodegenerative phenotype.

From a clinical perspective, as expected, muscle weakness was less frequent in the patients without (255/878, 29.0%) than with (155/222, 69.8%) exercise intolerance ($P < 0.0001$). The same finding was also observed when considering all the other myopathic signs included in our database: muscle pain (6.5% versus 27.0%, $P < 0.0001$), muscle wasting (14.6% versus 30.2%, $P < 0.0001$), eyelid ptosis/ophthalmoparesis (38.8% versus 58.6%, $P < 0.0001$), cardiomyopathy (4.9% versus 17.1%, $P < 0.0001$), increased plasma creatine kinase (CK) levels (12.6% versus 34.2%, $P < 0.0001$).

In those patients in whom muscle biopsy has been performed, ragged red fibers were less common in the group without (311/484, 64.3%) than with (127/169, 75.1%) exercise intolerance ($P < 0.05$). The same was observed for COX (cytochrome c oxidase)-negative fibers, with a stronger statistical significance (295/484 [61.0%] versus 124/169 [73.4%]) ($P \approx 0.005$). Finally, considering the patients for whom plasma lactate levels were available, this biomarker was increased in 269/502 (53.6%) patients without exercise intolerance and in 89/175 (50.9%) patients with exercise intolerance (P not significant).

5. Conclusions

Exercise intolerance and fatigue are difficult to assess clinically and remain an elusive symptom, even in the neuromuscular setting. New methods to quantify these rather common complaints are strongly needed in the clinical practice. Here we showed that more of 20% of mitochondrial patients complain of exercise intolerance. This symptom seems more strongly associated with specific mutations (i.e., A3243G). CK levels were increased in $\approx 34\%$ of the patients with exercise intolerance, not confirming the notion that CK levels are normal in the great majority of mitochondrial patients [2]. Moreover, all the other myopathic signs included in our database (muscle pain, muscle wasting, eyelid ptosis/ophthalmoparesis, cardiomyopathy) were associated with exercise intolerance. Ragged red fibers and, especially, COX-negative fibers were more frequent in the subjects with exercise intolerance, whereas lactate levels failed to predict the presence of exercise intolerance. Lactate is the most common marker of mitochondrial dysfunction in the clinical practice [2], but additional, possibly more reliable, markers are still strongly needed.

Admittedly, this survey presents the typical limitations of all retrospective studies, and probably underestimates the real prevalence of exercise intolerance in patients with mitochondrial diseases, being a symptom that sometimes could be missed when not actively searched. However, similar multicenter efforts are strongly needed for rare disorders such as mitochondrial diseases, and can prompt to more rigorous longitudinal studies. Multicenter studies

are also needed to better characterize the clinical picture and natural history of these diseases, and identify pharmacological, physical, or other countermeasures capable to benefit the patients suffering with these chronic, still incurable disorders.

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6. Conflict of interest

None

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