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Exercise intolerance in Mc Ardle Disease: functional and metabolic evaluation

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The aim was to define a multifunctional evaluation protocol in patients with Mc Ardle's disease in order to detect and quantify the impairment of both muscular energetic metabolism and motor performance. The protocol has been used to investigate the effect of a carbohydrate-rich diet integrated with tricarboxylic acid cycle intermediate and creatine on exercise intolerance and motor skills in these patients.

We studied 4 patients with complete myophosphorylase deficiency, 1 paucisymptomatic patient with partial myophosphorylase deficiency and 5 sex- and age-matched healty subjects, who have been evaluated by: 1) monitoring of physical activity with an electronic armband; 2) testing of cardiopulmonary, metabolic and respiratory responses to exercise with a cardiopulmonary exercise test (CPET) in wich subjects were asked to pedal on a bicycle ergometer, using a costant workload for 12 minutes followed by an incremental workload to exhaustion; 3) examination of oxidative stress biomarkers (AOPP and thiols) at rest and during exercise.

The same measurements were then repeated by the patients after three days of carbohydrate-rich diet (20% fat, 15% protein and 64% carbohydrate) integrated with tricarboxylic acid cycle intermediate and creatine.

The monitoring with armband showed that low levels of physical activity are prominent in patients with Mc Ardle's disease. During the costant workload exercise on the bicycle ergometer 3 patients experienced the characteristic "second wind", whereas in the patient with partial myophosphorylase deficiency (patient carrier) heart rate increased progressively, as in all the healty subjects. Heart rate was consistently lower in healty subjects then in patients, indicating that they were performing at a higher percentage of their exercise reserve. Maximal oxygen uptake was significantly lower in patients ($p < 0.05$), showing how Mc Ardle's disease has a significant effect on the maximal oxidative capacity. The sampling of oxidative stress biomarkers (AOPP and thiols) blood levels showed lower levels of AOPP and higher levels of thiols in patients than in healty subjects.

We did not observe significant differences between baseline and the results obtained after three days of carbohydrate-rich diet integrated with tricarboxylic acid cycle intermediate and creatine.

The protocol has confirmed the impairment of both anaerobic and oxidative metabolism in skeletal muscle. The sensitivity of the test allowed to appreciate the "second wind" phenomenon and to detect the case of the carrier patient, who had intermediate phenotypic characteristics between patients and healty subjects; by the way the test could be useful to obtain an objective, quantitative and longitudinal evaluation of the impairment to be used in the follow-up of patients with Mc Ardle's disease as well as in the assessment of therapeutic interventions.

P-4
Evaluating therapy outcome in Mysthenia Gravis

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Myasthenia gravis (MG) is an autoimmune disorder, in 90% of cases antibodies against the nicotinic acetylcholine receptor (AchRAb) are pathogenetic. Antibodies reduce acetylcholine receptors (AChR) number and impair their function at the neuromuscular endplate. The main feature is a variable weakness of the skeletal muscles, that may involve different districts. Symptoms are typically worse in the evening or after prolonged exercise and can be reduced with rest. The diagnosis is based on a detailed clinical history and neuromuscular examination, on pharmacological tests, measurement of AchRAb, and on appropriate neurophysiologic tests. Therapy involves the use of symptomatic drugs that can improve neuromuscular transmission, immunosuppressive and immunomodulant therapy, and thymectomy.

The task of our study was to compare the efficacy of different immunosuppressive regimens in patients with MG.

We carried out a study in 98 patients at the Clinical Centre for Neuromuscular diseases of Padova University: 36 were treated by combined immunotherapy with corticosteroids and Azathioprine (CS and AZA), 13 of them treated with a combination of corticosteroids and Cyclosporine (CS and CsA), and a third group of 49 patients in treatment with only corticosteroids (CS). We also report a follow-up study of 5 patients treated with Mycophenolate mofetil (MMT). All patients were evaluated using the MGFA (Myasthenia Gravis Foundation of America) clinical classification. Appropriate statistics have been performed, with multivariate analysis and Student T tests.

To evaluate the outcome of the 98 patients of the study, we considered the difference between patients with a MGFA score equal to zero (patients asymptomatic or in pharmacological remission) and patients with MGFA score different from zero (symptomatic, with various grades of severity). After one year of treatment the percentage of pharmacological remissions or asymptomatic status in the group of patients treated with AZA and CS resulted greater than in the group of patients treated with only corticosteroids or both with CsA and CS. Side effects resulted significantly ($p < 0.0001$) common in the groups of patients treated with the therapeutical combination of immunosuppressors, than in the group treated just with steroids. Three out of 5 patients treated with MMT achieved an improvement within the first year of treatment.

Combined therapy with immunosuppressive agents and corticosteroids, significantly increases the number and frequency of side effects ($p < 0.0001$). Our findings also reveal that Cushing's syndrome and osteoporosis were significantly common among patients treated only with steroids ($p < 0.003$ and $p < 0.03$). Additional studies are required to confirm the role of Mycophenolate Mofetil in the treatment of Myasthenia Gravis.