tempo alla progressiva sostituzione del tessuto musco-lare con tessuto fibroso o adiposo. In altre miopatie, ad esempio nelle miopatie neurogene o nella miopatia da corticosteroidi, si ha riduzione della massa musco-lare per prevalenza dei processi di degradazione proteica sui processi di sintesi proteica, e conseguente atrofia delle fibre muscolari senza che si abbia neces-sariamente, almeno nelle fasi iniziali, distruzione delle fibre stesse. Una condizione simile si verifica in numerose condizioni di atrofia muscolare, dalla cachessia secondaria a neoplasie o AIDS all'atrofia muscolare causata da malattie metaboliche o da inattività fino alla sarcopenia dell'anziano. Negli ultimi anni sono stati compiuti importanti progressi nell'identificazione dei meccanismi di degradazione proteica nel muscolo scheletrico, in particolare del ruolo relativo del sistema ubiquitina-proteasoma e del sistema autofagia-lisosoma e delle vie di segnale che li controllano. Il fattore di trascrizione FoxO3 ha un ruolo centrale nella regolazione della degradazione delle proteine muscolari e quindi nell'atrofia muscolare. Queste scoperte aprono nuove prospettive per l'identificazione di target terapeutici per combattere l'atrofia muscolare.

AIM Workshop

Muscle Fatigue and Exercise Intolerance. Physiopathology and Therapeutic Strategies

Human Muscle Fatigue and its Measurement

Argov Z
Department of Neurology, Hadassah-Hebrew university medical center, Jerusalem, Israel

Human muscle fatigue has many definitions and even more theoretical explanations. There are ba-sically two types of fatigue: 1. Experienced fati-gue - difficulty in sustaining voluntary activity. This is considered a 'subjective' sense of lack of energy and is usually measured by various que-stionnaires. 2. Physiological fatigue-exercise induced reduction in muscle maximal power out put. Physiological fatigue is subdivided to central and peripheral components. To complicate things even further the central and peripheral compo-nents interact, both in health and disease. As myologists we are interested in the evaluation of the muscle cases of fatigue, but although we can measure some metabolic and functional aspects of human muscle activity we do not know if they are the causes or just epi phenomenon of fatigue. Methods for evaluation of muscle fatigue include: 1. Combined measurement of maximal voluntary and electrically induced power output by dynamometer over time; 2. Graded exercise protocols (bicycle or tread-mill) with measure-ments of performance, cardiovascular response and metabolic factors (e.g. lactate); 3. Evaluation of muscle tissue metabolic response to exercise with direct biochemical measurements (by biopsy) or indirectly with noninvasive techniques (e.g. 31p-MRS). Each of these methods has its advantages and shortcomings in the evaluation of fatigue and their diagnostic sensitivity for metabolic diseases (mainly mitochondrial disorders) is limited. However as functional evaluation methods for following the myopathy and its treatment they provide an important tool.

Exercise intolerance and fatigue in muscular dystrophies

Siciliano G
Department of Neuroscience, University of Pisa, Italy

Muscular dystrophies represent a group of diseases characterized by progressive, genetically induced, skeletal muscle degeneration with loss of myofiber and substitution with connective and adipose tissues. Owing to the progression of the disease, muscle function results impaired in the different motor tasks during daily-life activities. Different pathogenetic mechanisms underlie myofiber degeneration final common pathway, depending upon the different molecular mechanisms which connote each single form of muscular dystrophy, this in turn being related to the mutated gene responsible for the disease. Changes in physical properties of contractile machinery appear the main mechanism involved in reduction of force generation and exercise intolerance, but factors related to altered mechanical transmission of force vectors along the subsarcolemmal dystrophin-associated struc-tural protein system can contribute to membrane disruption and myofiber damage. Additional mechanisms of cell damage and contractile insufficiency are postulated in some peculiar forms of limb girdle muscular dystrophy, such as calpainopathies and dysferlinopathies, owing to the peculiar roles of those proteins altered in these diseases. Finally, mechanisms related to abnormal sarcolemmal excitability and membrane repolarization are implicated in exercise intolerance and fatigue in myotonic dystrophies.

Exercise intolerance and fatigue in metabolic myopathies

Toscano A
UOC Neuropatologia, AOU Policlinico "G. Martino", University of Messina, Italy

"Exercise intolerance" describes a clinical condition characterized by different degrees of difficulty to perform an expected physical exercise according to age and physical condition, that can be associated to severe post-exercise pain, fatigue or other negative symptoms. It is very difficult to quantify exercise intolerance, especially if accompanied by a cohort of symptoms or signs as myalgias, painful contractures, muscle

weakness, myoglobinuria, hyperCKemia and relief after rest. Differential diagnosis should take into account muscular and non-muscular causes. Exercise intolerance together with fatigue, lethargy and weakness are the main complaints of patients with anaemia such as hypochromic microcytic, macrocytic or normochromic normocytic anaemia. A number of CNS diseases have also to be included in the list of differential diagnoses as multiple sclerosis, Parkinson disease, spastic paraparesis or other disorders with gait disturbances. Patients with fibromyalgia or chronic fatigue syndrome may also complain of exercise intolerance as well patients with muscle diseases as channellopathies, myasthenia, muscular dystrophies, congenital, inflammatory, toxic, iatrogenic, endocrine and metabolic myopathies. Metabolic myopathies may present with three clinical forms: 1) "dynamic" form or "acute and recurrent" characterized by episodes of myalgias, painful contractures and myoglobinuria, 2) "chronic" form with progressive muscle weakness, 3) "mixed form" where an acute form may progress to a "fixed" form. A classic example of "dynamic" myopathy is phosphoglycerate mutase (PGAM) deficiency (glycogenosis type X). Serum CK is very high after muscle efforts but may be normal in intercritical periods. Muscle biopsy can be normal but in 25% of patients tubular aggregates are present in muscle. Biochemical assay identifies PGAM deficit. Acid maltase deficiency (glycogenosis type II or Pompe disease) may represent a "chronic" form of a metabolic myopathy with infantile and late onset (juvenile or adult) forms. The infantile form (onset before 12 months of age) is more severe and is characterized by a severe cardiomyopathy, usually fatal in the first year of life. The late onset form is less progressive. Muscle weakness and respiratory involvement are common in both juvenile and adult forms. In conclusion, starting from "exercise intolerance", by means of appropriate clinical and laboratory approaches, it will be possible, in the majority of cases, to make a specific diagnosis. Nowadays, this is much more important considering the recent advances in treatment of metabolic myopathies.

Exercise intolerance and fatigue in mitochondrial myopathies

Vissing J
Neuromuscular Research Unit, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark

A key symptom in patients with mitochondrial disease is exercise intolerance and fatigue, which usually are not accompanied by muscle cramps, stiffness and myoglobinuria, that are common in other metabolic myopathies of carbohydrate and lipid metabolism. Important determinants of the degree of exercise intolerance are the type of mutation and the mutation load in muscle, which the patients carry. Exercise intolerance tends to be more progressive in nuclear encoded mitochondrial disorders compared to those caused by mtDNA defects. The primary cause of fatigue is the insufficient provision of ATP to contracting muscle, but a number of secondary factors may also influence exercise capacity, such as build up during exercise of hazardous metabolic products, and the occurrence, in some patients with mitochondrial disease, of progressive muscle wasting, which can resemble a muscular dystrophy. Lactate has repeatedly been implicated as a mediator of fatigue in these conditions, but evidence suggests that this marker of impaired oxidative capacity is an important substrate for muscle energy metabolism in mitochondrial myopathies. No effective treatment exists to improve the exercise intolerance found in these patients, but regular supervised aerobic exercise may open the metabolic bottleneck and raise exercise capacity by 30%.

Joint AIM & UILDM Meetings Workshop

Respiratory Dysfunction in Muscle Diseases

Enzyme replacement therapy in juvenile and adult forms of Glycogenosis type 2

Bembi B°, Ciana G*, Dominissini S*, Maya D°, Metka K§, Della Porta R§, Nevjyel M*, Addobbati R*, Confalonieri M§, Dardis A*
*°Coordinamento Regionale Malattie Rare – Azienda Ospedaliero Universitaria "S. Maria della Misericordia", Udine; *Unità di Malattie Metaboliche, I.R.C.C.S. Burlo Garofolo, §Unità di Pneumologia Ospedale di Gattinara, Trieste, Italy*

Glycogenosis type 2 (G2) is an autosomal recessive inherited disorder due to the deficiency of acid α-glucosidase (GAA) that results in impaired glycogen degradation and its accumulation in the lysosomes. The GAA gene has been localized to human chromosome 17q23. More than 120 mutations in the GAA gene have been described up to date. Clinically, G2 encompasses a continuous spectrum of phenotypes, from a rapidly progressive infantile form to a slowly progressive late-onset form (juvenile JG2 and adult AG2). Classic infantile G2 manifests soon after birth and is characterized by severe muscle weakness, cardiomegaly/cardio-myopathy and respiratory insufficiency, while the late onset G2 manifests as slowly progressive skeletal muscle weakness without cardiac involvement. Enzyme replacement therapy (ERT) with the human recombinant form of α-glucosidase has recently been available (Myozyme, Genzyme Co.). The aim of this study was to evaluate the efficacy and safety of the ERT in a group of 13 patients (7 juveniles and 6 adults) affected with G2. Three patients were tracheo-tomised (3 AG2, 1 JG2)