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

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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

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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)

and 4 received mask ventilatory support (3 AG2 and 1 JG2). ERT has been performed at the dosage of 20 mg/kg biweekly. The following laboratory and clinical parameters were evaluated every 3 months during the first year of treatment: a) general biochemistry and muscle enzymes, immunological parameters, anti-α-glucosidase antibodies; b) evaluation of muscle and pulmonary functions c) muscle imaging. Muscle biopsy was performed in 4 juvenile and 2 adult patients at the beginning of ERT. All patients had been studied for GAA residual activity and gene mutations. We observed an improvement of the respiratory function, with interruption of mechanical support through tracheotomy and non invasive nocturnal ven-tilation in 3 patients (2 JG2 and 1 AG2); a si-gnificant improvement in mobility in 10/13 pa-tients (6/7 JG2 and 4/6 AG2), and an impro-vement in the muscle functionality (6' walking test) in all of them. pCO2 improved in 7 out of 8 patients with abnormal parameter at T0 (3/3 JG2, 4/5 AG2), while a reduction of plasmatic muscle enzymes was observed in 6/7 JG2 and 4/6 AG2. The preliminary data show the efficacy of ERT in stabilizing/improving the respiratory and muscu-lar functions. No secondary adverse events had been observed during the follow-up period.

Surgical treatment of spinal deformities in Duchenne muscular dystrophy : a long term follow-up study

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Surgical treatment of spinal deformities in DMD is influenced by a number of factors, which have proven to be difficult challenges. Each case should be carefully evaluated, considering the natural history of the spinal deformity and patient general conditions. These should be assessed clinically and radiographically with other spe-cialists. Life expectancy should be determined according to the cardio-respiratory function, and both preoperative and postoperative quality of life should be taken into consideration, trying to imagine the functional status of each patient after surgery. From February 1985 to February 2000, 58 patients with spinal deformity in DMD were surgically treated with Luque method above all. Of 25 patients that were operated on between 1985 and 1995, only 20 were followed-up after 5 years because 5 of them had died during this time. In all cases we have fixed the pelvis. From March 2000 to December 2004, 30 patients with the same diseases were operated on using the post Cotrel-Dubousset (C-D) instrumentations. In this cases, treated more recently, we have considered the opportunity to not extend the arthrodesis until the sacrum. Of this patients, more recently treated, 12 were reviewed and are not included in the present study because the follow-up is not adequate, but we report our feeling. The 20 old cases reviewed presented with a mean angular value of scoliosis equal to 48° (range 10-92°). Spinal fusion with our modified Luque technique was performed in 19 cases, whereas CD instrumentation was applied in only one case. At the 5 year follow-up (range 5,6-10 years), the age ranged from 18 to 24 years and averaged 20,4 years. The preoperative angular value of scoliosis averaged 22° (58%, range 0-43°), the mean correction at follow-up was 28°(range 0-60°), and the mean loss of correction was equal to 6° (range, 0-11°). Vital capacity showed a slow progression, slightly inferior to its natural evolution in untreated patients. The severest complication was the death that occurred in one of the patients. According to the present study, an early surgery (angular value lower than 35-40°) dramatically reduces the rate of risk factors associated with spinal deformities in DMD, and its advantages far exceed the disadvantages, above all in terms of quality of life. The problem concerning the necessity of the pelvic fixation is still a controversial problem. In our early experience, if the pelvic obliquity, in X-ray supine is around 15 degrees, we can stop the instrumented arthrodesis in L5, especially if the deformity is early surgically treated.

Treatment of respiratory complications in childhood

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The development of significant respiratory muscle weakness is an integral feature in certain childhood onset neuromuscular disorders (NMD) e.g. spinal muscular atrophy (SMA), Duchenne muscular dystrophy and congenital muscular dystrophy. This can lead to the development of nocturnal hypoventilation followed by daytime ventilatory failure and/or respiratory tract infec-tions. Both factors are a major cause of morbidity and mortality in the NMD population. Monitoring respiratory function will help us identify when potential problems may arise and when to introduce certain techniques. Published guidelines recommend that individuals should have local respiratory function monitoring by baseline spirometry (FEV1 and FVC). In addition they should be questioned about symptoms that are indicative of nocturnal hypoventilation. Conti-nuous overnight pulse oximetry (and end-tidal or transcutaneous CO2 if available) during sleep should be performed annually when FVC is < 60% predicted, and is essential when FVC < 40% predicted; as these levels indicate diaphragmatic involvement, and therefore a high risk of nocturnal hypoventilation. Cough strength should also be measured annually in the form of PCF, and during any episode of chest infection to determine whether cough augmentation techni-ques are required. As a result of decreased oxygen and an increase in CO2 levels, sleep is a vulnerable time for children with NMD and early manifestations of ventilatory insufficiency will be seen during sleep, before the

daytime hypercapnia becomes apparent. There is consensus that non-invasive ventilatory (NIV) support is recom-mended in NMD patients with established ven-tilatory failure or severe sleep disordered brea-thing resulting in hypercapnia during sleep. It is important to take into account both the effect of the respiratory tract infection and the effect of the virus on respiratory muscle strength. Whilst NIV is the treatment of choice for hypercapnia in NMD, some children will fatigue or become hypercapnic with a respiratory tract infection. Our group has looked at a novel approach of providing early NIV in children with SMA as a tool for airway clearance, and the flexibility to be used as a method of supporting ventilation in more severe respiratory episodes, without increasing the strain of caring for a child with a severe physical disability. There is also some evidence to show that NIV can be used in SMA children to help reduce or prevent chest wall deformity. Effective cough is a protective mechanism against respi-ratory tract infections, which are the commonest cause of hospital admission in patients with respi-ratory muscle weakness due to NMD (Bach et al., 1997). Airway clearance is a major component in the care of children with NMD. Basic techniques should be carried out; breath stacking, intermittent positive pressure breathing and assisted coughs prior to the con-sideration of mechanical insufflation/exsufflation.

Acute respiratory faillure and tracheostomy in amyotrophic lateral sclerosis

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Although Acute Respiratory Failure (ARF) is uncommon, patients with Amyotropic Lateral Sclerosis (ALS) may present with it. Frequently, such patients are in extremis and are rapidly intubated with a tracheal tube and receive positive pressure ventilation (PPV). A large proportion of patients with respiratory failure due to ALS who undergo tracheal intubation and intermittent PPV (IPPV) as an emergency procedure may fail to wean adequately due to severe respiratory muscle weakness; as a consequence, they are administered tracheostomy to alleviate disconfort and the high risk of complications due to prolonged endotracheal intubation. Almost all of these patients need long-term ventilatory support and the degree of ventilator-dependence increases with time. Although there is limited knowledge about the course of ALS in patients who live beyond ARF, the overall survival seems to be poor after tracheostomy. In our personal experience 43 patients were studied: no one was liberated from mechanical ventilation; median survival was 11.2 and 17.5 months for patients with and without bulbar involvement, respectively. The ALS Functional Rating Scale, a validated instrument that assesses the functional status and disease progression in ALS, may predict long-term survival after tracheostomy. Despite the low prevalence of TIPPV, many patients administered this intervention are glad about this ventilatory approach: in our experience the majority of cases feels that life in general could still be satisfying although the life satisfaction is lower compared with that of general population.

AIM Muscle Club

Caso clinico: cardiopatia in una portatrice di distrofia muscolare di Duchenne

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La distrofia muscolare di Duchenne (DMD) è una malattia genetica X-linked che colpisce i muscoli scheletrici e il miocardio non solo dei maschi affetti ma anche di molte donne portatrici. Una 27enne portatrice di DMD si presentava con astenia, dispnea da sforzo ed episodi di cardiopalmo. L'ecocardiogramma mostrava una cardiomiopatia dilatativa (frazione di eiezione, EF 33%), peggiorata rispetto ai due anni precedenti (EF 40%). La paziente è stata indagata cardiologicamente con indagini di laboratorio, strumentali ed elettro-fisiologiche. Un trattamento combinato ha migliorato i sintomi, le aritmie e la funzione cardiaca (EF 40%) nei successivi due anni, senza segni di progressione clini-costrumentale della cardiomiopatia. L'elevata prevalen-za e la naturale progressione della cardiopatia nelle portatrici di DMD ne impongono un precoce inquadra-mento clinico-strumentale. Viene proposto un algorit-mo diagnostico e terapeutico cui fare riferimento.

Un caso inusuale di polimiosite.

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Un ragazzo ha presentato a 14 anni, durante attività sportiva (calcio), improvvisa e marcata ipostenia agli arti inferiori, mialgie e tumefazione delle cosce. Nel paziente, ricoverato in reumatologia pediatrica, fu ri-scontrato rialzo di CPK (22.000 U/l). La biopsia mu-scolare evidenziò presenza di fibre degeneranti e rigeneranti, sovraespressione fibrale di antigeni MHC-I e positività immuno-istochimica per linfociti (CD4+ >CD8+) circondanti le fibre. Distrofina ed α-sarco-glicano risultarono normali. Senza beneficio la terapia per alcuni mesi con steroide, immunoglobuline, ciclo-sporina e azatioprina. Il quadro fu interpretato come