Lectures by invited speakers

I-1
History of Myology in Italy and its international collections
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The history of Myology in Italy begins in 16th century with muscle anatomy pictures by Vesalius and Canani while in the 19th century the Neapolitan physician Gaetano Conte described Duchenne muscular dystrophy on clinical basis (1).

Myology reached a major development in the 20th century with the establishment of the CNR center in Padova (professor Massimiliano Aloisi) a cardiological and genetic center in Naples (professor Giovanni Nigro) and a neurological center in Milan (professor Guglielmo Scarlato). In the 60th prof. Aloisi and Federico Milcovich, a myodystrophic patient, started the Italian Muscular Dystrophy patients association (UILDM) with contacts with MDA (2). The first congress in Neuromuscular diseases took place in Milan in 1969 by the organization of professor Scarlato, Aloisi, Canal and was attended by several outstanding international muscle researchers such as AG Engel, WK Engel, LP Rowland, M. Fardeau and I. Hausmanowa-Petrusewicz. Eleven meetings in many countries followed this, up to the last XII international Congress on Neuromuscular Diseases in Naples in 2010.

Several laboratories arose in the country especially in Neurological Institutes; several researchers emigrated permanently or went for a stage to improve their myological skills especially in USA, UK, Canada, France both in basic and/or pathological, clinical research (Table 1). The laboratory of Columbia in New York, lead by professor Di Mauro was a common place of training especially in the field of mitochondrial myopathies.

As in other developed countries, the basis of neuromuscular research and diagnosis were expanded on immunohistochemical, biochemical and molecular grounds, during the 20th and the beginning of the 21st century. Enzo Ferrari – a race car factory engineer – was a support to research in muscular dystrophy in Milan, Padova and Modena. Telethon has contributed to support in neuromuscular disorders. Myology with the enlargement of scientific basis in the molecular era began to split in sub-specialities i.e. genetics, physiopathology etc. and a spectrum of knowledge was accumulated both for diagnostic and therapeutic purposes. In the field of metabolic diseases and limb-girdle myopathies several Italian laboratories described new entities. A number of treatments, beside the treatment of inflammatory myopathies and myasthenia gravis, were found and applied in metabolic myopathies: i.e. carnitine, Coenzyme Q, enzyme replacement in glycoproteinosis type II.

The continuous challenge of the treatment of the primary muscular dystrophy remains for the future since so far there are only emerging molecular therapies: antisense oligonucleotides in DMD, adeno viral therapy in sarcoglycanopathies, cell therapy might contribute to answer to a promises for muscular patients.

In the translation area many laboratories and Italian groups continue with new researchers and they have contributed to meetings of European Neuromuscular Center and to the Foundation and organisation of the World Muscle Society with meetings in Italy (Naples, Taormina), and to the Treat – NMD and Eurobiobank networks.

References
1. Angelini C. Handbook of clinical neurology - History of Neurology. In: Finger S, Boller F, Tyler KL, eds. Muscular Dystrophy. Vol. 95. Amsterdam: Elsevier 2010, pp. 477-88.
2. Angelini C, Aloisi M. Obituary. Neuromusc Disord 2000:10:1-2.

I-2
Can we bypass a muscle metabolic defect?
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The metabolic myopathies are thought to be more amenable to treatment once the defect in the biochemical pass way is identified. Some of the defects cause mainly exercise intolerance and its improvement can be regarded as therapeutic success. In others muscle weakness and degeneration is seen and functional and strength improvement is the goal.

Therapy of such muscle metabolic disorders can be achieved through enzyme replacement, e.g. therapy of acid maltase deficiency (Pompe’s disease) which is currently administered to young and adult patients. Enzyme upregulation can also be attempted and a case in point is bezafibrate in carnitine palmityl transferase 2 deficiency.

Table 1. The main international connections.

| USA | Mayo Clinic (Engel AG): Angelini, Mora, Milone, Fumagalli |
| USA | USA - USC Los Angeles (Engel WK, Askanas): Martinuzzi, Vita, Broccolli, Mirabella, Valterri |
| USA | USA - Columbia University (Rowland, Di Mauro): Trevisan, Bresolin, Bruno, Mancuso, Zeviani, Servidei, Ricci, Minetti, Moggio, Musumeci, Salviati |
| Canada | Canada - Montreal (Karpali): Armani |
| UK | UK - London (Dubowitz): Muntoni, Mercuri, Sorarù |
| UK | UK - London (Morgan-Hughes): Toscano |
| UK | UK - Newcastle (Walton, Bushby): Vita, Guglieri |
| UK | UK - Oxford (Vincent): Evoli |
| UK | UK - Liverpool (Edwards): Siciliano |
| France | France - Paris (Fardeau, Tomè): Villanova, Berardinelli |
| France | France - Nice (Desnuelle): Sacconi |
| France | France - Poitiers (Rideau): Nigro, Comi, Politano, Bianchi |
| Poland | Poland –Warsaw (Hausmanowa-Petrusewicz): (Nigro, Comi, Petretta, Politano) |

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Other potential modes of metabolic therapy include:
1. Supplementation of the missing compound, e.g. CoQ10 which is effective only in primary Q10 deficiency and is given to most patients with mitochondrial disorders even if deficiency is not tested; 2. Pharmacologically increasing the oxidative capacity of muscle (by giving various ‘cocktails’ of oxygen species scavengers that include: carnitine, vitamin C, riboflavin, and extra creatine); 3. Changing the diet composition in order to increase the availability of compensatory fuel sources (e.g. sucrose or a carbohydrate rich diet given before exercise in McArdle’s disease). Because of the rarity of metabolic myopathies no proper double blind studies were performed to assess these therapeutic modalities.

Hereditary inclusion body myopathy (HIBM) is a destructive muscle disease due to mutations in GNE, an enzyme in the synthetic pathway of sialic acid. Part of the pathogenic mechanism is thought to be sialylation deficiency so correcting it may affect the disease course. Providing orally a metabolic intermediate that is downstream to the defective site in the sialic acid pathway (e.g. ManNac) or sialic acid itself was shown to be effective in a mouse model of HIBM. With these considerations in mind, planned therapy of this progressive metabolic myopathy is now reaching human trials. Human and animal toxicity studies with various compounds are now in progress.

I-3

Treatment of CPT2 deficiency with bezafibrate
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The most prevalent fatty acid oxidation disorders (FAO) in adults are carnitine palmitoyl transferase II (CPTII), very-long chain Acyl-CoA dehydrogenase (VLCAD) and multiple Acyl-Coa dehydrogenase (MAD) deficiencies.

Proposed treatment strategies for FAO defects include avoidance of exacerbating factors, carnitine supplementation, riboflavin treatment and dietary modifications (medium-chain triglycerides and triheptanoin). Riboflavin treatment may induce a dramatic improvement of muscle symptoms and encephalopathy in some patients with riboflavin-responsive MAD deficiency.

Children with long-chain FAO defects are generally treated with a low long-chain fat diet and supplements of MCT, but the evidence for benefit is less convincing in patients whose problems are recurrent rhabdomyolysis. A remarkable improvement of cardiac and muscular symptoms occurred in three children with VLCAD deficiency and in seven patients with CPTII deficiency after dietary supplementation with triheptanoin, a seven-carbon medium-chain fatty acid, which supposed mechanisms are the production of C5 ketone bodies and propionyl-CoA, allowing to replenish the pool of catalytic intermediates of the citric acid cycle. Further clinical trials and prolonged clinical follow-up are needed to confirm the benefit of these treatments.

A recently tested alternative way to treat FAO disorders are agonists of peroxisome proliferators-activated receptors (PPARs), that are potent pharmaceutical tools stimulating FAO enzymes in a wide variety of cells. Recent data showed in vivo correction of CPT II and VLCAD deficiency in cultured patients’ fibroblasts, with bezafibrate a widely prescribed hypolipidemic drug. The potential for bezafibrate to correct inborn FAO disorders, has already conducted to the achievement of a pilot clinical trial in 6 adults with CPT II deficiency showing a clear improvement of FAO in muscle.

Another potential target for improving FAO oxidation is AMP-activated protein kinase (AMPK). Exercise, some drugs (metformine, rosiglitazone), and hormones such as leptin and adiponectine are known activators of AMPK in skeletal muscle and increase FAO in muscle. The development of new drugs modulating the activity of AMPK could also open new avenues for the treatment of FAO disorders.

I-4
Long-term follow-up effects on enzyme replacement treatment of adult form of acid maltase deficiency myopathy
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We evaluated the clinical efficacy of alglucosidase alpha enzyme replacement therapy (ERT) in 77 patients with late-onset glycogen storage disease type 2 (GSDII) at various stages of disease progression. Previous studies on efficacy led to demonstrate ERT efficacy against placebo in a 18 months study (LO-TOS van Der Ploeg, NEJM, 2010).

Seventy-seven juvenile or adult patients were treated with ERT in a multi-centre open label non-randomized study with regular clinical assessment for up to 54 months. Recombinant human alpha glucosidase (rh-GAA) was injected by intravenous route at 20 mg/kg i.v. every second week. For analysis, patients were divided in three groups: one group received ERT treatment for 12-18 months, a second group received ERT treatment for 24-30 months, and a third group patients were treated for over 36 months. Clinical assessment included a 6-minute walk test (6MWT), the Walton and Gardner-Medwin scale, forced vital capacity (FVC) and blood creatine kinase (CK). All tests were performed at baseline and every three months thereafter.

ERT was associated with a longer walking distance on the 6MWT, FVC was stabilized in most patients, and a significant decrease in number of hours off the ventilator was found in several patients. Few adverse effects were observed, leading to discontinuation of treatment in 1 patient.

ERT appears a long term reasonable safe treatment for all patients examined. The response pattern in a single patient was variable and not always correlated with treatment duration.