es significantly reduced the number of hours/day in ventilation. In this cohort of patients cardiac hypertrophy was seen in 14% of juvenile-adult cases, this enhances the importance of regular cardiac evaluation, even in adult patients. This large follow up study confirmed and extended the previous positive observations about efficacy and safety on late-onset GSDII patients (5).

Side effects of rhGAA

In all the above mentioned studies adverse events in patients on ERT were mild to moderate and infusion-related or during the first 2 hours post-infusion. No ERT related death occurred. Immunological responses were seen in the majority of the patients, who developed anti-rhGAA IgG antibodies within the first 3 months of ERT that limited the treatment efficiacy (4, 5).

Experimental therapies

Different therapeutic approaches are ongoing as alternative or associated treatment to ERT.

In particular, gene therapy for Pompe disease has been explored by several groups. The feasibility of this approach was firstly shown in vitro studies using retroviral and adenoviral vectors expressing human GAA. In order to improve the efficacy of the viral vectors and minimize the immune response, several approaches have been tried : modification of the GAA cDNA sequence, different promoters, and different AAV serotypes (6).

Enzyme enhancement therapy (EET) is based on the ability of pharmacological chaperones/active site inhibitors to rescue mis-folded or unstable proteins from ER-associated degradation by increasing the amount of protein that passes the cell's quality control system. Various inhibitors and derivatives of deoxynojirimycin (DNJ) have been tested in other lysosomal storage diseases. A number of missense mutations found in late-onset Pompe patients result in retention and premature degradation of the GAA precursor in the ER. These mutations may be amenable to chaperone-mediated therapy (7).

Another treatment approach under observation is based on the enhanced delivery of the therapeutic enzyme. Currently available preparations of rhGAA contains a relatively low number of M6P residues. In order to improve the delivery of the therapeutic enzyme and to facilitate a reduction of the drug dosage, a second generation of the rhGAA (neo-rhGAA) with a higher affinity for the CI-MPR was made. This process involves a chemical conjugation to rhGAA of an oligosaccharide ligand bearing M6P residues in the optimal configuration (8).

A recent therapeutic have emerged as a possibile relevant option to be combined with ERT, called substrate reduction therapy (SRT). It aims to decrease of the amount of glycogen, modulating glycogen synthesis. Glycogen synthesis (GYS) can be modulated by mTOR which is the mammalian target of rapamacin. A GAA-KO mice treated with rapamacin, exhibited a significant decrease of muscular glycogen due to the phosphorylation-mediated inhibition of GYS1 (8).

Conclusions

So far, ERT is the only approved treatment for Pompe disease. Whereas impressive results were obtained in infantile form, some limitations have emerged in late onset patients treated with ERT. However it is worthy to hypothesize that combination of two or more therapeutic strategies (ERT/induction of imuno tolerance, ERT/chaperone, ERT/SRT) could be more effective in GSDII patients.

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S2.4 The role of rehabilitation in the management of metabolic myopathies

Ilaria Riccio[1], Francesca Gimigliano[1], Giovanni Iolascon[1], Raffaele Gimigliano[1 2]

[1] Department of Rehabilitation Medicine, Second University of Naples; [2] Casa di Cura Santa Maria del Pozzo, Somma Vesuviana (NA)

E-mail: ilaria.riccio@unina2.it

According to the Union Européenne des Médecines Spécialistes (UEMS), Section of Physical and Rehabilitation Medicine, *rehabilitation* is the medical specialty concerning with the promotion of physical and cognitive functioning, activities, participation and modifying personal and environmental factors (1). This definition is in accordance with the International Classification of Functioning, Disability and Health published in 2002 by the World Health Organization (2). Rehabilitation activities require a holistic approach through the preparation of an individual rehabilitation project and its implementation by one or more rehabilitative programs containing the immediate and intermediate objectives and the final functional outcome. To settle the individual rehabilitation project it is first important to define the functional limitations and social participation restrictions of the patient using specific assessment scales. The comprehensive assessment of the person affected by a metabolic myopathy should include the evaluation of the following items: a. trunk and upper and lower limbs ROM (Range of Motion); b. upper and lower limbs strength with the MMT (Manual Muscle

Testing); c. pain with several scales such as VAS (Visual Analogic Scale), Pediatric Pain Objective scale, and BPI (Brief Pain Inventory) (3) global functioning with the Six Minute Walk (4) and the Gross Motor Function Measure (GMFM) (5) disability with the Pediatric Evaluation of Disability Index (PEDI), (6) the Pompe PEDI,(7) the Functional Independent Measure (FIM), (8) the WeeFIM, (9) the Barthel Index (10) and the ADL (11)/ IADL(12); quality of life with the Rotterdam Handicap Scale (RHS) (13) and the Short Form 12 (SF-12)(14). In particular, in patients with Pompe disease we have to deal with a deep, progressive and symmetrical muscle weakness, proximal more than distal, involving the lower extremities more frequently than the upper ones, that will determine contractures and deformities. Moreover there are often neck and trunk muscle weakness involving respiratory muscles (diaphragm, intercostals, abdominal and accessory muscles) and this might lead to respiratory failure. Facial and oralmotor weakness is responsible not only of problems of mastication and phonation, but can also give the typical myopathic facies. In terms of functional limitations, myopathic patients experience deficit of walking ability resulting in the need of orthoses or wheelchair, loss of personal autonomy in the activities of daily living, relational-communicative, mental and emotional disabilities. The rehabilitation management of Pompe disease should be comprehensive and preventive, based on an understanding of the pathogenesis of disease progression and on individual assessment. The key of management lies in considering the interaction between the presence, progression and potential remediation of weakness and fatigue. It should optimize and preserve motor and physiological function, prevent or minimize secondary complications, promote and maintain the maximum level of functional independence and participation, and improve the quality of life; maximize the benefits of therapy recombinant and other therapies when they become available.

The rehabilitative approach is nowadays mandatory for comprehensive management of patients affected by metabolic myopathies.

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S2.5 The nutritional approach to Pompe disease

Katia Esposito, Maria Rosaria Improta, Dario Giugliano
Division of Metabolic Diseases, Second University of Naples
E-mail: dario.giugliano@unina2.it

The progressive muscular damage in patients affected by Glycogenosis type II can be slowed down through lifestyle changes based on a specific dietotherapy and daily physical exercise. Dietary treatment provides for a diet made up of proteins (25-30%), carbohydrates (30-35%), fat (35-40%), that is a high-protein diet for the most part. Patients suffering such thesaurismosis need a higher amount of proteins since the increase in amino acids, which function as substrate for the synthesis of proteins, could make up for the proteolysis of muscular tissue. Proteins coming from meat, fish, egg, and dairy products are to be preferred; such food, moreover, is rich in alanine, an amino acid playing a key role in glycide metabolism and, consequently, in the employment of glucose as a source of energy. So much so that a further oral supplement is recommended, in a dose of 0,4g/kg divided 3-4 times per day. Lipids are recommended in the form of unsaturated fats (omega-3, which are mainly contained in bluefish) and saturated fats (omega-6, which are mainly contained in olive oil, dried fruit and cereals), reducing to a minimum saturated ones due to their aterogenic effect. The assumption of carbohydrates must not only be reduced to 30-35%, but also distributed in the space of a day. The "a little and often" rational consists in avoiding the build-up of glycogen on the one hand, and hypoglycaemia on the other. Among complex carbohydrates wholemeal ones such as cereals, legumes, and wholemeal pasta are to be preferred, in small helpings; whereas, among simple ones, dried or skinned (if fresh) fruit; such recommendation aims at increasing the input of fibres in order to counter constipation, which is often found in those patients. Muscular pain, in fact, can also concern the gastrointestinal system, with consequent dysphagia, gastroesophageal reflux, gastroparesis and a reduction in appetite. Such conditions are treated with dietary and pharmacological measures to avoid malnutrition. In the team in charge of treatment, the presence of a physiotherapist is essential to carry out exercises in coordination and contraction of facial muscles, postural training and rehabilitation to tasting. Anthropometric data and bodily composition represent param-