Therapeutic advances in the management of Pompe disease and other metabolic myopathies

Corrado Angelini, Anna Chiara Nascimbeni and Claudio Semplicini

Ther Adv Neurol Disord

[2013] 6(5) 311–321

DOI: 10.1177/
1756285613487570

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Abstract: The world of metabolic myopathies has been dramatically modified by the advent of enzyme replacement therapy (ERT), the first causative treatment for glycogenosis type II (GSDII) or Pompe disease, which has given new impetus to research into that disease and also other pathologies. This article reviews new advances in the treatment of GSDII, the consensus about ERT, and its limitations. In addition, the most recent knowledge regarding the pathophysiology, phenotype, and genotype of the disease is discussed. Pharmacological, immunotherapy, nutritional, and physical/rehabilitative treatments for late-onset Pompe disease and other metabolic myopathies are covered, including treatments for defects in glycogen metabolism, such as glycogenosis type V (McArdle disease), and glycogenosis type III (debrancher enzyme deficiency), and defects in lipid metabolism, such as carnitine palmitoyltransferase II deficiency and electron transferring flavoprotein dehydrogenase deficiency, or riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency.

Keywords: Glycogenosis type II, McArdle disease, RR-MADD, glycogenosis type III, CPT2 deficiency

Introduction

In the last few years the treatment of metabolic myopathies has been dramatically modified by the advent of enzyme replacement therapy (ERT), the first causative treatment for glycogenosis type 2 (GSDII) or Pompe disease. The availability of ERT changed the nature of the disease, first because of its efficacy in modifying the natural course of the disease, but also because of the increased interest that it indirectly produced, and which led to the development of relevant knowledge on the clinical features and retrospective course of the disease, study of the pathophysiology and autophagic mechanisms, research on genotype–phenotype correlations, etc. More than 400 PubMed entries on Pompe disease have been published in the last 5 years. However, many questions arose, and some are still unanswered. Unfortunately, advances in the therapy of other metabolic myopathies are still limited. In this review we focus on recent advances in GSDII and its treatment, and we review briefly the most recent ideas regarding the management and treatment of other metabolic myopathies, including both defects in glycogen metabolism, such as

glycogenosis type V (GSDV) (McArdle disease), and glycogenosis type III (GSDIII) (debrancher enzyme deficiency), and defects in lipid metabolism such as carnitine palmitoyltransferase II (CPT2) deficiency and electron transferring flavoprotein (ETF) dehydrogenase deficiency, or riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency (RR-MADD).

GSDII

GSDII or acid maltase deficiency is an autosomal-recessive disorder caused by a deficiency of the lysosomal enzyme acid α -glucosidase (GAA), which catalyzes the hydrolysis of α -1,4 and α -1,6 links of glycogen. The enzyme deficiency leads to an accumulation of glycogen and the disruption of tissue architecture in various organs, especially the skeletal muscles, heart, and liver.

The spectrum of clinical phenotypes ranges from an infantile-onset rapidly fatal form to a slowly progressive adult form [Angelini and Engel, 1972; Hirschhorn and Reuser, 2001]. As a general rule, the lower the residual enzymatic level, the earlier

Correspondence to:
Corrado Angelini, MD
IRCCS, San Camillo, Lido,
Venice 35100, Italy
corrado.angelini@unipd.it
Anna Chiara Nascimbeni,
PhD
Claudio Semplicini, MD
Department of
Neurosciences NPSRR,
University of Padova,
Padova, Italy

the onset, the faster the progression of the disease, and the worst the prognosis [Laforêt *et al.* 2000; Herzog *et al.* 2012]. The classic infantile-onset form presents in the first months of life with generalized hypotonia and muscle weakness, severe cardiomegaly, feeding difficulties, failure to thrive, and respiratory failure. Untreated patients usually die in the first year of life due to progressive cardiorespiratory failure [Kishnani *et al.* 2006a]. In the juvenile forms symptoms appear between 2 years and 5 years of age, and cardiomyopathy is rarely seen. Late-onset GSDII is characterized by progressive proximal and axial muscle weakness, which leads to a progressive loss of motor function, an altered posture, and the alteration of normal patterns of movement [Hagemans *et al.* 2006]. Diaphragmatic weakness and respiratory insufficiency are frequent. Cardiac involvement is rarely reported in adult patients, it is usually less severe than in infantile and juvenile patients, and is characterized by cardiac hypertrophy (involving the left ventricular wall or the interventricular septum), and conduction abnormalities [Angelini *et al.* 2012a; Schüller *et al.* 2012]. In untreated late-onset patients, muscle strength and pulmonary function usually deteriorate over the years, leading to wheelchair use, and respiratory support in most of cases. It has been demonstrated that untreated adult GSDII patients present an invariably progressive disease, have higher mortality than the general population, and present a poor quality of life [Hagemans *et al.* 2004; Gungor *et al.* 2011].

The incidence of the disease is still uncertain, and varies in different ethnic groups. An accurate population study based on a screening of newborns performed in Taiwan calculated the prevalence at live birth of all types of Pompe disease as approximately 1 in 18,108, the prevalence of infantile-onset Pompe disease was 1 in 57,343, and the prevalence of late-onset Pompe disease was 1 in 26,466 [Chien *et al.* 2011].

Histopathological features of Pompe disease are intriguing and variable in the different phenotypic forms of the disease. The histopathological characteristic of the disease is muscle fiber vacuolization. Most of the infantile and childhood-onset forms typically exhibit fibers with huge vacuoles that contain basophilic amorphous periodic acid-Schiff-positive materials. The diagnosis of the adult-onset form is sometimes challenging as vacuoles can be rare and sometimes compartmentalized by inner membranes (Figure 1). The histopathological

findings can be misdiagnosed as muscular dystrophy or inflammatory myopathy. Acid phosphatase-positive globular inclusions for adult-onset Pompe disease can be found in a small proportion of patients, and have been proposed as a characteristic of Pompe disease, and a useful diagnostic marker for adult-onset Pompe disease lacking typical vacuolated fibers [Tsuburaya *et al.* 2012].

When considering diseases of muscle metabolism, the first therapy implemented to modify the clinical course of the disease is usually dietary treatment. Slonim and colleagues observed an improvement in the clinical status of GSDII patients by administering high-protein and low-carbohydrate doses, supplemented with L-alanine [Slonim *et al.* 1983, 2007]. In addition, they proposed physical aerobic submaximal exercise. The objective of nutrition and exercise therapy was to decrease the deposition of glycogen in lysosomes, to antagonize the muscle protein catabolism typical of GSDII patients with dietary treatment, and to stimulate fatty acid utilization in muscles as an energy resource with aerobic exercise. This therapeutic scheme was demonstrated to be effective in slowing the progressive deterioration of muscular function to some extent, but compliance with the therapy was poor, and in some patients led to an increase in weight, that worsened motor function [Slonim *et al.* 2007]. Furthermore, it was considered that this was not a causative treatment.

ERT

The first effective approach to ERT was recombinant human acid α -glucosidase (rhGAA) derived from hamster ovary cells. The treatment was soon demonstrated to be effective in infant patients in markedly reducing left ventricular mass and improving cardiomyopathy, which are characteristic of the infantile form, and the primary cause of death in infant patients. Furthermore, rhGAA treatment reduced the risk of death by 99%, and markedly reduced the risk of invasive ventilation compared with an untreated historical control group [Kishnani *et al.* 2006b]. In contrast to the natural course in untreated patients, most treated infants acquired motor and functional skills, and some patients remained ambulant at the age of 11 years [van der Ploeg, 2010a]. It was thought that ERT, started early in life in infant patients, would lead to a shift toward a juvenile or 'late-onset' phenotype, but this was not the case: these long-term survivor infant patients presented peculiar clinical characteristics that need further

Figure 1. Quadriceps femoris muscle biopsy from a 28-year-old man with late-onset glycogenosis type II. Serial cross-sections (the asterisks indicate the same fiber in serial sections) show some atrophic and vacuolated fibers with hematoxylin and eosin stain (a), filled with periodic acid-Schiff-positive material (b), and positively reacting for acid phosphatase (c). Immunolabeling with caveolin-3 antibody (d) shows positive labeling at the sarcolemma, in the inner membranes, and faintly in the cytoplasm. Microscope magnification $\times 100$.

investigation to be completely understood [Ebbink *et al.* 2012; Prater *et al.* 2012].

The slowly progressive nature of adult GSDII patients and the wide variability of organ involvement make it difficult to establish a prognosis, to predict the clinical evolution of the disease, and to define the impact of therapies such as ERT on its nature. The only randomized placebo-controlled study is the Late Onset Treatment Study, in which 90 patients between 10 years and 70 years of age were treated with rhGAA (60 patients), or placebo (30 cases), for 18 months [van der Ploeg *et al.* 2010b]. The treatment improved walking distance measured with the 6-min walk test, and stabilized pulmonary function in the rhGAA group compared with a slight worsening of walked distance and respiratory function in the placebo group. Other open-label studies showed a rather variable course of neuromuscular deficits in chronic adult-onset GSDII patients during long

observational periods of ERT, demonstrating a variable effect in prolonging walked distance and respiratory function [Angelini *et al.* 2012a; Regnery *et al.* 2012]. For a better evaluation of natural course and treatment efficacy, work has been carried out to define accurate quantitative outcome measures. Apart from the manual muscle testing for muscle strength, examination of patients usually includes functional tests, such as the 6-min walk test, and timed tests include, for example, the gait, climbing stairs, Gowers' maneuver and arise from a chair (GSGC) score. The 6-min walk test is a useful measurement of functional endurance during prolonged ambulation, widely used for nonwheelchair-dependent patients [van der Ploeg *et al.* 2010b; Angelini *et al.* 2012a]. The GSGC score was validated in the clinical follow up of GSDII cases [Angelini *et al.* 2012b], as well as in other myopathies. It can be used for patients at different stages of the disease; it is well related to daily life activities, and

sensitive to even small differences in the clinical course of treated and untreated patients [Angelini *et al.* 2012b]. An increasing role in the evaluation of muscle disease has been acquired by magnetic resonance imaging of muscle, an accurate and noninvasive test that can evaluate muscle morphology and fibro-fatty muscle degeneration, quantify glycogen, and detail the changes with spectroscopic studies [Carlier *et al.* 2011]. The glucose tetrasaccharide, Glc1-6Glc1-4Glc1-4Glc (Glc4), is a glycogen-derived limited dextrin that correlates with the extent of glycogen accumulation in skeletal muscle. It is used in GSDII as a biomarker of tissue damage, and to monitor the response to ERT with very good sensitivity and specificity, but it does not provide information on the location and distribution of excess glycogen accumulation [Young *et al.* 2012].

Limitations of ERT. The profile of tolerability of ERT is generally good, and most adverse events (AEs) are related to the infusion and are mild to moderate in severity. In a recent review by Toscano and Schoser, all the studies on the efficacy of ERT in adult patients were systematically analyzed [Toscano and Schoser, 2013]. The authors identified severe or serious AEs in four patients (one fatal tracheal hemorrhage, one severe emphysema and pneumothorax during treatment, one pneumothorax, which led to tracheostomy, and one severe tongue edema). They also analyzed the data on the development of antibodies to α -glucosidase, which was available to 128 patients: between them, 121 patients developed antibodies against rhGAA, and three developed adverse reactions probably correlated with antibodies. The issues of immune therapy and induction of immune tolerance are still being debated: several drugs have been tried to prevent the development of, or eliminate antibodies against ERT, such as rituximab (anti-CD20 monoclonal antibody), methotrexate, intravenous immunoglobulin, and other drugs. Between them, the combination of rituximab and methotrexate with intravenous immunoglobulin has been able to successfully tolerate Infantile Pompe Disease (IPD) (Lacama *et al.* 2012) patients to rhGAA in the naïve or early ERT. Bortezomib (Velcade®, Millenium Pharmaceuticals, Inc., MA, USA) is a proteasome inhibitor that targets mature antibody-producing plasma cells. It has been tried recently in association with other drugs and demonstrated to be an effective and safe treatment strategy in infantile Pompe disease with high-sustained antibody titers [Banugaria *et al.* 2013].

No clear correlation between antibody titers and clinical outcome has so far been demonstrated [Patel *et al.* 2012]. However, Regnery and colleagues reported an important AE in the case of an adult female patient who developed very high antibody titers (up to 1:819,000), and subsequently presented a worsening of motor function requiring the discontinuation of ERT [Regnery *et al.* 2012].

The analysis of clinical efficacy in adult patients made by Toscano and Schoser demonstrated that response is widely variable in each patient [Toscano and Schoser, 2013]. Furthermore, it is important to underline that up to a third of patients do not show significant improvement during treatment, or may even present a worsening of motor and respiratory function. The factors underlying this variability of clinical response to ERT need further investigation.

The efficacy of treatment needs to be accurately studied in every patient. The cost of therapy is an crucial problem, and it will become even more important for national health institutions, now that more and more rare disease are becoming treatable with emerging therapies.

Consensus on ERT. A debated issue is when to start and stop ERT. Recent guideline from the American Association of Neuromuscular and Electrodiagnostic Medicine recommends commencing ERT in symptomatic patients and in asymptomatic patients who have proximal muscle weakness detectable by manual muscle testing, or a reduction in respiratory parameters [Cupler *et al.* 2012]. Patients who have no symptoms or objective signs should be examined every 6 months and muscle strength and pulmonary function evaluated, and ERT should be started at the earliest onset of symptoms or objective signs. In fact, it is now known that early treatment is crucial in order to obtain the best results for ERT, especially in infants [Kishnani *et al.* 2012].

For severely affected patients no randomized clinical trial has provided evidence regarding the effectiveness of ERT, and the available data are scarce and controversial [Orlikowski *et al.* 2011]. The biweekly hospitalization for enzyme infusions may have a significant impact on the daily life of patients (e.g. limitation in movements, respiratory support, etc.). For these reasons, Cupler and colleagues suggested that ERT should be administered for at least 1 year to adult patients, and later decisions regarding the continuation of

ERT should be made on a case-by-case basis [Cupler *et al.* 2012]. Conversely, no agreement has so far been reached on the timing of possible ERT interruption, since ERT is the only therapy demonstrated to be effective in this disease. The American consensus suggested that, because of the high variability of the natural course and the only mild differences that have been demonstrated after ERT, the treatment should be administered for at least 1 year, after which the physician should discuss with the patient whether or not to continue ERT. The ongoing studies on the identification of nonresponder-patient categories may help insurance companies and national health institutions in this decision.

What is new in GSDII?

In the last few years, new diagnostic tests have been carried out, mostly using enzyme analysis on dried blood spots with fluorometric or mass spectrometry methods [Burton, 2012]. These techniques seem useful for early diagnosis, or as diagnostic tools in the newborn screening programs that are being carried out by various national health institutions. At the same time, the accurate clinical evaluation of Pompe patients in the last few years has led to the identification of unusual phenotypes, widening the clinical spectrum of the disease. In a recent German case series, Schuller and colleagues identified up to 16% of patients presenting a combination of severe scoliosis with lumbar hyperlordosis, incomplete rigid spine syndrome, and a low mean body mass index, apart from the more frequent limb girdle weakness associated with diaphragmatic weakness [Schuller *et al.* 2012]. Cardiac involvement in adult patients is not uncommon, as previously mentioned, and seems quite responsive to ERT [Angelini *et al.* 2012a; Fernandez *et al.* 2012]. Tongue weakness may be present as an axial sign of late-onset GSDII, even relatively early in the course of the disease, and it may contribute to the differential diagnosis of this now treatable condition, along with dysphagia and dysarthria [Dubrovsky *et al.* 2011]. The involvement of smooth muscle is well known, manifesting, for example, with vascular abnormalities (e.g. intracranial aneurysms) [Schüller *et al.* 2012; Hobson-Webb *et al.* 2012]. Urinary and fecal incontinence can be due either to the involvement of striated and smooth pelvic floor muscle, or lower motor neuron or autonomic involvement, which was occasionally observed in late-onset adult patients [Remiche *et al.* 2012]. Incontinence

is associated with a poorer quality of life, and can be present at all stages of the disease. For these reasons, it should be investigated regularly, and used as an additional parameter to be considered in the decision to start ERT, the more so because incontinence seems to be responsive to ERT.

Gene modifiers

It is known that modifying factors have a sizeable effect on the clinical course of GSDII [Kroos *et al.* 2012]. de Filippi and colleagues observed a correlation between the presence of a specific polymorphism in the angiotensin-converting enzyme (ACE) and the phenotype, being the DD genotype of the ACE gene associated with an earlier age of onset [de Filippi *et al.* 2010]. The mechanism by which variation in ACE activity may influence muscle function and exercise performance is complex. The DD genotype is associated with a higher ACE activity that results in a lower half-life of bradykinin and increased production of angiotensin II, with a consequent vasoconstriction. Thus, the physiological impact of the ACE genotype may take place by reduced endothelium-dependent vasodilatation and decreased substrate delivery to the working muscles. This point may be of particular relevance in a disorder primarily due to the inability of muscle to use stored glycogen, so that the muscle energy supply becomes fully dependent on circulating glucose. The D allele is also associated with an increase in type II fibers, which are less rich in mitochondria and thus more sensitive to oxidative stress (Shang *et al.* 2003). Other proposed mechanisms include an influence of bradykinin on increasing muscle blood flow and glucose extraction rate, and a stimulation of protein synthesis [Woods *et al.* 2000].

Autophagy and GSDII

Autophagy, the major degradation pathway for long-lived proteins and organelles, is essential for cell homeostasis and its dysfunction has been linked to a number of muscle disorders that are typically characterized by massive autophagic buildup. This was first shown in Pompe disease in a mouse model, where the areas of cellular debris, seen predominantly in type IIB myofibers, were associated with resistance to ERT [Fukuda *et al.* 2006]. In patients, as in the mouse model, the enormous buildup, rather than the enlarged, glycogen-filled lysosomes outside the autophagic regions, appears to cause the muscle damage [Raben *et al.* 2007]. What is

emerging from recent studies on GSDII patients is that autophagy impairment contributes to disease progression and atrophy [Nascimbeni *et al.* 2012]. A residual functional autophagic flux has been shown to be important also for efficient ERT and GAA maturation. Indeed, most of the cellular trafficking, including endosomal trafficking, needed for recombinant GAA uptake and delivery to lysosomes, uses proteins that also participate in autophagy, and the autophagosome accumulation that characterizes GSDII can sequester these factors. The maturation steps of GAA from the synthesis of the immature protein in the endoplasmic reticulum to the final cleaved active protein in lysosomes are complex and require a functional system of vesicle trafficking.

These findings highlight the importance of developing new drugs to restore the autophagic flux in these patients in order to improve the uptake of recombinant GAA.

Other metabolic myopathies

No causative treatment is presently available for other myopathies due to metabolic defects. Nevertheless, in the last few years several dietary and replacement treatments and physical training schemes have been demonstrated to be effective in ameliorating the clinical course of some of these diseases.

GSDIII or debrancher enzyme deficiency

The clinical forms of the disease include a predominantly hepatic form (i.e. hepatomegaly, hypoglycemia, and hypertriglyceridemia), and a muscular form (i.e. myopathy and cardiomyopathy) [Okubo *et al.* 2011; Dagli *et al.* 2010]. Usual recommendations include frequent high-carbohydrate meals in the day and raw cornstarch or continuous feeding during the night, which prevent fasting hypoglycemia but do not influence the course of cardiac and muscular manifestations (Kishnani *et al.* 2010). Recently, Valayannopoulos and colleagues proposed an experimental treatment for a 2-month-old infant with a severe familial form of GSDIII complicated by severe cardiomyopathy, whose sister had died from severe cardiomyopathy on a standard nutritional protocol [Valayannopoulos *et al.* 2011]. The authors combined the use of synthetic ketone bodies (D,L-3-OH butyrate) as an alternative energy substrate for the heart, a 2:1 ketogenic diet to reduce glucose intake, and a high-protein diet to enhance gluconeogenesis. After 2

years of treatment, echocardiography showed an improvement in the cardiomyopathy. Growth and liver size remained normal, and no side effects were observed. These preliminary results of a case report need confirmation in a larger series.

GSDV or McArdle disease

McArdle disease is a rare disease and is due to a deficiency of the glycogenolytic enzyme myophosphorylase. The disease is clinically characterized by fatigue and exercise-induced myalgia, and, in some cases, by myoglobinuria with acute renal failure due to recurrent rhabdomyolysis. A small proportion of patients develop a progressive weakness of the proximal muscles, especially in the upper limbs [Quinlivan *et al.* 2010a; Lucia *et al.* 2012b]. Due to the rarity of the disease, its high variability (and paucity) of symptoms, and the difficulties in defining precise outcome measures, no trial could demonstrate efficacy of any drug, dietary treatment, or exercise scheme. One of the most interesting treatments is vitamin B6. In normal individuals the skeletal muscle contains 80% of the total pool of vitamin B6 bound as pyridoxal 50-phosphate (PLP) to muscle phosphorylase, playing an important role in enzyme activity. In McArdle patients decreased phosphorylase substantially diminishes PLP in skeletal muscle [Haller *et al.* 1983]. Recently, a Japanese patient was treated for more than 2 years with vitamin B6 supplementation, and the authors could demonstrate an amelioration in symptoms, increase of enzymatic levels on muscle biopsy, and increase of lactate in response to effort during the grip test [Sato *et al.* 2012]; it is worth noting that previous studies including small case series could not demonstrate a real efficacy of this supplementation. Along with methodological limits (i.e. outcome measures, numbers in cohort), Sato and colleagues postulated that the action of vitamin B6 supplementation may require the presence of some residual muscle phosphorylase and probably would not have been seen in patients with null mutations, including the R50X mutation, which is most common among Whites [Sato *et al.* 2012]. They hypothesized that vitamin B6 supplementation can restore some stability to the mutant enzyme and enhance the residual phosphorylase activity in skeletal muscle, followed by improvement in insufficient anaerobic glycolysis of skeletal muscle. These hypotheses need further confirmation in larger controlled studies. The intervention that demonstrated some amelioration in clinical

symptoms included dietary treatment and physical training [Quinlivan *et al.* 2010b, 2011]. The infusion of sucrose before exercise can markedly improve exercise tolerance, probably by increased availability of bloodborne glucose, which partially rescues muscle oxidative metabolism in myophosphorylase-deficient muscle early in exercise [Andersen *et al.* 2008]. A carbohydrate-rich diet seems more effective than a high-protein diet [Andersen and Vissing, 2008]. A regular aerobic training program can potentially improve metabolic capacity and exercise tolerance by conditioning muscles for oxidative phosphorylation. Moderate aerobic exercise (30 min/day, 4 days a week, at an intensity corresponding to 60–70% of maximal heart rate) was tested in eight patients for 14 weeks [Lucia *et al.* 2012a]. This training program was safe, increased average work capacity, oxygen uptake, cardiac output, and mitochondrial enzyme levels without causing pain or cramps or increasing serum creatine kinase. Randomized studies are needed to confirm these preliminary results. The impact of ACE polymorphism on the disease, as discussed for GSDII, was previously described in GSDV by Martinuzzi and colleagues who demonstrated a strong correlation between the severe phenotype and the number of D alleles [Martinuzzi *et al.* 2003]. A double-blind, randomized, placebo-controlled trial involving eight patients treated with an ACE inhibitor (2.5 mg ramipril) demonstrated a significant change in disability score, even if it failed to show any treatment effect in the objective measures of exercise performance and muscle metabolism chosen as primary endpoints for the overall population [Martinuzzi *et al.* 2008]. The treatment seemed to modify exercise physiology in DD patients, raising the possibility of a differential haplotype-linked sensitivity to the treatment that still needs confirmation. The principal limitations of the study were the small study population and the outcome measures.

CPT2 deficiency

CPT2 deficiency is a rare autosomal disorder of mitochondrial fatty acid oxidation (FAO), clinically characterized by muscle stiffness, myalgia, exercise intolerance, and episodes of myoglobinuria, usually triggered by prolonged exercise, cold, or fasting [Liang and Nishino, 2010]. In a large series of patients, Fanin and colleagues divided molecularly defined patients into mild or severe categories according to the number of myoglobinuric episodes [Fanin *et al.* 2012]. Patients affected by CPT2

deficiency usually can control their symptoms by avoiding trigger factors and with an accurate dietary treatment using high-carbohydrates doses [Ørngreen *et al.* 2003]. Glucose infusion is of benefit in CPT2-deficient patients, but oral glucose did not achieve the same effects, probably because of the low glucose availability, and because of the insulin response that inhibits muscle glycogenolysis [Ørngreen *et al.* 2002]. In the past few years, new drugs have been tested to increase FAO. Fibrates are a class of hypolipidemic drugs that increase high-density lipoprotein levels by mRNA upregulation of many lipid-metabolism genes through interaction with the steroid/thyroid transcription factor PPARα. Recent studies demonstrated that bezafibrate increases CPT2 mRNA and normalizes enzyme activity in mild forms of CPT2-deficient cultured fibroblasts and myoblasts [Bonnefont *et al.* 2009]. A trial including six patients treated with bezafibrate was conducted in France, the primary outcome being the level of FAO in muscle evaluated in biopsies. The authors demonstrated normalization of the FAO level in all patients: a significant increase in palmitoyl-L-carnitine oxidation, increased CPT2 mRNA, and the translated protein. In addition, they observed a reduction of episodes of rhabdomyolysis, amelioration of quality of life measured by SF-36, and no AEs. There was also an increase in physical activity and a decline in muscular pain [Bonnefont *et al.* 2009, 2010]. Further collaborative studies and *in vivo* studies are needed to confirm the long-term efficacy and safety of these therapies.

ETF, ETF-dehydrogenase or RR-MADD

This disease is a rather unrecognized cause of myopathy with lipid storage [Wang *et al.* 2011]. RR-MADD is caused by defects in ETF or ETF-dehydrogenase, two mitochondrial enzymes that contain flavin adenine dinucleotide as prosthetic group. A defect of ETF and ETF dehydrogenase can affect all dehydrogenases in fatty-acid beta-oxidation. The disease is characterized by glutaric aciduria type 2 and lipid storage myopathy (Figure 2). The phenotype is heterogeneous: late-onset patients manifest proximal myopathy, high creatine kinase levels, vomiting, and hypoglycemia. The measurement of serum carnitine, the acylcarnitine profile, and urinary organic carnitine is useful for diagnosis [Liang and Nishino, 2011].

The disease appears very responsive to treatment, since riboflavin (100–400 mg/day) alone or in combination with carnitine supplementation

Figure 2. Muscle biopsy from a 22-year-old woman with lipid storage myopathy (riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency). Vacuolated and atrophic fibers, hematoxylin and eosin stain (a), and lipid droplets in many fibers stained with oil red O stain (b).

can reverse the prominent weakness in a few months and normalize the deficiency [Cornelius *et al.* 2012].

Conclusion

Much more needs to be discovered and scientifically proven in the large field of metabolic myopathies, but the recent findings that we have described can make researchers and patients optimistic that a greater number of treatments will be available for such rare diseases, together with an increased effectiveness of therapeutic approaches.

Funding

This research received support from Telethon GUPI2001D, AFMTélèthon (14199) and Eurobiobank.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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