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ORIGINAL ARTICLES

State of the art in muscle glycogenoses

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The recognition of a series of metabolic/enzymatic dysfunctions in glycogenoses has allowed new therapeutic advances for their treatment due to the development of recombinant enzyme. A recent advance appears enzymatic replacement therapy (ERT) in glycogenosis type II in both infantile, juvenile and adult form. Targeted manipulation of diet has been tried both in glycogenosis type II (Pompe disease) and type V (Mc Ardle disease).

Key words: Glycogenosis, Pompe disease, McArdle disease, enzyme replacement therapy

Introduction

Glycogenoses are a group of diseases characterized by an impairment in energy production in skeletal muscles. They include defects in glycogen synthesis, glycogen breakdown or glycolysis (Table 1). Clinically, they range from multisystemic and rapidly fatal diseases, to isolated slowly progressive myopathies (e.g. glycogenosis type II), or to episodic muscle dysfunction during exercise (e.g. McArdle's disease). A rapid diagnosis is now increasingly important to give patients the chance of the new treatments becoming available in the last years.

Glycogenosis type II

Glycogen storage disease type II (GSDII) is an autosomal recessive disorder caused by the deficiency of the lysosomal enzyme acid α-glucosidase (GAA) or acid maltase, which catalyses the hydrolysis of α-1,4 and α-1,6 linkages of glycogen. The enzyme deficiency leads to lysosomal accumulation of glycogen that results in different clinical phenotypes (severe or infantile, juvenile and adult onset).

The severe infantile form of GSDII (Pompe disease) is characterized by marked hypotonia and cardiomyopathy usually due to complete GAA deficiency, and patients die within the first year of life, if untreated, for cardiorespiratory failure (1).

The juvenile and adult forms, named late-onset GSDII, are slowly progressive myopathies mimicking limb-girdle dystrophy, frequently characterized by an early respiratory involvement with diaphragmatic paralysis and restrictive respiratory insufficiency (2); a residual enzyme activity is usually found (3).

The histopathological hallmark is muscle fiber vacuolization and autophagy. The vacuoles can vary for size and shape, show PAS-positivity and strong reaction for lysosomal acid phosphatase. In the infantile form, the muscle fiber structure is severely compromised, while the degree of vacuolization is extremely variable in late-onset patients, and appeared sometimes to be independent of age of onset, disease duration or clinical features (3).

Genotype-phenotype correlations showed that although the nature of the mutation sometimes matches the phenotype, in most cases the disease phenotype is hard to predict on the basis of gene mutations alone. Furthermore, the age at onset and the disease course may be quite different in patients with identical genotypes (e.g. siblings), suggesting a modulating role of both the genetic background and of exogenous factors on GAA gene expression, which might produce a shift in the enzyme biosynthesis rate (3).

Knowledge of the natural history of the late-onset disease is still poorly investigated, mostly because of its extremely heterogeneous course.

Trials with replacement therapies

Several replacement therapies have been tried in GSDII patients since 1967, when an enzyme derived from *Aspergillus niger* was unsuccessfully tested (4). Decades ago it was recognized that various cell types need specific receptors for uptake of exogenous lysosomal enzymes. In muscle and liver it was the mannose-

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Table 1. Clinical features in muscle glycogenoses.

Pathway	Deficiency	Type	Exercise intolerance	Myoglobinuria	Weakness	Cardiomyopathy
Glycogenolysis	Acid alpha-glucosidase	II	-	-	+	+
	Debrancher	III	-	-	+	+
	Phosphorylase	V	+	+	+	-
Glycolysis	Aldolase A	XII	-	+	-	-
	PFK	VII	+	+	-	-
	PGK1	IX	+	+	-	-
	PGAM	X	+	+	-	-
	Enolase B	XIII	+	+	-	-
	LDH-M	XI	+	+	-	-
Glycogen synthesis	Glycogen synthetase	0	+	-	-	+
	Brancher	IV	-	-	-	+
	Phosphorylase	VIII	-	+	-	+
	kinasebrancher	IV	-	-	-	+
	Phosphorylase kinase	VIII	-	+	-	+
	Glycogenin-1	-	-	-	+	+

Table 2. Italian GSDII patients treated with enzyme replacement therapy.

Clinical features		Number	%
	Patients	78	
	Treating centres	18	
Sex	M	36	46
	F	42	54
Age at onset (years)	Average	29	
	SD	15	
	Range	1 - 60	
Disease duration at start of ERT (years)	Median	14	
	SD	8	
	Range	1 - 35	
Walking	Yes	52	66
	Unilateral support	9	11
	Bilateral support	10	12
	Not walking	7	9
Ventilatory support	None	49	62
	Night-only	9	11
	< 12 h	7	9
	> 12 h	13	16
Cardiomyopathy	Yes	7	9
	No	71	91
ERT duration (months)	Range	12 - 54	
	Median	24	
Adverse reactions	Moderate	2	2
	Mild	4	5
	None	72	92

6-phosphate receptor (M6P). This gave new chance to the research.

In the meantime, other therapeutical options have been tried. A dietary treatment with high-protein and low-carbohydrates, with supplementation with L-alanine, and associated with physical aerobic sub-maximal exercise (5) was proposed. The purpose of the dietary treatment was to decrease the deposition of glycogen in lysosomes, and to antagonize the protein catabolism in muscles observed in GSDII patients' tissues, and stimulating fatty-acid utilization in muscles as an energy source during aerobic exercise. The theoretic substrate of this therapy is confirmed by the case of a 26-year old patient, followed at our center, who presented acute respiratory failure after 2 months of vegetarian diet, resolved after ventilatory therapy and hyperproteic diet. The clinical outcome in Slonim's study was surprisingly good, even if the compliance to the scheme was not easy, and the increase of body weight of some patients worsened their motor function.

In 2000 Genzyme-Pharming announced the discontinued development of enzyme replacement therapy with recombinant human enzyme from rabbit milk, then Genzyme believed the production in CHO cells to be quicker and more efficient.

Recombinant enzyme replacement

In infantile Pompe disease an enzyme replacement treatment with recombinant alpha-glucosidase (rGAA) has been tried both in the US and Europe (1, 6), with major benefits on survival and cardiomyopathy.

Only relatively few treated late-onset patients in Europe have been so far extensively reported (7-9). This fact demonstrates that it is difficult to compare the action of ERT in late-onset cases, because of the heterogeneous clinical features and the slow progression of the disease in those patients. Since ERT treatment has been approved in Europe, a blind trial would not be accepted by patients and therefore it is now impossible to carry it out. Otherwise, it is important to investigate in a multidisciplinary and quantitative way the treated GSDII patients, to describe the natural course of the disease, to underline the benefits of ERT and to identify the non-responder patients. We are conducting a multicenter observational study in 18 centers in Italy that has so far collected 78 treated cases including walking and non-walking patients (Table 2).

It is clear that ERT is a safe therapy: only mild infusion-related adverse reactions have been observed (Table 2). It is clear that ERT is effective in infantile form, especially on reducing the cardiomegaly and prolong the survival. Otherwise it is not easy to demonstrate the real efficacy of the therapy in late-onset GSDII, on the slowly progressive motor and respiratory failure, and the long term efficacy. A randomized double-blind study has been done in 60 walking patients proving an efficacy, although of modest degree, in 6-minute-walk-test and stabilization of respiratory function (10).

The most important limits of the enzymatic therapy are the difficulty to reach the target, in muscles fibers were the M6P receptors density is much lower than in the heart, and the formation of antibodies that may reduce the efficacy of the protein and the presence of structural alteration of muscle with build up of connective tissue. The first one can be overcome by the conjugation of the recombinant enzyme with a synthetic oligosaccharide containing M6P (11), resulting in an improved affinity for the M6P receptor and delivery to muscle cells. The use of chaperones is still experimental and their use in two US patients has led to more pronounced weakness.

Glycogenosis type V – McArdle Disease

McArdle disease is a metabolic myopathy caused by the genetic deficiency of the glycolytic enzyme myophosphorylase. It is clinically characterized by exercise intolerance, fatigue and exercise induced myalgia, and, in some cases, by myoglobinuria resulting in acute renal failure due to rhabdomyolysis. A small proportion of patients develop a progressive weakness of proximal muscles, especially of upper limbs.

The enzymatic defect causes a global impairment in muscle metabolism. The impossibility to mobilise glycogen subsarcolemmal deposits during anaerobic metabolism, the reduction of pyruvate production in the tricarboxylic acid cycle and the subsequent oxidative phosphorylation impairment bring to a reduction of Acetyl-CoA production, with a cyclic worsening of function of tricarboxylic acid cycle.

The breakdown of fatty acid can, in some trained patients, generate some alternative quantities of Acetyl-CoA; the shift to fatty acid oxidation is the basis of the "second wind" phenomenon, the possibility of patients to continue the exercise after some minutes of rest, when the pain occurs.

Many drugs or dietary treatments have been tried to reduce symptoms in this rare disease, but all of them failed to demonstrate a significant amelioration in these patients. It is important to underline that every study was designed with a small number of patients, furthermore the clinical heterogeneity prevented the establishment of measurable primary outcomes.

Aminoacids, high protein diet, and fatty acid supplementation have been tried to improve alternative energy sources instead of glycolytic metabolism (12), but only in single anecdotic cases a success has been claimed.

References

1. Kishnani PS, Corzo D, Nicolino M, et al. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. Neurology 2007;68:99-109.
2. Laforêt P, Nicolino M, Eymard PB, et al. Juvenile and adult-onset acid maltase deficiency in France: genotype-phenotype correlation. Neurology 2000;55:1122-8.
3. Nascimbeni AC, Fanin M, Tasca E, et al. Molecular pathology and enzyme processing in various phenotypes of acid maltase deficiency. Neurology 2008;70:617-26.
4. Hug G, Schubert WK. Lysosomes in type II glycogenosis. Changes during administration of extract from Aspergillus niger. J Cell Biol 1967;35:C1-C6.
5. Slonim AE, Bulone L, Goldberg T, et al. Modification of the natural history of adult-onset acid maltase deficiency by nutrition and exercise therapy. Muscle Nerve 2007;35:70-7.
6. Hagemans ML, van Schie SP, Janssens AC, et al. Fatigue: an important feature of late-onset Pompe disease. J Neurol 2007;254:941-5.
7. Winkel LP, Van den Hout JM, Kamphoven JH, et al. Enzyme replacement therapy in late-onset Pompe's disease: a three-year follow-up. Ann Neurol 2004;55:495-502.
8. Angelini C, Semplicini C, Tonin P, et al. Progress in Enzyme Replacement Therapy in glycogen storage disease type II. Therap Adv Neurol Disord 2009;2:143-53.
9. Strothotte S, Strigl-Pill N, Grunert B, et al. Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. J Neurol 2010;257:91-7.
10. Van der Ploeg AT, Clemens PR, Corzo D, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med 2010;362:1396-406.
11. Zhu Y, Li X, Kyazike J, et al. Conjugation of mannose 6-phosphate-containing oligosaccharides to acid-glucosidase improves the clearance of glycogen in Pompe mice. J Biol Chem 2004;279;50336-41.
12. Quinlivan R, Beynon RJ, Martinuzzi A. Pharmacological and nutritional treatment for McArdle disease (Glycogen Storage Disease type V). Cochrane Database Syst Rev 2008;16:CD003458.