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Tarui disease and distal glycogenoses: clinical and genetic update

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Phosphofructokinase deficiency (Tarui disease) was the first disorder recognized to directly affect glycolysis. Since the discovery of the disease, in 1965, a wide range of biochemical, physiological and molecular studies have greatly contributed to our knowledge concerning not only phosphofructokinase function in normal muscle but also on the general control of glycolysis and glycogen metabolism. Studies on phosphofructokinase deficiency vastly enriched the field of glycogen storage diseases, making a relevant improvement also in the molecular genetic area. So far, more than one hundred patients have been described with prominent clinical symptoms characterized by muscle cramps, exercise intolerance, rhabdomyolysis and myoglobinuria, often associated with haemolytic anaemia and hyperuricaemia. The muscle phosphofructokinase gene is located on chromosome 12 and about 20 mutations have been described. Other glycogenoses have been recognised in the distal part of the glycolytic pathway: these are infrequent but some may induce muscle cramps, exercise intolerance and rhabdomyolysis. Phosphoglycerate Kinase, Phosphoglycerate Mutase, Lactate Dehydrogenase, β-Enolase and Aldolase A deficiencies have been described as distal glycogenoses. From the molecular point of view, the majority of these enzyme deficiencies are sustained by "private" mutations.

Key words: Phosphofructokinase deficiency, Tarui disease, Glycogen Storage Disease VII or GSD VII

Introduction

Phosphofructokinase (PFK) is a key regulatory enzyme of the glycolytic cycle that catalyses the conversion of fructose-6-phosphate to fructose-1.6-diphosphate. PFK is a complex isozyme consisting of three subunits: Muscle type (M), Liver type (L) and Platelet type (P). The P type is also known as Fibroblast type (F).

The genes of the PFK-M, PFK-L and PFK-P have been assigned, respectively, to human chromosomes 12, 21 and 10 (1).

PFK deficiency is associated with a heterogeneous group of clinical symptoms, mainly characterised by myopathy and/or haemolysis or by an asymptomatic condition (2).

Clinical features

Very recently, a clinical classification has been reported dividing patients with GSD VII into four different clinical subclasses: classical form, late-onset form, infantile form and haemolytic form (1). The classical form is characterised by exercise intolerance, muscle cramps, pain and, sometimes after intense physical efforts, nausea and vomiting. It is also possible to observe jaundice accompanied by elevated creatine kinase (CK) levels, hyperuricaemia, reticulocytosis and increased serum bilirubin. The late-onset form presents with cramps and myalgias in later life although exercise ability is low already in childhood; a mild muscle weakness may appear in the fifth decade leading to severe disabilty. Patients with the infantile form may manifest as "floppy babies" and they die within the first year of life. They can also show evidence of arthrogryposis and mental retardation. The haemolytic form presents with hereditary non-spherocytic haemolytic anaemia but with no muscle symptoms.

Morphological features

Muscle biopsies often show internal vacuolization with glycogen storage that can be revealed by PAS stain although, in some cases, morphological aspects are almost normal. Electron microscopy can confirm the glycogen deposition in sub-sarcolemmal and inter-myofibrillar areas (3).

Biochemical and molecular genetic analysis

PFK enzymatic activity is often virtually lost; consequently glycolytic intermediates, in muscle biopsies, showed increased values of glycogen, glucose-1-phosphate, glucose-6-phosphate, and fructose-6-phosphate whereas fructose-1.6-biphosphate and triose-phosphates are decreased. There is no clear correlation between biochemical and clinical aspects; i.e., in a recent series of our PFK-deficient patients, in one case we found normal rise of serum lactate after ischemic exercise test, suggesting a normal **A**TP production (4). The genes of PFK-

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M, PFK-L and PFK-P have been located, respectively, on chromosomes 12, 21 and 10. The human PFK-M gene is a single copy gene that contains approximately 30 kb of genomic DNA and 24 exons. The first PFK-M gene mutation was described in 1990; it appeared as a homozygous mutation causing an in-frame deletion of 75 bp found in a domain likely encompassing a ADP/AMP activation site (1). Since then, less than 20 mutations as such as missense mutations, nonsense mutations, frameshift mutations and splicing mutations have been reported. PFK-M deficiency seems to be prevalent in the Ashkenazy Jewish population. The most frequent change is a splicing defect at the 5' donor site of intron 5 resulting in an in-frame deletion of the exon 5 sequence in the transcript (5). So far, due to the molecular genetic heterogeneity, a clearcut genotype-phenotype correlation has not been recognized in patients with PFK deficiency.

Distal glycogenoses

These diseases are due to defects of terminal glycolysis: the most recurrent symptoms are rhabdomyolysis and exercise intolerance. Phosphoglycerate Kinase, Phosphoglycerate Mutase, Lactate Dehydrogenase, Enolase and Aldolase A deficiencies have been described.

Phosphoglycerate Kinase deficiency

Phosphoglycerate Kinase deficiency (PGK – GSD type IX) is a X-linked recessive disorder. Patients present with severe muscle cramps after brief and intense physical exercise. This symptomatology is often accompanied by jaundice, haemolytic anaemia and gout arthritis. Some patients may show progressive myopathy with myoglobinuria and mental retardation. Muscle biopsy often revealed non-specific changes. The enzyme activity is intensely decreased and different molecular changes have been documented in this disease (5).

Phosphoglycerate Mutase deficiency

Phosphoglycerate Mutase deficiency (PGAM – GSD type X). The onset of the disease is characterized by myalgias, myoglobinuria and rhabdomyolysis after strenuous muscle exercise. Muscle biopsy may show a mild glycogen storage but can also be non-specific; in a number of cases, "tubular aggregates" have been found (6), residual enzyme activity is quite low (range 2-10%). The majority of patients were Afro-Americans but also Italians and Japanese (6, 7). The gene is located on chromosome 10. Molecular genetic analysis revealed one very common mutation, a non-sense mutation TGG (Trp) to TAG (stop) in many of the Afro-American individuals whereas missense mutations were detected in Afro-American, Italian and Japanese cases (6).

Lactate Dehydrogenase deficiency

Lactate Dehydrogenase deficiency (LDH – GSD type XI) has been reported in few Caucasian and Japanese patients with myoglobinuria, myalgias and exercise intolerance. The gene has been assigned to chromosome 12. Only 5 mutations have been reported, so far, in LDH-deficient subjects (3).

Aldolase A deficiency

Aldolase A deficiency (GSD XII) has been described only in one patient (male), in 1996 (8), who complained of exercise intolerance, muscle weakness and hyperCK-aemia. Muscle biopsy was unremarkable and the residual enzyme activity was 11%. A missense mutation was considered pathogenic in this case.

β-*Enolase deficiency*

β-Enolase deficiency (GSD type XIII) has recently been described in an adult patient with easy muscle fatigability, myalgias and increased CK values after intense physical exertion. The gene involved in the disease maps to chromosome 17. Muscle biopsy was considered normal but residual enzyme activity was about 5%. The patient was heterozygous for two different missense mutations of ENO3 gene (9).

Conclusions

Despite the large amount of new information concerning PFK deficiencies and Distal Glycogenoses reported in the last 15 years, a variety of problems remain unsolved. In fact, genotype-phenotype correlation is still weak and no therapy is available at present. More patients and extensive studies in this field are necessary to better understand the pathophysiology of these disorders and to suggest appropriate treatment options, as recently obtained in Pompe disease or Acid Maltase deficiency (GSD type II) (10).

References

1 Nakajima H, Raben N, Hamaguchi T, et al. Phosphofructokinase deficiency; past, present and future. Curr Molecular Med 2002;2:197-212.

2 Hirano M, Di Mauro S. Metabolic myopathies. Motor disorders. Philadelphia: Lippincott Williams & Wilkins 1999;10:123-37.

3 Di Mauro S, Hays AP, Tsujino S. Metabolic disorders affecting muscle. Myology. New York: McGraw-Hill 2004;55:1535-58.

4 Musumeci O, Bruno C. Mongini T, et al. Clinical, biochemical and genetic features of 5 Italian unrelated families with Phosphofructokinase (PFK) deficiency. Neurology 2007, (abstract at the 59° AAN Meeting, in press).

5 Fujii H, Miwa S. Other erythrocyte enzyme deficiencies associated with non-haematological symptoms: phosphoglycerate kinase and phosphofructokinase deficiency. Baillieres Best Pract Res Clin Haematol 2000;13:141-8.

6 Oh SJ, Park KS, Ryan HF, et al. Exercise-induced cramp, myoglobinuria, and tubular aggregates in phosphoglycerate mutase deficiency. Muscle Nerve 2006;34:572-6.

7 Toscano A, Tsujino S, Vita G, et al. Molecular basis of muscle phosphoglycerate mutase deficiency (PGAM-M) in the Italian kindred. Muscle Nerve 1996;19:1134-7.

8 Kreuder J, Borkhardt A, Repp R, et al. Inherited metabolic myopathy and hemolysis due to a mutation in aldolase A. New Engl J Med 1996;334:1100-4.

9 Comi GP, Fortunato F, Lucchiari S, et al. β-Enolase deficiency, a new metabolic myopathy of distal glycolysis. Ann Neurol 2001;50:202-7.

10 Winkel LPF, Van der Hout JMP, Kamphoven JHJ, et al. Enzyme Replacement Therapy in late onset Pompe's disease: a three-year follow-up. Ann Neurol 2004;55:495-502.