Pompe disease (glycogen storage disease type II) : clinical features and enzyme replacement therapy

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Abstract

Pompe disease (glycogen storage disease type II, acid maltase deficiency) is a progressive metabolic myopathy caused by deficiency of the lysosomal enzyme acid α-glucosidase. This leads to an accumulation of glycogen in various tissues of the body, most notably in skeletal muscle. The disease has an autosomal recessive inheritance with a predicted frequency of 1 :40.000. Pompe disease is a continuous spectrum but for clinical practice different subtypes are recognized. The classic infantile form of the disease occurs in infants (shortly after birth) and is characterized by generalized hypotonia, failure to thrive, and cardiorespiratory failure. Patients usually die within the first year of life. The non-classic or late-onset form of the disease may occur at any age in childhood or adulthood. It presents predominantly as a slowly progressive proximal myopathy, with or without respiratory failure. Enzyme replacement therapy (ERT) is under study as treatment for the disease. The first results with recombinant human α-glucosidase are promising and a registered therapy seems near. Beneficial effects of ERT have been reported both in patients with the classic infantile form as well as in patients with the non-classic or late-onset form of the disease. The best therapeutic results are achieved when ERT is started early in the course of symptom development and before irreversible muscular damage has occurred. Detailed knowledge about the natural course of the disease becomes more and more essential to determine the indication and timing of treatment.

Key words : α-glucosidase ; acid maltase deficiency ; lysosomal storage disorders ; natural course ; enzyme replacement therapy.

Introduction

Pompe disease (glycogen storage disease type II, acid maltase deficiency) is a lysosomal storage disorder caused by the deficiency of the enzyme acid α-glucosidase (Hirschhorn and Reuser, 2001). This deficiency leads to accumulation of glycogen in different tissues of the body, but most severely affects skeletal muscle. In this manuscript the history, pathophysiology, diagnosis, clinical features, therapy and future perspectives for the disease are discussed.

History

Pompe disease was named after the Dutch pathologist dr. J.C. Pompe, who presented the first case report in 1932. It concerned a patient with a hypertrophic cardiomyopathy and progressive generalized muscle weakness who died at the age of 7 months. The crucial observation made by dr. Pompe was that the infant's symptoms were associated with massive storage of glycogen in virtually all tissues, but most prominent in heart and skeletal muscle. In 1963 it was discovered that Pompe disease was due to a deficiency of the lysosomal enzyme acid α-glucosidase. This made Pompe disease the first recognized lysosomal storage disorder. Presently, over 40 lysosomal storage disorders are known. Each specific disease results from storage of a substrate in the lysosomal compartment of the cell. The majority of the lysosomal storage disorders is caused by the deficiency of a single lysosomal protein.

Pathophysiology

Pompe disease is caused by deficiency of the lysosomal enzyme acid α-glucosidase due to various mutations in the acid α-glucosidase gene (GAA). This results in intra-lysosomal accumulation of glycogen in virtually all body tissues, leading to progressive and irreversible structural damage, most notably in skeletal muscle.

Incidence and inheritance

Pompe disease is an inherited autosomal recessive disease (Martiniuk *et al.*, 1998 ; Ausems *et al.*, 1999b ; Hirschhorn and Reuser, 2001). The reported incidence varies depending on the ethnic group and geographic area studied. The estimated frequency in the Western world is 1 : 40.000. The GAA gene is located on chromosome 17q25.3. At

present approximately 150 mutations in the GAA gene are known. Frequent mutations among Caucasian people are c.2481 + 102_2646 + 31del (del exon18), c.525del (delT525), and c.925G > A (Kroos *et al.*, 1995 ; Kroos *et al.*, 1998). The most common mutation of all probably is c.-32-13T > G (IVS1-13T>G), which is estimated to occur in 70% of patients with non-classic Pompe disease.

Diagnostic procedures

Diagnostic procedures in patients with suspected Pompe disease can include aspecific measurements like serum Creatine Kinase (CK) value and evaluation of muscle tissue, or specific diagnostic procedures like measurement of α-glucosidase activity in various tissues (leukocytes, fibroblasts, muscle tissue) and DNA analysis.

In patients with classic infantile Pompe disease, chest X-ray and echocardiography can be used to demonstrate the characteristic cardiomegaly. Echocardiography reveals an increased thickness of the left ventricular posterior wall and interventricular septum, which may lead to outflow tract obstruction and subsequent cardiac failure. In general, attention should also be paid to pulmonary status by means of pulmonary function testing and blood gas analysis to diagnose (nocturnal) hypoventilation.

Routine laboratory measurements

More than 90% of all patients with Pompe disease show an elevated CK value (Ausems *et al.*, 1999a ; Winkel *et al.*, 2005). In accordance to this ASAT, ALAT, and LDH also are often elevated (to a lesser extent). A normal CK value does not exclude the disease.

Measurement of α-glucosidase activity

Acid α-glucosidase is present in all tissues and cells. For diagnostic purposes the enzyme activity is usually measured in fibroblasts, leukocytes/lymphocytes or muscle tissue. Measurement of residual α-glucosidase activity is most reliably performed in cultured fibroblasts. Determination of acid α-glucosidase activity in total leukocytes is error prone because of the interference of maltase-glucoamylase. Recently, a new diagnostic assay was developed in which the maltase-glucoamylase activity is eliminated, enabling a reliable diagnosis of Pompe disease in total leukocytes (Okumiya *et al.*, 2005).

Muscle biopsy

Muscle biopsies mostly reveal vacuolar glycogen storage. The glycogen contained in the vacuoles can be visualized with Periodic Acid Schiff (PAS) staining. The vacuoles also show an increased staining for acid phosphatase, indicating an increased lysosomal compartment.

The intracellular accumulation of glycogen causes displacement or compression of normal cellular organelles, leading to damage of muscle fibers. Ultimately this may lead to replacement of muscle fibers by connective tissue and fat. In the classic infantile form vacuolization is eventually present in all muscle fibers. In the non-classic phenotype muscles are involved more heterogeneously. In about 20% of patients with non-classic Pompe disease, muscle biopsy shows neither glycogen accumulation nor other morphologic abnormalities (Winkel *et al.*, 2005).

Urine analysis

A common biochemical characteristic in Pompe disease is the presence of a tetrasaccharide in urine on thin layer chromatography. The origin of this tetrasaccharide band is unknown. It is suggested that undegraded glycogen is released into the circulation and degraded by serum amylase to the oligosaccharide present in urine.

Clinical features and natural course

In the past, different nomenclature has been used to describe clinical subtypes. Names found in literature are : infantile, infantile-onset, non-typical infantile, childhood, juvenile, adult, late-onset, classic, non-classic, muscular variant, adolescent. We now conclude Pompe disease presents a continuous spectrum of phenotypes with variation in age of onset, rate of disease progression and severity of symptoms (Hirschhorn and Reuser 2001 ; Engel *et al.* 2004). For clinical practice it is useful to divide the spectrum in the classic infantile subtype of Pompe disease and the non-classic or late-onset subtype of Pompe disease (which then comprises all clinical phenotypes other than the classic infantile subtype). In general disease severity relates to the level of residual enzyme activity.

Classic infantile Pompe disease

Patients with classic infantile Pompe disease have virtually no residual α-glucosidase activity caused by a set of two fully deleterious mutations in the acid α-glucosidase gene. Infants develop symptoms within the first months of life. Poor motor development and failure to thrive are noticed first. Patients usually do not reach major motor milestones like rolling over, sitting and standing due to generalized hypotonia and progressive muscular weakness.

Patients with the classic infantile form of Pompe disease have an average life expectancy of less than

a year due to cardiac and respiratory failure (Van den Hout *et al.*, 2003).

NON-CLASSIC OR LATE-ONSET POMPE DISEASE

Non-classic Pompe disease may present in infancy, or at juvenile or adult age. It is dominated by a slowly progressive proximal myopathy with involvement of respiratory muscles, leading to respiratory failure in a subset of patients. It is a very heterogeneous group of patients that differs in (age of) presentation and disease progression.

A recent literature review and a cross-sectional study in 255 patients showed that the first symptoms in patients with non-classic Pompe disease were mostly related to mobility and limb-girdle weakness (Winkel *et al.*, 2005 ; Hagemans *et al.*, 2005b). The most frequently mentioned problems were running, performing sports, climbing stairs, rising from an armchair and lying position and walking. Respiratory problems were reported by 11% of the patients as their first complaints. Fatigue and pain were also frequently mentioned. More than 50% of the patients indicated having trouble with mobility as a child. Severe loss of pulmonary function may occur even in patients with minor mobility problems. Various case reports have mentioned respiratory insufficiency as the presenting symptom (2% of the patients) (Laforet *et al.*, 2000 ; Winkel *et al.*, 2005 ; van der Ploeg, 2005). It is therefore useful to monitor pulmonary function in patients with Pompe disease regularly independent of limb-girdle muscular function. A significant postural drop may be found due to diaphragmatic weakness. Therefore pulmonary function should be measured in sitting and in supine position. Polysomnography and blood gas analysis may be helpful to diagnose nocturnal hypoventilation.

In this non-classic or late-onset form of Pompe disease, progression is more slowly. The course of the disease can vary substantially between patients with respect to age of onset and rate of disease progression. Although there is a (weak) relation between pulmonary function and motor function (Pellegrini *et al.*, 2005), no clear sequence could be detected in the involvement of respiratory and skeletal muscles (Laforet *et al.*, 2000 ; Mellies *et al.*, 2001 ; Pellegrini *et al.*, 2005 ; Hagemans *et al.*, 2005a). Disease severity, as measured by the percentage of patients requiring a wheelchair or ventilator, is mainly determined by disease duration and not by age. However, a subset of children (25%) under the age of 15, had a more severe course of the disease, requiring intensive respiratory, ambulatory (wheelchair use) and nutritional support (Hagemans *et al.*, 2005a).

In the course of the disease many patients develop respiratory problems due to respiratory muscle weakness, and approximately one third finally requires artificial ventilation (Winkel *et al.*, 2005).

Respiratory failure is the most frequently reported cause of death.

Therapeutic measures

First of all, supportive/symptomatic treatment such as physiotherapy has to be taken into account. Respiratory insufficiency should be treated by installation of proper respiratory support by means of (non)invasive ventilation. This may help to improve the patient's quality of life and to prevent incidents of acute respiratory failure (van der Ploeg, 2005).

ENZYME REPLACEMENT THERAPY (ERT)

The clinical application of enzyme replacement therapy for Pompe disease is under investigation since January 1999. Promising results were reported, first with recombinant human acid alpha-glucosidase extracted from the milk of transgenic rabbits and later with the same enzyme produced in genetically engineered Chinese Hamster Ovary (CHO) cells. The therapeutic approach of ERT is to supplement the deficiency of α-glucosidase by intravenous administration of highly purified enzyme, finding its way to the lysosomes via endocytosis. The same type of treatment has been applied in other lysosomal storage disorders (e.g. Fabry disease, Gaucher disease, Mucopolysaccharidosis type I), whereby recombinant human enzymes are used and produced in genetically modified animal or human cells.

EFFECT OF ERT IN CLASSIC INFANTILE POMPE DISEASE

In 1999 a first study was performed in four patients with classic infantile Pompe disease. Two patients started treatment early in the course of the disease (age 2.5 and 3 months old), two other patients started treatment in an end-stage of the disease after considerable loss of muscle function. A significant effect was found on cardiac hypertrophy, which resulted in improved cardiac function in all patients. In accordance with this a remarkable increase of survival was seen (Van den Hout *et al.*, 2001 ; Van den Hout *et al.*, 2004). All patients reached the age of 4 years, whereas life expectancy of untreated patients is less than one year. One patient died at the age of four after a short period of untraceable fever, unstable blood pressure and coma. The other three patients are still alive to date. The effect on respiratory function was dependent on the condition of the patients at start of therapy. Respiratory insufficiency could be prevented in the best performing patient, but could not be reversed in the patients with end-stage disease. The progress in motor function varied considerably among the patients. In the two patients who had started ERT in an end-stage of disease no gain in motor function

was found, as was measured using the Alberta Infant Motor Scale (AIMS), whereas in the patients who started early in the course of the disease an increase in motor function was seen. The youngest and best performing patient, who started ERT at 2.5 months of age learned to walk unsupported at 16 months and the number of PAS positive vacuoles in the muscle biopsy decreased (Van den Hout *et al.*, 2004).

The few other studies with ERT in patients with classic infantile Pompe disease described in literature show similar results. ERT is generally well tolerated, safe and induces a good response of the heart and a significant increase in survival. The effect on motor development and pulmonary function is variable (Amalfitano *et al.*, 2001 ; Klinge *et al.*, 2005a ; Klinge *et al.*, 2005b).

NON-CLASSIC OR LATE-ONSET POMPE DISEASE

Experience with ERT in older children and adults with Pompe disease is still limited. In 1999 we started Enzyme replacement Therapy in two adolescents and one adult (11 years, 16 years and 32 years of age). These three patients were all wheelchair bound at start of therapy and two of them used artificial ventilation. The two most affected patients remained dependent on respiratory and ambulatory (wheelchair) support. There was no real gain in vital capacity, however, their pulmonary function did not deteriorate further. These patients showed minimal improvements in muscle strength. All patients however reported an improvement in quality of life. The initially least affected patient showed an impressive response to ERT. At start of therapy this patient was wheelchair bound and not able to stand or walk. After 72 weeks of therapy he could raise with difficulty from a chair and 96 weeks after start of ERT he could walk, run and play football. This patient showed a steady increase in pulmonary function according to age. The CK level dropped in all patients (in two patients CK level reached normal values) and a repeated muscle biopsy in the best performing patient showed clear improvement in muscle morphology (Winkel *et al.*, 2004).

The overall conclusion of intravenous enzyme replacement therapy is that it can be administered safely. The remarkable increase in survival in infants is due to the favorable response of the heart, thus preventing cardiac failure. For improvement of motor function (and effect on skeletal muscle) it is essential to start ERT before irreversible damage has been done. This also seems to account for preservation of pulmonary function. Longer follow-up and treatment of larger groups of patients at different ages are required to learn the full effects of enzyme therapy. At present, a randomized controlled trial is being performed in patients with non-classic Pompe disease.

Future perspectives : Gene therapy ?

Gene therapy for Pompe disease is still in the pre-clinical phase. The rationale of gene therapy is to transfer a copy of the unaffected acid α-glucosidase cDNA to the patients' somatic cells, so that they start producing enzyme. Until now three types of vectors have been used in vitro and in animal models including knock-out mice and quail with Pompe disease. Adenovirus (Ad), Adeno-associated virus (AAV) and hybrid Ad-AAV vector systems. Besides, various ways of administration have been attempted, intravenously, intracardiac and intramuscular. Most procedures have shown local or more generalized effects in terms of increased α-glucosidase activity followed by short or long term correction of the glycogen storage in one or several target tissues (Ellinwood *et al.*, 2004 ; Franco *et al.*, 2005 ; Sun *et al.*, 2005). None of these procedures has until now been tested in clinical studies since hurdles related to general safety and long-term efficacy have to be overcome first.

Conclusion

Pompe disease presents a continuous clinical spectrum, with the severe classic infantile form of the disease, characterized by hypotonia, failure to thrive, and cardiorespiratory failure, on one end of the spectrum and the non-classic or late-onset form of the disease, presenting predominantly as a slowly progressive proximal myopathy with or without respiratory failure, on the other end. Enzyme replacement therapy is under development and beneficial effects have been reported in patients with the classic infantile form as well as milder forms of the disease. These first studies with enzyme replacement therapy indicate that the best results are achieved when treatment is started early in the course of the disease, before irreversible damage has occurred. Therefore, detailed knowledge of the natural course of the disease and standardized follow-up of the patients, both before and after start of treatment, is important to install proper supportive care and to decide when to start therapy. Timely start of enzyme replacement therapy seems crucial to obtain the most optimal outcome.

REFERENCES

AMALFITANO A., BENGUR A. R., MORSE R. P., MAJURE J. M., CASE L. E. *et al.* Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II : results of a phase I/II clinical trial. *Genet. Med.*, 2001, **3** : 132-138.

AUSEMS M. G., LOCHMAN P., VAN DIGGELEN O. P., PLOOS VAN AMSTEL H. K., REUSER A. J. *et al.* A diagnostic protocol for adult-onset glycogen storage disease type II. *Neurology*, 1999a, **52** : 851-853.

AUSEMS M. G., VERBIEST J., HERMANS M. P., KROOS M. A., BEEMER F. A. et al. Frequency of glycogen storage disease type II in The Netherlands : implications for diagnosis and genetic counselling. Eur. J. Hum. Genet., 1999b, 7 : 713-716.

ELLINWOOD N. M., VITE C. H., HASKINS M. E. Gene therapy for lysosomal storage diseases : the lessons and promise of animal models. J. Gene Med., 2004, 6 : 481-506.

FRANCO L. M., SUN B., YANG X., BIRD A., ZHANG H. et al. Evasion of immune responses to introduced human acid alpha-glucosidase by liver-restricted expression in glycogen storage disease type II. Mol. Ther., 2005, 12 : 876-884.

HAGEMANS M. L., WINKEL L. P., HOP W. C., REUSER A. J., VAN DOORN P. A. et al. Disease severity in children and adults with Pompe disease related to age and disease duration. Neurology, 2005a, 64 : 2139-2141.

HAGEMANS M. L., WINKEL L. P., VAN DOORN P. A., HOP W. J., LOONEN M. C. et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. Brain, 2005b, 128 : 671-677.

HIRSCHHORN R., REUSER A. J. J. Glycogen storage disease type II ; acid-glucosidase (acid maltase) deficiency. In : SCRIVER C. R., BEAUDET A. L., SLY W., VALLE D. (eds.). The metabolic and molecular bases of inherited disease. 8th ed. New York : McGraw-Hill, 2001, 3389-3420.

KLINGE L., STRAUB V., NEUDORF U., SCHAPER J., BOSBACH T. et al. Safety and efficacy of recombinant acid alpha-glucosidase (rhGAA) in patients with classical infantile Pompe disease : results of a phase II clinical trial. Neuromuscul. Disord., 2005a, 15 : 24-31.

KLINGE L., STRAUB V., NEUDORF U., and VOIT T. Enzyme replacement therapy in classical infantile pompe disease : results of a ten-month follow-up study. Neuropediatrics, 2005b, 36 : 6-11.

KROOS M. A., VAN DER KRAAN M., VAN DIGGELEN O. P., KLEIJER W. J., REUSER A. J. et al. Glycogen storage disease type II : frequency of three common mutant alleles and their associated clinical phenotypes studied in 121 patients. J. Med. Genet., 1995, 32 : 836-837.

KROOS M. A., VAN LEENEN. D., VERBIEST J., REUSER A. J., HERMANS M. M. Glycogen storage disease type II : identification of a dinucleotide deletion and a common missense mutation in the lysosomal alpha-glucosidase gene. Clin. Genet., 1998, 53 : 379-382.

LAFORET P., NICOLINO M., EYMARD P. B., PUECH J. P., CAILLAUD C. et al. Juvenile and adult-onset acid maltase deficiency in France : genotype-phenotype correlation. Neurology, 2000, 55 : 1122-1128.

MARTINIUK F., CHEN A., MACK A., ARVANITOPOULOS E., CHEN Y. et al. Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease. Am. J. Med. Genet., 1998, 79 : 69-72.

MELLIES U., RAGETTE R., SCHWAKE C., BAETHMANN M., VOIT T. et al. Sleep-disordered breathing and respiratory failure in acid maltase deficiency. Neurology, 2001, 57 : 1290-1295.

OKUMIYA T., KEULEMANS J. L., KROOS M. A., VAN DER BEEK N. M., BOER M. A. et al. A new diagnostic assay for glycogen storage disease type II in mixed leukocytes. Mol. Genet. Metab., 2005.

PELLEGRINI N., LAFORET P., ORLIKOWSKI D., PELLEGRINI M., CAILLAUD C. et al. Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease. Eur. Respir. J., 2005, 26 : 1024-1031.

SUN B., ZHANG H., FRANCO L. M., BROWN T., BIRD A. et al. Correction of glycogen storage disease type II by an adeno-associated virus vector containing a muscle-specific promoter. Mol. Ther., 2005, 11 : 889-898.

VAN DEN HOUT H. M., HOP W., VAN DIGGELEN O. P., SMEITINK J. A., SMIT G. P. et al. The natural course of infantile Pompe's disease : 20 original cases compared with 133 cases from the literature. Pediatrics, 2003, 112 : 332-340.

VAN DEN HOUT J. M., KAMPHOVEN J. H., WINKEL L. P., ARTS W. F., DE KLERK J. B. et al. Long-term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk. Pediatrics, 2004, 113 : e448-e457.

VAN DEN HOUT J. M., REUSER A. J., DE KLERK J. B., ARTS W. F., SMEITINK J. A. et al. Enzyme therapy for pompe disease with recombinant human alpha-glucosidase from rabbit milk. J. Inherit. Metab. Dis., 2001, 24 : 266-274.

VAN DER PLOEG A. T. Monitoring of pulmonary function in Pompe disease : a muscle disease with new therapeutic perspectives. Eur. Respir. J., 2005, 26 : 984-985.

WINKEL L. P., HAGEMANS M. L., VAN DOORN P. A., LOONEN M. C., HOP W. J. et al. The natural course of non-classic Pompe's disease ; a review of 225 published cases. J. Neurol., 2005, 252 : 875-884.

WINKEL L. P., VAN DEN HOUT J. M., KAMPHOVEN J. H., DISSELDORP J. A., REMMERSWAAL M. et al. Enzyme replacement therapy in late-onset Pompe's disease : a three-year follow-up. Ann. Neurol., 2004, 55 : 495-502.

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