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Genetic counseling in Pompe disease

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Pompe disease is caused by glycogen accumulation due to a deficiency of the lysosomal acid alpha-glucosidase enzyme by which it is degraded. It is a rare disease, accounting for 1:40.000 births. It is inherited as an autosomal recessive trait so that a couple presents a recurrent risk of 25% to have a child affected, at each pregnancy. The diagnosis could be achieved by biochemical and/or molecular testing. Carrier detection and prenatal diagnosis are available when the molecular defect is known.

Key words: Pompe disease, genetic counselling, prenatal diagnosis

Introduction

Pompe disease, also known as glycogen storage disease type II (GSDII), is caused by glycogen accumulation due to a deficiency of the lysosomal acid alpha-glucosidase enzyme by which it is degraded (1).

A total or partial deficiency of this enzyme causes lysosomal glycogen storage leading to a systemic disorder characterized by cardiomyopathy, muscle weakness, hypotonia, and respiratory disorders (1-4). The severity of the disease and the age of onset are related to the degree of enzyme deficiency. *Early onset* (or infantile) *Pompe disease* is the result of complete or near complete deficiency of GAA. Symptoms begin in the first months of life, with feeding problems, poor weight gain, muscle weakness, floppiness, and head lag. Respiratory difficulties are often complicated by lung infections. The heart is grossly enlarged. If untreated, patients die within one year (3, 4).

Late onset (or juvenile/adult) *Pompe disease* is the result of a partial deficiency of GAA. The onset can be as early as the first decade of childhood or as late as the sixth decade of adulthood. The primary symptom is muscle weakness progressing to respiratory weakness and death from respiratory failure, after a course lasting several years. The heart is usually not involved.

The standard test for conclusively diagnosing Pompe disease is an enzyme assay, which measures the levels of the GAA enzyme activity. People affected by the disease have lower than normal enzyme activity, usually in the range of 1-40% of normal levels. A diagnosis of Pompe disease can be confirmed by screening for the common genetic mutations on DNA blood samples (3-7).

Genetics

The GAA gene (MIM# 606800) located in the human chromosome 17q25.2-25.3 produces an inactive 110 kD precursor which is transported to the lysosomal compartment and processed into the 95 kD intermediate and the fully active forms of 76 and 70 kD (1, 10). More than 200 mutations in the GAA gene have been described up to date (http://www2.eur.nl/fgg/ch1/pompe) (8-10).

GSD II (Pompe disease) is inherited as an autosomal recessive trait. The most common inheritance scenario which results in Pompe disease is when both parents are carriers, usually asymptomatic. In this case, in each pregnancy the chances are:

- 1 in 4 (25%) that the child will receive two defective genes and thus inherit the disease
- 2 in 4 (50%) that the child will inherit only one defective gene and become a carrier
- 1 in 4 (25%) that the child will be completely unaffected (Fig. 1).

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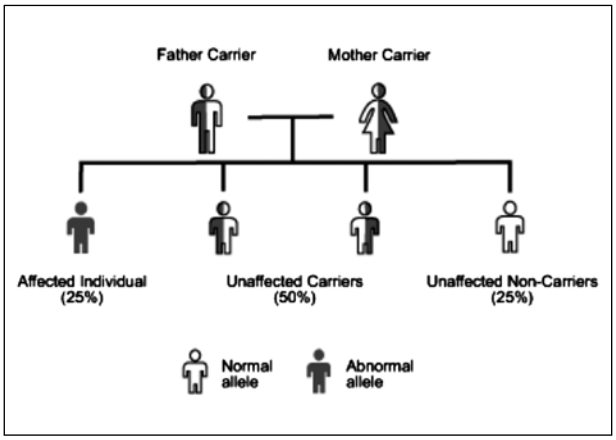

Figure 1. Characteristics of an autosomal recessive inheritance.

Far less common inheritance scenarios include:

- If both parents have Pompe disease, then every child will inherit the disease
- If one parent has the disease and the other is a carrier, each child has a 50% chance of inheriting the disease and a 50% chance of being a carrier

Historically, children with classic infantile Pompe disease do not survive enough to reproduce, although the availability of therapy may alter this expectation through improved fitness of those individuals who respond to enzyme replacement therapy. In contrast, many individuals with later-onset disease survive into their 50's and 60's. The offspring of an individual with a later-onset form of GSD II are obligate carriers for a disease-causing mutation in GAA. Furthermore, each sib of an obligate heterozygote is at a 50% risk of being a carrier (11-14).

Carrier detection

In families in which a diagnosis of Pompe disease has been made, there is a risk that relatives may also have the disease or be carriers. Therefore it is important to test siblings of an affected child. Carrier detection can be achieved by two main genetic approach: biochemical testing, and molecular testing (7, 15, 16).

Biochemical testing

Measurement of acid alpha-glucosidase enzyme activity in skin fibroblasts, muscle, or peripheral blood leukocytes is unreliable for carrier determination because of significant overlap in residual enzyme activity levels between obligate carriers and the general (non-carrier) population.

Molecular testing

Mutation analysis is the only way to identify carriers, who do not have the disease, but "carry" the gene defect and may pass it on to their own children (15, 16).

Genetic counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the mode of inheritance and genetic risks to other family members as well as information about natural history, treatment and available consumer-oriented resources.

It is appropriate to offer sibs of a proband either testing of GAA enzyme activity or molecular genetic testing (if the disease-causing mutations have been identified in affected family members) so that morbidity and mortality can be reduced by early diagnosis and treatment with Enzyme Replacement Therapy (ERT) (17, 18). Similarly it is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being carriers.

Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible only if the disease-causing mutations in the family are yet identified. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

An informed consent (IC) is requested from all individuals performing molecular genetic testing. The IC will contain the possibility to store the biological sample in a genetic biobank for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals (19).

Prenatal diagnosis

It can be offered, on request, to the couples who already had a child affected, or to couples at risk for an affected child. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis – usually performed at approximately 15 to 18 weeks' gestation – or chorionic villus sampling (CVS), performed at approximately 10 to 12 weeks' gestation. As indicated above, we stress the concept that both disease-causing alleles of an affected

family member must be identified before performing the prenatal testing.

Prenatal testing is also possible by measuring GAA enzyme activity in uncultured chorionic villi or amniocytes (biochemical testing); however molecular testing remains the preferred method in the case of known familial mutations (20).

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified.

Newborn screening

It can be achieved by measuring acid α-glucosidase activity in dried blood spots of newborns. A large-scale newborn screening pilot program was conducted between October 2005 and March 2007 in Taiwan, involving spots of ~45% of newborns (21). Out of the 132.538 newborns screened, 1093 (0.82%) were retested, and 121 (0.091%) recalled for additional evaluation. Pompe disease was confirmed in 4 newborns. This number was similar to the number of infants who received a diagnosis of Pompe disease in the control group (n = 3); however, newborn screening resulted in an earlier diagnosis of Pompe disease (<1 month old compared with 3 to 6 months old in the control group). This was the first large-scale study to show that newborn screening for Pompe disease is feasible and allows for earlier diagnosis and earlier treatment.

Conclusions and key points for parents

- A diagnosis of Pompe disease can be overwhelming and raise many questions.
- Genetic counselors are health care professionals specially trained to educate families on the disease's inheritance patterns and risks, as well as to support them through testing and family-planning decisions.
- Couples should be aware that the results of prenatal testing cannot predict the age of onset, clinical course, or degree of disability.
- Parents must be reassured that not all infants identified as having low GAA activity through newborn screening will have Pompe disease.
- If the infant will develop Pompe disease, treatment is available which may ameliorate the clinical symptoms of the disorder.

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