Danon disease

Authors: Doctors Roseline FROISSART and Irène MAIRE
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Abstract

Danon disease (or "glycogen storage disease due to LAMP-2 deficiency" or "Lysosomal glycogen storage disease with normal acid maltase activity") is a lysosomal glycogen storage disease due to LAMP-2 (Lysosomal-Associated Membrane Protein 2) deficiency. The precise functions of LAMP-2 are not known but it seems to play an important role in autophagy. Danon disease is an X-linked disorder. The disease is extremely rare as about 15 male cases only have been proven to date. Typically, the disease begins in males after the first decade. Severe cardiomyopathy and variable skeletal muscle weakness are constant features and mental retardation is very frequently associated. Both sexes may be severely affected, but females generally present with a later onset. Four early onset cases of autophagic vacuolar myopathy have been reported but Danon disease was excluded in the 2 studied cases. The biological diagnosis relies on the finding of a normal or elevated acid maltase activity and the study of a muscle biopsy showing large vacuoles (with a high glycogen content and cytoplasmic degradation products) and LAMP-2 deficiency by immunohistochemistry. Several mutations have been identified in the LAMP-2 gene, localised in Xq24. Antenatal diagnosis will be easily performed by DNA analysis. No specific therapy is available. Only cardiac supportive therapy is given to patients and one patient underwent a successful heart transplant.

Keywords
Danon disease, cardiomyopathy, vacuolar myopathy, lysosomal glycogen storage disease, LAMP-2 deficiency, autophagy.

Disease name and synonyms
Danon disease is also referred to as "glycogen storage disease due to LAMP-2 deficiency" or "Lysosomal glycogen storage disease with normal acid maltase activity".

Excluded diseases
X-linked vacuolar myopathy with excessive autophagy: XMEA (OMIM 310440).
Glycogenosis type II (OMIM 232300).

http://www.orpha.net/data/patho/GB/uk-Danon.pdf
Diagnosis criteria/definition
Danon disease is an X-linked recessive lysosomal glycogen storage disease with normal acid maltase caused by mutations in the Lysosomal-Associated Membrane Protein 2 or LAMP-2 gene (Nishino et al. 2000).

Differential diagnosis
**Glycogenosis type II (Pompe disease)**
Danon disease differs from juvenile or adult forms of glycogenosis type II by the severe cardiac involvement, the frequent association with mental retardation, the absence of diaphragmatic involvement, the autosomal recessive inheritance and the normal activity of acid maltase (Verloes et al. 1997, Nishino et al. 2000).

**X-linked vacuolar myopathy with excessive autophagy**
The clinical course of Danon disease differs from the initial description of this condition by Saviranta et al. (1988) and Kalimo et al. (1988) by the presence of cardiac and neural involvement. The gene responsible for XMEA was mapped to Xq28 (Villard et al. 2000). Distinct pathologic features in XMEA patient's muscle include normal immunostaining with antibodobodies against LAMP-2 and intense deposition of complement C5b-9 surrounding muscle fibers and multilayered basal lamina (Yamamoto et al. 2001). Similar findings have been found in the muscle biopsy of the early onset case of lysosomal storage disease without acid maltase deficiency described by Morisawa et al. (1998). However, it is not known to date if this infantile form and XMEA are allelic disorders (Yamamoto et al. 2001).

**Other autophagic vacuolar myopathy (AVM) have been described.** Infantile AVM (Verloes et al. 1997, Morisawa et al. 1998) presented as hypotonia during early infancy with mild cardiac involvement. In these cases, LAMP-2 was present in skeletal muscle and no alteration was found in the LAMP-2 gene (Yamamoto et al. 2001). Features of AVM were also reported in a case of fetal hydrops (Atkin et al. 1984) and a case with early cardiomyopathy, dysmorphism and hypolony (Dayan et Renaud 2001). In these 2 cases LAMP-2 was not studied. A late-onset AVM with multiorgan involvement and presence of LAMP-2 was also reported (Kaneda et al. 2003).

Prevalence
The disease is extremely rare and approximately forty suspected cases have been reported (Verloes et al. 1997). To date, only fifteen male cases have been proven (Nishino et al. 2000, Mundy et al. 2001, Beesley et al. 2001, Horvath et al. 2003, Sugie et al. 2003).

Clinical description
Danon et al. (1981) reported two unrelated 16-years old boys with hypertrophic cardiomyopathy, proximal muscle weakness and mental retardation. Verloes et al. (1997) collated 40 cases of highly likely late onset cardioskeletal “pseudo-Pompe” disease. A cardiomyopathy was observed in all cases but one. Typically, the disease begins in males after the first decade. Sudden arrhythmia was the reason of death in early adulthood for 7 males. Muscular involvement was observed in most cases ranging from severe proximal myopathy to mild weakness. Mental retardation was frequent but was not a constant feature and was variable. Both sexes may be severely affected (Byrne et al. 1986), but females generally present with a later onset. The median age at diagnosis was 16 years (range: 1.5 to 23 years) in 23 males and 30 years (range: 31 to 41 years) in 12 females. The median age at death was 18 years in 12 males and 37 years in 7 females.

In all proven cases with Lamp-2 mutations (Nishino et al. 2000, Mundy et al 2001, Beesley et al. 2001, Horvath et al. 2003), cardiomyopathy (confirmed by echocardiogram, electrocardiogram or both) was a constant feature, as skeletal muscle weakness (except in the case of Horvath et al. 2003). Mental retardation was frequent but not an obligatory feature.

Management
No specific curative treatment is available. Only cardiac supportive therapy is given to patients. One patient underwent a successful heart transplant: four years after transplant, he had occasional rejection episodes while his muscle condition remained stable as mental impairment (Dworzak et al. 1994).

Etiology
A deficiency of LAMP-2, a major constituent of the lysosomal membrane proteins is the primary defect in Danon disease (Nishino et al. 2000). The gene encoding LAMP-2 is located in Xq24 (Mattei et al. 1990). The complete cDNA has been isolated by Konecki et al. (1994). The Lamp-2 open reading frame consists of 1,233 nucleotides and encodes 410 aminoacids. The gene contains 9 exons. Exons 1-8 and part of exon 9 encode a luminal domain while the remainder of exon 9 encodes a transmembrane domain and a short cytoplasmic domain containing a lysosomal targeting signal (Gough et al. 1999). LAMP-2 is a heavily glycosylated protein with approximately 50% of its mass being carbohydrate. LAMP-2a and LAMP-2b result from alternative splicing of exon 9, in a tissue-

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http://www.orpha.net/data/patho/GB/uk-Danon.pdf
specific manner. LAMP-2b is more abundantly expressed than LAMP-2a in heart, skeletal muscle and brain at the mRNA level (Konecki et al. 1995, Furuta et al. 1999). Several mutations in the Lamp-2 gene have been found in Danon disease (Nishino et al. 2000, Mundy et al. 2001, Beesley et al. 2001, Horvath et al. 2003). All mutations were obviously severe leading to complete deficiency or trace amount of LAMP-2 protein by Western Blot analysis of patient’s muscle biopsies (Nishino et al. 2000), except the missense mutation W321R (Beesley et al. 2001). Interestingly the mother of this patient was unaffected, but she could not be studied. The function of LAMP-2 is unknown. It has been suggested that it could protect the lysosomal membrane from autodigestion, maintain the acidic environment of the lysosome and serve as an adhesion molecule when expressed on the plasma membrane (Lichter-Konecki et al. 1999). LAMP-2a acts as a receptor for a selective pathway of degradation of cytosolic proteins in lysosomes by chaperone-mediated autophagy (Cuervo and Dice 2000).

LAMP-2 deficient mice have been generated to investigate the functions of LAMP-2 (Tanaka et al. 2000, Saftig et al. 2001). LAMP-2 deficient mice manifest a vacuolar cardiomyopathy similar to human Danon disease. Ultrastructurally, an extensive accumulation of autophagic vacuoles is observed in many tissues. These mice provide a relevant model to study the role of LAMP-2 in autophagy and the consequences of altered autophagy in various tissues.

Diagnostic methods
The diagnosis is established on the basis of 4 criteria:
- a cardiomyopathy and a skeletal muscle weakness,
- a muscle biopsy showing a characteristic vacuolar myopathy with vacuoles containing glycogen and cytoplasmic degradation products
- and a normal or elevated acid maltase activity. The diagnosis needs to be confirmed in the muscle biopsy by immunohistochemistry showing LAMP-2 protein deficiency, whereas LAMP-2 is present in muscle biopsy of other autophagic vacuolar myopathy patients (Nishino et al. 2000, Yamamoto et al. 2001). Further confirmation can be brought by identification of LAMP-2 mutations.

Genetic counseling
Danon disease is an X-linked recessive disorder. The prognosis is difficult as the presentation is heterogeneous even within males of the same family (Dworzak et al. 1994): if the cardiomyopathy is a constant feature, mental retardation, although frequent, is not a constant finding and the degree of muscle involvement is highly variable. Females are also affected in most cases, although they present with a later onset: the age of diagnosis of cardiac symptoms was ranging between 20 and 45 years, but heart insufficiency was the reason of death in 6 females (Verloes et al. 1997).

Antenatal diagnosis
In severely affected families, antenatal diagnosis by DNA analysis can be performed easily if the mutation has been previously identified in the family.

Unresolved questions
The physiopathology of Danon disease is still poorly understood and further studies are necessary to better understand the role of LAMP-2 in the autophagic process and to analyse the consequences of an impaired autophagic pathway in the various tissues (Saftig et al. 2001).

Lysosomal glycogen storage disease with normal acid maltase is a genetically heterogeneous condition including several diseases, and Danon disease must be redefined to date on the basis of its genetic cause: LAMP-2 deficiency.

References


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