Danon disease

Authors: Doctors Roseline FROISSART[1] and Irène MAIRE
Creation Date: January 2001
Update : November 2004

Scientific Editor: Professor Jean-Marie SAUDUBRAY

[1]Service de biochimie pédiatrique, Hôpital Debrousse, 29 Rue Soeur Bouvier, 69322 Lyon Cedex 5, France. roseline.froissart@chu-lyon.fr

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).

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 antibobodies 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, dysmorphy and hypotony (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-

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 cardioskeletal myopathy 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
Atkin J., Snow J.W.Jr., Zellweger H., Rhead W.J. (1984). Fatal infantile cardiac glycogenosis without acid maltase deficiency presenting as congenital hydrops. (Letter). Eur. J. Pediatr. 142, 150.
Beesley C., Davies N., Mundy H., Lee P., Estruch E., Holton J., Hanna M., Elliott P., Lake B., Winchester B. (2001). Identification of mutations in the LAMP-2 gene in patients with Danon disease. Abstracts of the 13th ESGLD (European Study Group on Lysosomal Diseases) Woudschoten. The Netherlands, September 20-23 2001.
Byrne E., Dennett, X., Crotty B., Trounce I., Sands J.M., Hawkins R., Hammond J., Anderson S., Haan E.A., Pollard A. (1986). Dominantly inherited cardioskeletal myopathy with lysosomal glycogen storage and normal acid maltase levels. Brain 109, 523-536.
Cuervo A.M., Dice J.F. (2000). Regulation of Lamp2a Levels in the Lysosomal Membrane. Traffic 1, 570-583.
Danon M.J., Oh S.J., DiMauro S., Manaligod J.R., Eastwood A., Naidu S., Schliselfeld L.H. (1981). Lysosomal glycogen storage disease with normal acid maltase. Neurology 31, 51-57.

Dayan R.M., Renaud D.L. (2001). Early-onset lysosomal glycogen storage disease with normal acid maltase. J. Inher. Metab. Dis. 24, 504-506.
Dworzak F., Casazza F., Mora M., De Maria R., Gronda E., Baroldi G., Rimoldi M., Morandi L., Cornelio F. (1994). Lysosomal glycogen storage with normal acid maltase: a familial study with successful heart transplant. Neuromusc. Disord. 4, 243-247.
Furuta K., Yang X.-L., Chen J.-S., Hamilton S.R., August J.T. (1999). Differential expression of the lysosome-associated membrane proteins in normal human tissues. Arch. Biochem. Biophys. 365(1), 75-82.
Gough N.R., Zweife M.E., Martinez-Augustin O., Aguilar R.C., Bonifacino J.S., Fambrough D.M. (1999). Utilization of the indirect lysosome targeting pathway by lysosome-associated membrane proteins (LAMPs) is influenced largely by the C-terminal residue of their GYXXF targeting signals. J.Cell Sci. 112, 4257-4269.
Horvath J., Ketelsen U.P., Geibel-Zehender A., Boehm N., Olbrich H., Korinthenberg R., Omran H. (2003). Identification of a novel LAMP2 mutation responsible for X-chromosomal dominant Danon disease. Neuropediatrics 34(5), 270-273
Kalimo H., Savontaus M.L., Lang H., Paljarvi L., Sonninen V., Dean P.B., Katevuo K., Salminen A. (1988). X-linked myopathy with excessive autophagy : a new hereditary muscle disease. Ann. Neurol. 23, 258-265.
Kaneda D., Sugie K., Yamamoto A., Matsumoto H., Kato T., Nonaka I., Nishino I. (2003). A novel form of autophagic vacuolar myopathy with late-onset and multiorgan involvement. Neurology 61(1), 128-131.
Konecki D.S., Foetisch K., Schlotter M., Lichter-Konecki U. (1994). Complete cDNA sequence of human lysosome-associated membrane protein-2. Biochem. Biophys. Res. Commun. 205, 1-5.
Konecki D.S., Foetisch K., Zimmer K.P., Schlotter M., Lichter-Konecki U. (1995). An alternatively spliced form of the human lysosome-associated membrane protein-2 gene is expressed in a tissue specific manner. Biochem. Biophys. Res. Commun. 215, 757-767.
Lichter-Konecki U., Moter S.E., Krawisz B.R., Schlotter M., Hipke C., Konecki D.S. (1999). Expression patterns of murine lysosome-associated membrane protein 2 (Lamp-2) transcripts during morphogenesis. Differentiation 65, 43-58.
Mattei M.-G., Matterson J., Chen J.W., Williams M.A., Fukuda M. (1990) Two human lysosomal membrane glycoproteins, h-lamp-1 and h-lamp-2, are encoded by genes localized to chromosome 13q34 and chromosome Xq24-25, respectively. J. Biol. Chem. 265, 7548-7551.
Morisawa Y., Fujieda M., Murakami N., Naruse K., Okada T., Morita H., Sawada K., Miyazaki J., Kurashige T., Nonaka I. (1998). Lysosomal glycogen storage disease with normal acid maltase with early fatal outcome. J. Neurol. Sci. 160, 175-179.
Mundy H., Lee P., Davies N., Holton J., Hanna M., Elliott P., Beesley C., Estruch E., Winchester B. (2001). LAMP-2 deficiency in a Greek Cypriot family with hypertrophic cardiomyopathy. J. Inherit. Metab. Dis. 24 (Suppl. 2), 183-184.
Nishino I., Fu J., Tanji K., Yamada T., Shimojo S., Koori T., Mora M., Riggs J.E., Oh S.J., Koga Y., Sue C.M., Yamamoto A., Murakami N., Shanske S., Byrne E., Bonilla E., Nonaka I., DiMauro S., Hirano M. (2000). Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). Nature 406, 906-910.
Saftig P., Tanaka Y., Lüllmann-Rauch R., von Figura K. (2001). Disease model: LAMP-2 enlightens Danon disease. Trends Mol. Med. 7 (1), 37-39.
Saviranta P., Lindlof M., Lehesjoki A.-E., Kalimo H., Lang H., Sonninen V., Savontaus M.-L., de la Chapelle A. (1988). Linkage studies in a new X-linked myopathy, suggesting exclusion of DMD locus and tentative assignment to distal Xq. Am. J. Hum. Genet. 42, 84-88.
Sugie K., Koori T., Yamamoto A., Ogawa M., Hirano M., Inoue K., Nonaka I., Nishino I.(2003). Characterization of Danon disease in a male patient and his affected mother. Neuromuscul.Disord.13(9), 708-711.
Tanaka Y., Guhde G., Suter A., Eskelinen E.L., Hartmann D., Lüllmann-Rauch R., Janssen P.M., Blanz J., von Figura K., Saftig P. (2000). Accumulation of autophagic vacuoles and cardiomyopathy in LAMP-2-deficient mice. Nature 406, 902-906.
Verloes A., Massin M., Lombet J., Grattagliano B., Soyeur D., Rigo J., Koulischer L., Van Hoof F. (1997). Nosology of lysosomal glycogen storage diseases without in vitro acid maltase deficiency: delineation of a neonatal form. Am. J. Med. Genet. 72, 135-142.
Villard L., des Portes V., Levy N., Louboutin J.-P., Recan D., Coquet M., Chabrol B., Figarella-Branger D., Chelly J., Pellissier J.F., Fontes M. (2000). Linkage of X-linked myopathy with excessive autophagy (XMEA) to Xq28. Eur. J. Hum. Genet. 8, 125-129.
Yamamoto A., Morisawa Y., Verloes A., Murakami N., Hirano M., Nonaka I., Nishino I. (2001). Infantile autophagic vacuolar myopathy is distinct from Danon disease. Neurology 57, 903-905.