Danon Disease - NORD (National Organization for Rare Disorders)

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Danon Disease

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Synonyms of Danon Disease

- Antopol disease
- glycogen storage cardiomyopathy
- glycogen storage disease type IIB
- GSD IIB
- lysosomal glycogen storage disease without acid maltase deficiency
- pseudoglycogenosis II
- vacuolar cardiomyopathy and myopathy, X-linked

General Discussion

Danon disease is a rare genetic disorder characterized by an X-linked dominant inheritance pattern, as a result of which males are more severely affected than females. Among boys, the key features are diseased heart muscle (cardiomyopathy), weakness of the body muscles (skeletal myopathy) and intellectual disability ranging from mild learning problems to overt intellectual disability. In many males, the disease progresses until a heart transplant is required or death occurs in the second to third decade of life. Females are also affected, although usually more mildly, and often onset is delayed until they reach adulthood. However, some females will progress to being considered for cardiac transplantation during their second decade of life, similar to what is observed in males. Other features include heart arrhythmias, which can lead to a need for medications or a pacemaker, and eye disease affecting the retina; the retinal disease does not always affect vision, especially early in the disease. Danon disease is not usually evident at birth unless blood tests are done in a suspected case (i.e. a son born to a mother known to have the disease).

Signs & Symptoms

Symptoms of Danon disease vary from case to case and depend on gender. Boys usually show early signs of muscle problems (difficulty sitting or walking) and motor skills may be awkward or delayed. Intellectual disability is usually noticed by parents and/or teachers and can be quite mild. The development of heart disease can lead to further fatigue and shortness of breath. Visual complaints are also prevalent with serious color vision disturbances and near-complete loss of retinal pigment in some patients.

In general, young girls may have no symptoms and will report normal muscle strength and have normal intellect. As females age, symptoms of heart disease can begin to develop. Muscle symptoms are reported by some girls and women but overt findings of frank muscle weakness are usually absent.

Visual complaints may also be reported in women and can be an early feature of the disease, although manifestations are less severe than in men.

Clinical researchers believe that the skeletal muscle involvement in Danon disease preferentially involves the muscles of the back, shoulder, upper legs and the neck muscles. These are the proximal muscles; that is, those closest to the center of the body. Symptoms of weakness in these muscles can include back pain and difficulty raising one's arms over the head, getting out of a chair, or walking up steps. In a young boy, these problems may be suggested by problems meeting motor milestones (sitting, crawling, and walking, running). An experienced neurologist can recognize the extent of muscle disease by performing a physical examination.

The diseased heart muscle (cardiomyopathy) can lead to a thickened, stiff heart (hypertrophic cardiomyopathy) or to an enlarged heart (dilated cardiomyopathy). Hypertrophic cardiomyopathy is more common in males (approximately 90% hypertrophic and 10% dilated), whereas females are more apt to show features of dilated cardiomyopathy (approximately 50% hypertrophic and 50% dilated). Sometimes the cardiomyopathy can be the first sign of disease in male children. In both instances, problems with heart function and symptoms of heart failure (shortness of breath, fatigue, fluid gain) can occur. Death from the heart disease seems to occur frequently in males, especially as they reach the second and third decades of life. Heart transplantation has been performed successfully and can greatly improve symptoms and extend life.

The extent of intellectual disability in affected males has been described in some epidemiological studies. In the original description of Danon disease, the intellectual disability was classified as a form of mental retardation. However, it is clear that the majority of boys will be mildly affected cognitively, usually allowing them to achieve the ability to read, hold jobs, form relationships, and live independently. Furthermore, providing education and learning support may help some boys improve their intellectual functioning. In women, intellect appears to be normal, although very little information in the literature addresses this question.

Less prevalent symptoms also include liver and lung involvement, although these have not been studied extensively and might be secondary to muscle involvement (e.g. serum liver enzyme elevation and respiratory muscle weakness). Some speculation also exists on psychiatric disease, with some case reports detailing depression, psychosis, suicidal ideation, and attention-deficit hyperactivity disorder in Danon disease patients. However, it is unclear if psychiatric episodes are related to Danon disease.

Males with Danon disease typically have abnormalities on certain laboratory tests. The creatine kinase (sometimes referred to as the CPK level) in the blood is often elevated, and is a reflection of ongoing muscle damage. The CPK is usually elevated in males, but can be normal in some females who have Danon disease. Abnormalities in liver enzyme tests are common in males; in some cases these are mistakenly interpreted as a sign of primary liver disease rather than a reflection of skeletal muscle dysfunction; frank liver dysfunction has not been well-described in Danon disease. The electrocardiogram (ECG), which measures electrical impulses made by the heart, is often abnormal. This abnormality in conduction and electrical impulse is also known as an arrhythmia. Frequently, an arrhythmia called Wolff-Parkinson-White syndrome or a pre-excitation syndrome will be seen on the ECG. An examination of the retina by an experienced eye doctor (ophthalmologist) will often detect changes in the pigment of the retina. This can be a useful sign in women, as the retinal changes appear to precede other symptoms of the disease in some cases.

Causes

Danon disease is caused by a genetic defect (mutation) in a gene called LAMP2. To date, there are over 70 different mutations in the LAMP2 gene identified in case reports that could lead to Danon disease. Mutations that lead to a complete absence of LAMP2 protein have been shown to be most

detrimental in terms of prognosis. Other mutations that lead to an incomplete LAMP2 protein that is only missing a component is less deleterious.

In many instances the disease is inherited from a parent, typically the mother who is far more apt to remain healthy enough to reach reproductive age than the typically affected male. Without a heart transplant, only a few males may be healthy enough to father their own children. New genetic mutations (sporadic mutations) could also account for the first case in a family, but these have not been widely reported. Affected mothers will pass on the genetic defect to half of their children (both sons and daughters). Affected fathers who are healthy enough to have children will pass on the genetic defect to all of their daughters and none of their sons. This pattern of inheritance is consistent with what occurs in other X-linked genetic conditions.

Since females have two X chromosomes (and males have one), females are somewhat protected from the Danon disease genetic defect. This is explained by the fact that each woman with Danon disease is expected to have one mutated X chromosome (containing a Danon disease mutation) and one normal X chromosome (where the LAMP2 gene is functioning normally). The normal X chromosome protects females and explains, in part, the less severe symptoms and the delay in onset of symptoms until adulthood. However, some women with Danon disease have progressed to the point of needing a heart transplant.

The location of the malfunctioning gene has been traced to gene map locus Xq24. The genetic characteristics of this gene (LAMP2) are transmitted as an X-linked dominant trait.

Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22 and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome and females have two X chromosomes. Each chromosome has a short arm designated “p” and a long arm designated “q”. Chromosomes are further sub-divided into many bands that are numbered. For example, “chromosome Xq24″ refers to band 24 on the long arm of the X chromosome. The numbered bands specify the location of the thousands of genes that are present on each chromosome.

Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother.

All individuals carry a few abnormal genes. Parents who are close relatives (consanguineous) have a higher chance than unrelated parents to both carry the same abnormal gene, which increases the risk to have children with a recessive genetic disorder.

X-linked recessive genetic disorders are conditions caused by an abnormal gene on the X chromosome. Females have two X chromosomes but one of the X chromosomes is “turned off” and all of the genes on that chromosome are inactivated. Females who have a disease gene present on one of their X chromosomes are carriers for that disorder. Carrier females usually do not display symptoms of the disorder because it is usually the X chromosome with the abnormal gene that is turned off. A male has one X chromosome and if he inherits an X chromosome that contains a disease gene, he will develop the disease. Males with X-linked disorders pass the disease gene to all of their daughters, who will be carriers. A male cannot pass an X-linked gene to his sons because males always pass their Y chromosome instead of their X chromosome to male offspring. Female carriers of an X-linked disorder have a 25% chance with each pregnancy to have a carrier daughter like themselves, a 25% chance to have a non-carrier daughter, a 25% chance to have a son affected with the disease, and a 25% chance to have an unaffected son.

X-linked dominant disorders, like Danon disease, are also caused by an abnormal gene on the X chromosome, but in these rare conditions, females with an abnormal gene are affected with the disease. Males with an abnormal gene are more severely affected than females, and many of these males do not survive. In the case of Danon disease, males can survive to adulthood, however, their

medical problems and the typical need for heart transplantation likely limits their ability to have many children.

The function of the LAMP2 protein (made from the LAMP2 gene) is not well understood. It appears that the LAMP2 protein is important for the function of the cell's lysosomes. Lysosomes, often compared to waste disposal plants, are small structures inside cells that are responsible for breaking down certain molecules and compounds in cells. When the lysosomes do not function properly, cellular products accumulate. One such product that may build-up is glycogen and in some cases the diagnosis of Danon disease is suggested because of excess glycogen seen on a skeletal muscle biopsy. However, it is important to realize that excess glycogen is not always visible on a single muscle biopsy.

Affected Populations

At present, it is thought that Danon disease can affect all ethnic populations. The prevalence of Danon disease is unknown, but may be rising due to increased detection from wider availability of LAMP2 gene testing. Histories of affected patients at birth are usually normal. As discussed, males are more severely affected in this X-linked dominant disease.

Related Disorders

Until recently, Danon disease and Pompe disease were thought to be closely related because in each case, skeletal and cardiac muscles are involved. Under the microscope, Danon disease shows many features (i.e. increased glycogen content), that are typical of Pompe disease. Two main features distinguish the two diseases: 1) the inheritance pattern in Pompe disease is autosomal recessive while that in Danon disease is X-linked dominant, and 2) the enzyme deficient in Pompe disease (acid maltase or acid alpha glucosidase) is present in normal amounts in Danon disease.

X-linked myopathy with excessive autophagy is a disorder similar to Danon disease. Currently, it is felt to be a separate disorder, although the gene causing the disorder has not yet been definitively identified. Some studies point to a defect in the VMA21 gene as the etiology. Skeletal muscle involvement and elevated CPK are seen. Heart involvement and intellectual disability, commonly seen in Danon disease, appear absent in X-linked myopathy with excessive autophagy. The inheritance pattern is X-linked recessive.

Lethal, congenital glycogen storage disease of the heart is caused by genetic mutations in a gene called PRKAG2. The disease is severe and characterized by low blood sugar (hypoglycemia), cardiomyopathy, congestive heart failure, and an autosomal recessive pattern of inheritance. It is sometimes referred to as glycogen storage disease of the heart, which is a descriptive term and may sometimes include Danon disease.

Lastly, infantile autophagic vacuolar myopathy is another disease similar to Danon disease. The causative gene defect has not been identified. An X-linked recessive inheritance pattern has been described with infantile onset of lethal cardiomyopathy and skeletal muscle weakness.

Diagnosis

Because Danon disease is rare and unfamiliar to most physicians, diagnosis is difficult and takes substantial time. The diagnosis is suggested on the basis of a family history compatible with X-linked dominant inheritance and symptoms in affected relatives (cardiomyopathy, skeletal myopathy, intellectual disability, Wolff-Parkinson White, etc.). Skeletal muscle biopsy is probably done in some males in an effort to determine the cause of muscle weakness. If, in the course of examining the biopsy materials, glycogen buildup and/or empty spaces appear in the cells of the muscle tissue (vacuolization), Danon disease must be considered. This also holds true for the analysis of a heart

biopsy. A muscle biopsy that yields evidence of glycogen build-up and empty spaces in the muscle cells are key signs and indications that a diagnosis of Danon disease is a high probability.

It is important to recognize that, in early stages of Danon disease, and probably also in women, the muscle biopsy can be non-specific. Thus, a normal or non-specific muscle biopsy does not exclude Danon disease. If other features of Danon disease are present, a non-diagnostic muscle biopsy should not discourage more definitive genetic testing. Patients who appear to have Pompe disease (based on muscle biopsy for instance) but have normal acid maltase activity, should be evaluated for Danon disease. Unexplained hypertrophic cardiomyopathy in males is probably due to Danon disease in some proportion of cases.

Antibodies to the LAMP-2 protein are available and tissue staining (of a muscle biopsy) for the absence of LAMP-2 protein is another potential, but not widely available, diagnostic approach. LAMP-2 antibody testing is likely to be normal in women with Danon disease and if done should be interpreted with caution due to the possibility of a false-negative result.

Genetic testing of the LAMP2 gene is currently the gold standard for diagnosis and is available in specialized genetics laboratories. Most genetic mutations causing Danon disease predict reduced levels or even absence of the LAMP2 gene product, the LAMP-2 protein. Although the sensitivity of LAMP2 genetic testing is not known at this time, it is the best that is available. The noninvasive nature of DNA-based testing and the inclusion of LAMP2 gene testing in hypertrophic cardiomyopathy genetic diagnostic panels favor this method as the most common route to diagnosis.

Standard Therapies

Treatment

The treatment of Danon disease is directed toward the specific symptoms that are apparent in each individual. It requires a team that should include a primary care physician as well as several specialists, including a cardiologist, neurologist, ophthalmologist, geneticist, genetic counselor, rehabilitation physician, educational specialist, and physical therapist. Currently there is no specific therapy that is known to slow the underlying biological problems caused by LAMP-2 protein deficiency.

The severity of cardiomyopathy is the major prognostic factor. Imaging studies including echocardiography and cardiac magnetic resonance can assess heart function, extent of hypertrophy, and degree of cardiac fibrosis (formation of scar tissue on the heart). Medications for heart disease should be given when indicated by clinical signs and symptoms. The rapid progression of the cardiomyopathy in some males necessitates prompt consideration for heart transplantation. Early involvement of electrophysiology to study the electrical conduction system of the heart is warranted in patients with arrhythmias. A device called a Holter monitor can be used to continuously record the electrical impulses of the heart. For symptomatic arrhythmias, early implantation of a cardioverter-defibrillator may be appropriate. Cardiac ablation therapy, which is a technique utilized to destroy the abnormal focus in the heart generating the irregular rhythm, can also be performed. As the disease can progress rapidly in males, consideration for early defibrillator implantation and evaluation for cardiac transplantation are appropriate in males as cardiomyopathy progresses.

Assessment of muscle strength, especially the proximal muscles of the shoulder, neck, and legs, should be performed regularly. Physical therapy can be helpful in maintaining muscle strength and flexibility. Intellectual disability should be screened for in males and appropriate educational interventions applied as needed. Regular eye examinations, to track the development and progression of retinal disease, should be considered. Biological relatives who are at risk for Danon disease should be evaluated by a physician for early signs of disease. At a minimum, evaluation of such relatives should include a medical history, physical examination (attention to cardiac, neurological, and ocular exams), CPK testing, ECG, and echocardiogram. Genetic consultation and counseling is recommended for all patients and families so that inheritance and reproductive risks are clearly

communicated.

Investigational Therapies

Future investigation should focus on the biochemical role of the LAMP2 gene in Danon disease. Information on its molecular function can provide insight on its pathogenesis and help initiate investigations to novel therapy.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, contact:
www.centerwatch.com

For information about clinical trials conducted in Europe, contact:
https://www.clinicaltrialsregister.eu/

Danon disease results from a missing protein, LAMP-2. Other diseases that result from insufficiency or lack of other proteins have been successfully treated with protein replacement therapies. This approach is theoretically possible in Danon disease, but has not been developed to date. There is no evidence or rational to support a high protein diet to treat Danon disease and any protein replacement effort would have to involve the LAMP-2 protein.

A researcher in Colorado, Matthew Taylor, MD, PhD, has developed a registry of Danon disease patients and families to collect information that may advance the understanding of this disease and be helpful in the future development of treatments. He may be contacted at:

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