

Danon Disease

Introduction:

This document is designed to provide some basic information about Danon disease for families and their physicians. At the moment the *unknown* vastly exceeds the *known* for this disorder.

Danon disease is a rare genetic disorder characterized by an X-linked dominant inheritance pattern where males are more severely affected than females. Boys are typically affected by cardiomyopathy (disease of the heart muscle), skeletal myopathy (weakness of the body muscles), and intellectual disability ranging from mild learning problems to mental retardation. In many males, the disease will progress to the point that death or heart transplantation occurs in the second to third decade of life. Female can also be affected, although usually more mildly and often not until they reach adulthood. 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. 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).

Major Symptoms:

Danon disease symptoms are quite variable and depend on both age and gender. Boys may have early signs of muscle problems (difficulty sitting or walking) and may lose some of their motor skills (i.e. can regress). Intellectual disability can be observed by parents and/or teachers. Heart disease can lead to further fatigue and shortness of breath. Young girls may have no symptoms and will report normal muscle strength and have normal intellect. As they age, symptoms of heart disease or muscle weakness may be reported. Visual complaints may also be reported in women and can be an early feature of the disease.

The disease is particularly difficult to diagnose because it is so rare, having been first described only in 1981 and probably less than a 100 cases have been reported worldwide; many more cases probably remain undiagnosed. Sometimes Danon disease can be suspected on the basis of a muscle biopsy. This is usually done in a patient (typically a male) who is having significant muscle weakness. Certain microscopic findings can suggest the diagnosis of Danon disease, or other related conditions. These features include an increase in a carbohydrate compound called "glycogen" and evidence of increased vacuoles ("vacuolization") as seen by the pathologist looking at the biopsy. It is important to recognize that sometimes a single muscle biopsy in Danon disease can look normal or show only nonspecific findings.

The skeletal muscle disease is believed to preferentially involve the proximal muscles and neck muscles. Proximal muscles are those closest to the center of the body, including back, shoulder, and upper leg muscles. 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 heart muscle disease ('cardiomyopathy') can lead to a thickened, stiff heart ('hypertrophic cardiomyopathy') or to an enlarged heart ('dilated cardiomyopathy'). Sometimes the cardiomyopathy can be the first sign of disease in male children. An echocardiogram (ultrasound of the heart) is currently the standard method to identify the cardiomyopathy. 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. Many persons will progress to the point of needing a heart transplant.

Very little is known about the extent of intellectual disability in males and personal experience (Taylor) suggest that mild cognitive problems are more likely than moderate or severe mental retardation. 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.

Patients with Danon disease typically have abnormalities on certain laboratory tests. The creatine kinase ('CPK') in the blood is often elevated, especially in males. The electrocardiogram (ECG), which measures electrical impulses made by the heart, is often abnormal and typically shows a conduction abnormality called "Wolff-Parkinson-White syndrome" or a "Pre-excitation syndrome". An examination of the retina by an experienced ophthalmologist (eye doctor) will frequently find changes in the pigment of the retina. This can be a useful sign in women, as the retinal changes may precede other symptoms of the disease.

A careful study of the family history can be helpful in diagnosing Danon disease. The inheritance pattern is "X-Linked" and can be recognized by a knowledgeable physician or other healthcare professional. Although the "pattern" of X-Linked inheritance is recognizable, Danon disease itself is unlikely to be familiar to most physicians and health care professionals.

Genetic testing is available from a small number of laboratories. This approach is currently the best way to get definitive 'proof' of the diagnosis of Danon disease. The involvement of a geneticist or genetic counselor can be helpful in obtaining and interpreting the correct test. The hardest part of reaching a diagnosis of Danon disease is probably still the necessary first step of 'thinking of this as a possible diagnosis'. Sometimes, having a muscle biopsy reviewed by an expert in glycogen storage diseases of the muscle is necessary.

The treatment team for a patient with Danon disease should include a primary care physician and may include several specialists: cardiologist, neurologist, ophthalmologist, geneticist, genetic counselor, rehabilitation physician, educational specialist, physical therapist.

What causes Danon Disease?

Danon disease is caused by a genetic defect ("mutation") in a gene called LAMP-2. In many instances the disease is inherited from a parent, commonly the mother as many affected males may not be healthy enough to have children (unless they have a heart transplant). New genetic 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 function of the LAMP-2 protein (made from the LAMP-2 gene) is not well known. It appears that the LAMP-2 protein is important for the function of the "lysosomes". Lysosomes are small structures inside cells and are responsible for breaking down certain molecules and compounds in cells. When the lysosomes do not function properly, cellular products, including glycogen, accumulate. It is important to realize that excess glycogen is not always visible on a single muscle biopsy.

Epidemiology:

So far, it is believed that Danon disease can affect all ethnic populations. As discussed, males are more severely affected in this X-linked dominant disease. In theory, for an X-linked disease one would expect to find a larger number of females affected. This is explained by the fact that 2/3 of all the X-chromosomes are found in females, giving females a higher chance of having a LAMP2 mutation. However, since Danon disease can be much milder in females, it is possible that more females than males remain undiagnosed. So far, most families in our registry report symptoms for many years before the correct diagnosis is made.

Similar Diseases:

Danon disease was originally thought to be related to Pompe disease, due to the skeletal and cardiac muscle involvement. Under the microscope, Danon disease shows many features (i.e. increased glycogen) content, which is 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 normal 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 been discovered. 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.

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

Diagnosis

Diagnosis is difficult as the condition is unfamiliar to many primary care physicians and specialists. 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, mental retardation, Wolff-Parkinson White, etc.). Often the skeletal muscle biopsy is done before the clinician has considered Danon disease as a possible diagnosis. Finding glycogen buildup or abnormal vacuoles under the microscope should prompt a consideration of Danon disease. 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. In other circumstances a condition such as Pompe disease may be considered initially; once Pompe disease has been excluded, other diagnoses (including Danon disease) can be pursued. Unexplained hypertrophic cardiomyopathy in males, is due to Danon disease in a proportion of cases.

Genetic testing of DNA for LAMP-2 mutations can also lead to a diagnosis. Our laboratory and others perform this type of testing.

Treatment

The treatment of Danon disease is directed toward the symptoms and problems apparent in each individual. Currently there is no specific therapy that is known to slow the underlying biological problems caused by LAMP2 protein deficiency. There are no specific Danon disease-directed therapy recommendations at this time.

Physical therapy may be helpful in maintaining muscle strength and flexibility. Medications for heart failure should be given when indicated by clinical signs and symptoms. The rapid progression of the cardiomyopathy in some males necessitates prompt considerations for eligibility for heart transplantation. Intellectual disability should be screened for in males and appropriate educational interventions applied as needed. Eye examinations to track the development and progression of retinal disease may be considered. Living relatives at risk for also having Danon disease should be evaluated by a physician. At a minimum, the following should be considered for these relatives: 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.

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