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Cardiac Involvement in Hereditary Ataxias

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Abstract

Although much attention has been focused on the neurological sequelae of the hereditary ataxias, patients with these conditions also may develop cardiac complications that represent a significant cause of disability and even death. In this paper, we describe the hereditary ataxias with known cardiac involvement, discuss underlying causes, and review guidelines for screening and treatment. Continued progress will require coordinated clinical trial networks, interdisciplinary care teams, and team science.

Keywords

ataxia; carbohydrate-deficient glycoprotein syndrome type Ia; cardiomyopathy; Dandy-Walker syndrome; dilated cardiomyopathy with ataxia; Friedreich ataxia; heart; Kearns-Sayre syndrome; spinocerebellar ataxia; Wilson disease

Patients with hereditary ataxias typically have a spectrum of neurological manifestations that produce progressive impairment of gait, speech, swallowing, and other complications.[1] There is increasing recognition that cardiac involvement may contribute to death and disability in patients with ataxias, leading to ongoing efforts to define standards for cardiac evaluation and management. In this review, we summarize current understanding of cardiac involvement in the hereditary ataxias, and describe possible underlying mechanisms, detection and treatment, and future directions.

Ataxias With Known Cardiac Involvement

Ataxias known to have cardiac manifestations include Friedreich ataxia, Kearns-Sayre syndrome, carbohydrate-deficient glycoprotein syndrome type Ia, spinocerebellar ataxias, Wilson disease, Dandy-Walker syndrome, and dilated cardiomyopathy with ataxia.

The incidence of Friedreich ataxia is estimated to be 1 in 30 000 people, making it the most common inherited ataxia.[2] Cardiac dysfunction may develop early in the course of the disease. While incidence of cardiac involvement in Friedreich ataxia is high when evaluated at autopsy, clinical severity varies during life. Nonetheless, cardiac disease is now recognized as the leading cause of death in Friedreich ataxia.[3] This potential discrepancy may result from impaired mobility that obscures recognition of cardiac disease if practitioners rely on typical exertional signs and symptoms characteristic of cardiac disease in non-ataxic patients.

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While Friedreich ataxia classically has been thought to produce hypertrophic cardiomyopathy,[4] more recent studies recognize a spectrum of cardiac phenotypes. The term `concentric remodeling,' a well-recognized form of abnormal cardiac geometry associated with poor outcomes just like frank left ventricular hypertrophy ,[5] may better capture the relative increase in wall thickness for the cavity volume in patients with Friedreich ataxia whose absolute left ventricular mass does not meet left ventricular hypertrophy criteria. We have similarly found impaired myocardial perfusion reserve using vasodilator stress perfusion imaging, which may reflect impaired energetics at the microvascular level.[6]

Cardiac conduction abnormalities and cardiomyopathy have long been recognized as complications of Kearns-Sayre syndrome.[7–9] Clinical sequelae include syncope, congestive heart failure, and cardiac arrest.[9, 10]

In carbohydrate-deficient glycoprotein syndrome type Ia, cardiac manifestations have ranged from hypertrophic cardiomyopathy[11] to pericardial effusion and tamponade.[12] Conotruncal abnormalities have also been reported.[13] Among all congenital disorders of glycosylation, mean age of onset of cardiac involvement is 5 months.[14] About 20% of patients with carbohydrate-deficient glycoprotein syndrome type Ia die within the first year of life, often due to serious cardiac complications.[14] In one study of children with congenital disorders of glycosylation, 2 out of 5 with carbohydrate-deficient glycoprotein syndrome type Ia died due to cardiac complications before the age of 3 months.[14]

Spinocerebellar ataxia types 1,2, and 3 may produce cardiovascular abnormalities, particularly abnormal heart rate variability.[15] Autonomic disturbances have been most commonly reported.[16, 17] While one report describes a case of sudden cardiac death in a patient with `spinocerebellar ataxia,'[18] lack of molecular diagnosis and clinical similarity to Friedreich ataxia make it difficult to know whether spinocerebellar ataxia was truly the underlying disorder.

Cardiac abnormalities in Wilson disease, a disorder of copper metabolism, include concentric remodeling and supraventricular tachycardia.[19] Pathology suggests there may be myocardial inflammation and interstitial fibrosis.[20] Most electrocardiographic abnormalities in patients with Wilson disease are subclinical, but arrhythmias demonstrated on electrocardiography may portend increased risk of cardiac death.[21]

Dandy-Walker malformations may be associated with congenital heart disease, including ventricular septal defects, patent ductus arteriosus, transposition of the great arteries, and pulmonic stenosis.[22] Systemic anomalies associated with Dandy-Walker malformations (excluding central nervous system malformations) occur in around 25% of cases, according to Hart and colleagues.[23] Patients with Dandy-Walker malformations with cardiac involvement often present early with symptoms of cardiac insufficiency (in the first year of life), and prognosis is dependent on the nature and severity of the specific cardiac malformation.[24, 25]

Patients with dilated cardiomyopathy with ataxia can present with cardiac disease before the age of 3, including sequelae of dilated cardiomyopathy and long QT syndrome.[26] Seventy percent of patients die of progressive cardiac failure or sudden cardiac death, often within the first few years of life.[26, 27]

Juvenile GM2 gangliosidosis has also been reported to cause autonomic dysfunction, though cardiovascular sequelae are not typically apparent.[28]

Underlying Mechanisms of Cardiac Involvement in the Ataxias

Friedreich ataxia results most commonly from a GAA triplet expansion in the first intron of the frataxin gene on chromosome 9q21.11, and occasionally as a result of point mutations. Frataxin is an essential and highly expressed protein that functions in mitochondrial iron homeostasis.[29] In a cellular environment where frataxin is diminished or absent, free iron accumulates in the mitochondria, and the creation of iron-sulfur prosthetic groups is decreased, leading to decreased energy production via the electron transport chain as well as free radical generation and oxidant stress via electron loss.[30–33] This reduced energy production due to frataxin deficits has severe effects on cardiomyocytes, whose sarcomeres lack adequate levels of adenosine triphosphate for normal contractile function. A disruption of the normal mitochondria-to-sarcomere ratio is observed.[34] How frataxin deficiency translates to concentric remodeling, however, remains unknown. It has been postulated that impaired energy-dependent vasodilatation of the coronary microcirculation contributes,[6] as it does in hypertrophic cardiomyopathies due to sarcomeric mutations.[35] We have also identified features of the metabolic syndrome in addition to the long-known ~10% incidence of frank diabetes in patients with Friedreich ataxia.[36] In several studies, increased number of GAA repeats has correlated with cardiomyopathy severity and earlier onset.

Cardiac involvement in Kearns-Sayre syndrome is often associated with large-scale mitochondrial DNA deletions; between 15% to 40% of a patient's mitochondrial DNA within the heart muscle can be lost.[10] These deletions may be due to a deficiency in the p53R2 subunit of ribonucleotide reductase, caused by missense mutations in its nuclear encoding DNA region, RRM2B.[37] Deletions beginning at a certain base pair number of mitochondrial DNA called the “hot spot”[38] are thought to be the cause of cardiac conduction defects in patients with Kearns-Sayre syndrome evaluated in correlation studies.[39] Though the exact mechanism of how conduction defects manifest is unknown, many biopsy studies performed with electron microscopy on patients with Kearns-Sayre syndrome who have conduction defects have shown abnormal mitochondrial structure, number, and placement within the myocardial cells. These morphological effects on the conducting tissue of the heart are thought to cause conduction defects such as left anterior hemiblock, right bundle branch block, and left bundle branch block, often progressing toward complete AV block in patients with Kearns-Sayre syndrome.[9] It is hypothesized that the metabolic and morphological anomalies initially mostly affect conduction tissue, although in later years contractile tissue can be affected as well, leading to clinical myocardial disease.[9]

Carbohydrate-deficient glycoprotein syndrome type Ia, also referred to as phosphomannomutase 2 deficiency, is caused by a defect in the second step in the synthesis of guanosine diphosphate-mannose. Deficiency of guanosine diphosphate-mannose induces hypoglycosylation of serum proteins, membranous glycoproteins, and lysosomal enzymes.[40] Gehrmann and colleagues have suggested that the cardiomyopathy seen in carbohydrate-deficient glycoprotein syndrome type -Ia arises from hypoglycosylation of dystrophin-associated glycoproteins in the sarcolemmal plasma membrane.[14] The authors suggest that the alteration in structure of these proteins affects signal transduction pathways and calcium homeostasis, leading to myocardial disease. An embryological mechanism has been proposed for conotruncal heart defects in carbohydrate-deficient glycoprotein syndrome type Ia patients by Romano and colleagues, wherein abnormal neural crest cell migration causes cardiac anomalies.[13] Many cell adhesion molecules, transcription factors, growth factors, and their receptors are involved in neural crest cell migration.[41] The authors believe that hypoglycosylation of glycoproteins involved in this process due to phosphomannomutase 2 deficiency creates abnormal neural crest cell migration, leading to congenital heart anomalies such as conotruncal heart defects.[13]

The etiology of Wilson disease has been mapped to mutations in a gene on chromosome 13 encoding the ATP7B membrane protein, which resides in hepatocytes in the trans-Golgi network.[42, 43] Alterations in this protein causes copper accumulation first in the liver; when the liver's capacity to store copper is exhausted, copper is released into the circulation and deposits in other tissues, including heart muscle.[44] Hlubocká and colleagues suggest the pathophysiology of cardiac involvement in Wilson disease is similar to that of the liver, wherein generation of free radicals due to excess intra-and extracardiac copper accumulation causes an atrophic response in cardiac muscle.[19] Further studies to support this hypothesis are needed.

The exact pathophysiology by which the Dandy-Walker malformation occurs is still unknown. The high incidence of cardiac anomalies in patients with Dandy-Walker malformation suggests an embryonic developmental linkage. However, the available medical literature provides no direct evidence of the mechanistic underpinnings of cardiac disease in these patients.

Dilated cardiomyopathy with ataxia is an autosomal recessive disorder that arises from a point mutation in the nuclear *DNAJC19* gene.[26] This gene encodes a chaperone protein likely located in the inner mitochondrial membrane involved in the folding of newly synthesized proteins and in prevention of abnormal folding and aggregation of proteins during cellular conditions of stress.[26] It has been suggested that disruption in mitochondrial protein import from the cytosol caused by the point mutation in *DNAJC19* leads to aerobic metabolic deficiency, which causes the dilated cardiomyopathy.[27] Further preclinical studies may better inform pathophysiologic mechanisms linking genotype with cardiac phenotype.

Guidelines for Cardiac Screening and Treatment

For ataxic disorders where cardiomyopathy is known to be the leading cause of death, early diagnosis is possible. Electrocardiography is widely and readily available, and often shows nonspecific ST and T-wave abnormalities. Electrocardiographic abnormalities are seen in 75% to 100% of patients with Friedreich ataxia, with nonspecific repolarization abnormalities occurring commonly.[45, 46] Echocardiography identifies concentric left ventricular hypertrophy and diastolic dysfunction in 62% of patients with Friedreich ataxia.[47] What one does at the initial detection of myocardial involvement remains uncertain, and the rare nature of the disease leads to highly variable practice across a variety of community versus tertiary care centers. In the absence of curative approaches, we are left with applying guidelines developed for other forms of myocardial disease.[48] Most commonly used are angiotensin-converting enzyme inhibitors and beta-blocking drugs, although no randomized controlled trial or even registry has been conducted using such agents in Friedreich ataxia cardiomyopathy.

Antioxidant therapies to protect against mitochondrial damage to the heart remain appealing. While clinical trials to date have not demonstrated a sustained benefit of antioxidant or any other pharmaceutical therapy in the treatment of Friedreich ataxia cardiomyopathy,[49] Myers and colleagues importantly point out the potential major confounding effect of nonprescription antioxidant use in such trials.[50] Bone marrow-derived mesenchymal stem cells increase frataxin production and decrease oxidative stress in fibroblast mitochondria from patients with Friedreich's ataxia in vitro;[51] in vivo studies are needed.

Given the conduction system disease in Kearns-Sayre syndrome, it would seem prudent to perform early and routine electrocardiographic screening in these patients. Affected or at-risk family members can also be readily evaluated with this simple tool.[10] Because of the risk of sudden death from AV block in patients with Kearns-Sayre syndrome, consideration

of pacemaker implantation is recommended with or without clinical symptoms based on detection of high-grade conduction system disease by electrocardiography.[10]

Little has been written regarding cardiac treatment in patients with Dandy-Walker malformation, as most of the medical literature focuses on the neurological effects of the disease. Sparkes and colleagues advocate routine electrocardiographic and echocardiographic assessment in patients with dilated cardiomyopathy with ataxia regardless of whether clinical symptoms are present because of the high incidence of cardiac complications associated with the disease.[27] Better understanding of the pathogenesis of dilated cardiomyopathy in this disorder may identify potential targets for preventive therapy.[27]

Symptomatic and presymptomatic Wilson disease patients are typically treated with copper chelating agents that bind free copper and reduce mitochondrial damage in affected organs. Though these agents are known to have beneficial effects on hepatocytes, remarkably little has been reported on the utility of agents such as D-penicillamine once myocardial disease has ensued. The impact of liver transplantation on cardiomyopathy in Wilson disease remains poorly characterized.

Bedside evaluation of volume status is one of the most important yet perhaps least appreciated components of the clinical exam of any patient with cardiac disease. Limitations imposed by body habitus and chest wall deformities make the inspection of the jugular venous pressure challenging in patients with many forms of neuromuscular disease, including the hereditary ataxias. The risks of not paying adequate attention to intravascular volume include poor tolerance of indiscriminate volume overload in patients with diastolic abnormalities, such as the patient with Friedreich ataxia who is undergoing noncardiac surgery. Similarly, excess volume depletion may exacerbate low cardiac output symptoms.

Future Directions

A review of the literature reveals obvious gaps in the collective knowledge of cardiac involvement in the hereditary ataxias, particularly regarding etiology, pathophysiology, optimal diagnostic strategies, and treatment. The rarity of these disorders coupled with a predominant focus on neurological complications are ongoing challenges that can be overcome with recognition and strategic planning. Coordinated clinical trial networks, interdisciplinary care teams, and team science in preclinical studies are absolutely required for any progress to be made. With such efforts, cardiac involvement in the hereditary ataxias can be better recognized and treated, reducing a major source of morbidity and mortality for these patients.

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