Cardiomyopathy in Friedreich Ataxia
Exemplifying the Challenges Faced by Cardiologists in the Management of Rare Diseases

Morten Kvistholm Jensen, MD, PhD; Henning Bundgaard, MD, DMSc

Friedreich ataxia (FA) is an autosomal recessively inherited neurodegenerative disease that most often presents in childhood or in young adulthood. A substantial proportion of patients with FA also develop a cardiomyopathy that usually presents as left ventricular hypertrophy (FA-CM). The mean life expectancy is significantly reduced to ~40 years, and ~60% of patients with FA die from cardiac causes.1,2 The prevalence of FA is 0.1 to 4.7:100,000, and an estimated 9000 Americans are affected.3 The potential ability to reduce the prevalence of FA is 0.1 to 4.7:100,000, and an estimated 9000 Americans are affected. The potential ability to reduce disease progression or even to reverse FA-CM by antioxidants underscores the importance of early identification of the disease and the development of clinically identifiable markers of cardiac involvement. In the current issue of Circulation, the Mitochondrial Protection With Idebenone in Cardiac or Neurological Outcome (MICONOS) study group investigated such markers.4

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Early identification of FA as the cause of a newly identified cardiomyopathy depends on the cardiologist’s ability to identify the extracardiac manifestations of FA. These include progressive limb ataxia and weakness, dysarthria, nystagmus, and loss of proprioception and may also include scoliosis, diabetes mellitus, and impaired vision and hearing. A majority will lose the ability to walk and require wheelchairs. Cardiac involvement is rarely found in other inherited ataxias.5 However, the phenotype is highly variable, and in some patients the first manifestation is cardiomyopathy.3 On the other hand, the pediatrician’s or neurologist’s knowledge about cardiac involvement and the importance of early referral for cardiac assessment is equally important.

The Genetic Basis of FA: A Mitochondrial Disease
In 1996, Dürr et al8 reported that FA in most cases is caused by expansion of the DNA triplet intron repeat (GAA) in the FXN gene. This reduces the transcription and expression of the mitochondrial inner membrane protein, frataxin, which may reduce the density of respiratory chain enzyme complexes and limit ATP repletion. In combination with decreased iron chelating capacity in the mitochondria, iron overload may cause oxidative damage.7 Correspondingly, abnormal cardiac energetics has been found by magnetic resonance (MR) spectroscopy8 and impaired myocardial perfusion reserve and fibrosis has been found by cardiac MR imaging (cMRI).9

The availability of genetic testing has drawn attention to family history, and family screening has gained increasing importance. The prognosis is associated with the number of GAA repeats.1,3 Like what has been observed in other rare diseases, the clinical spectrum of FA has expanded considerably because family screening and genetic testing have enabled earlier diagnosis in asymptomatic or mildly symptomatic relatives.

FA-CM: Diagnostic Approach
In patients with FA, the standard cardiac evaluation of morphology and systolic and diastolic function is echocardiography, although cMRI is increasingly available and has gained more widespread use. The rapid development of advanced echocardiography and cMRI modalities enables cardiologists to detect more discrete abnormalities in morphology and function, and clinical application of these modalities in the evaluation of early disease manifestations seems rational.10 However, to identify cardiac involvement on the basis of new modalities calls for solidly documented normal reference data, which for most new echocardiographic parameters are not available. Most echocardiographic parameters are influenced by age, body size (eg, body surface area [BSA]), or both. This emphasizes the need for normal reference data, particular when applying these technologies on children for assessment of presence and degree of FA-CM.

In this issue of Circulation, the MICONOS study group, representing 13 centers from 6 European countries, presents a carefully performed cross-sectional study of 205 patients with FA. On the basis of cMRI and echocardiographic evaluation and application the Henry nomogram, the group suggests a classification of severity of FA-CM. In agreement with previous studies, the authors found that approximately two thirds of the patients had some degree of FA-CM.

The Henry nomogram, used to adjust for age and BSA, may represent the best available reference data to apply when analyzing cardiac dimensions. However, considering that the Henry nomogram was developed in 1980 with the echocardiographic technology of that time and was based on ~200
subjects, the use of this nomogram may have limitations.\textsuperscript{11} The natural history of FA includes, in most cases, mild to severe muscle wasting, resulting in reduced BSA.\textsuperscript{12} Consequently, BSA-adjusted cardiac dimensions may overestimate the true degree of hypertrophy, and FA-CM may be suspected in a number of FA patients with normal cardiac dimensions. This phenomenon is also known in other conditions (eg, in hypertrophic cardiomyopathy where obesity may affect the BSA and thus interfere with the diagnostic criteria in children). However, the MICONOS study group addressed these challenges by the finding of good agreement between cMRI and echocardiographic FA-CM categorizations.

**Suggested New Classification of FA-CM**
The MICONOS study group suggests a classification of FA-CM into “no,” “mild,” “intermediate,” and “severe.” They present data showing that the 4 defined subgroups are different in terms of cardiac dimensions, ejection fraction, and ECG changes. However, as pointed out by the authors, the cross-sectional design of the study does not allow decision on whether the suggested classification represents a continuum from unaffected to severely affected hearts or whether it rather represents different courses of the disease.

**Clinical Use of the Present Findings**
The International Cooperative Ataxia Rating Scale (ICARS) and the Friedreich Ataxia Rating Scale (FARS) scores are established as tools for monitoring of neurological state in FA, but at present, no criteria for identifying and monitoring cardiac involvement in FA have been established. The MICONOS study group should be complimented for their efforts in developing this new classification of FA-CM. There was no correlation between neurological scores and FA-CM groups, and exercise capacity was not related to the FA-CM group, but to the neurological scores. On this basis, the authors conclude that, irrespective of neurological status, all patients with FA need an initial cardiac evaluation including cMRI and echocardiography and a regular echocardiographic follow-up.

**Treatment of FA-CM**
The basic pathophysiological features in FA are mitochondrial iron accumulation due to reduced chelation by frataxin, formation of reactive oxygen species, and oxidative damage.\textsuperscript{3} On this basis, administration of antioxidants is considered a rational therapeutic approach. Attention has been drawn to the antioxidant idebenone, a promising drug with a structure similar to coenzyme Q\textsubscript{10}. However, reports on cardiac changes in response to idebenone treatment are inconsistent (see the online-only Data Supplement). Negative results may relate to inclusion of a substantial number of patients without significant myocardial hypertrophy in order to assess neurological effects of idebenone or short observational time. Mariotti et al has analyzed the effects of idebenone in a population of patients with significant FA-CM (interventricular septal diastolic thickness or left ventricular posterior wall diastolic thickness $>12$ mm) in a double-blind randomized clinical trial.\textsuperscript{13} They found a significant reduction of interventricular septal diastolic thickness and left ventricular mass index after 12 months treatment with idebenone. This illustrates the potential value of treatment with idebenone and the importance of categorizing cardiac involvement.

Until specific tailored treatment regimens are definitely established, conventional treatment should be offered. Thus, treatment of patients with FA-associated heart failure symptoms, systolic left ventricular dysfunction, or arrhythmia may include conventional heart failure drugs, antiarrhythmic drugs, and device implantations.

**Future Studies of FA-CM**
The possible regression of myocardial hypertrophy during idebenone treatment may be a major step forward in treatment of patients with FA. However, because of the limited number of patients with FA available for clinical trials, it will be difficult to definitely establish a survival benefit for idebenone. Clinical studies of FA cardiomyopathy may therefore focus on surrogate end points like arrhythmia, syncope, disease progression, and heart failure (ie, end points that in other cardiomyopathies have been associated with mortality). The MICONOS study group shows us that in patients with FA there seems to be no relation between cardiac involvement and exercise capacity. Therefore, exercise capacity may not be useful as a surrogate end point when analyzing cardiac function. In conclusion, a broad range of classic cardiac investigations like ECG, Holter recordings, and echocardiography, along with more advanced echocardiographic modalities and cMRI (and in subgroups of patients perhaps also electrophysiological studies and left/right sided catheterization) may be of value for monitoring FA patients in clinical praxis and clinical trials. Incorporating a wide range of methods in cardiac evaluation in future studies will enhance our understanding of the pathophysiology of FA and the effects of future treatments. The MICONOS study group shows that standard echocardiography is of great value in patients with FA, but also that there is a place for highly sensitive echocardiographic modalities like strain and strain rate analysis in detection of minor abnormalities in myocardial function. This corresponds with previous findings in FA where small functional changes precede the development of morphological abnormalities.\textsuperscript{10}

Having well described this FA cohort, the MICONOS study group has a unique opportunity to follow the development of FA cardiomyopathy over time, to enhance our knowledge of the natural history of FA, and to determine the clinical value of the suggested classification. With great expectations we will await follow-up data from this group to give a clear indication on the rate of progression (ie, the rate of recommended screening interval). At the same time, the group’s multicenter and multidisciplinary approach offers the best possible potential to investigate new therapies.

**Need for Clinical Algorithms to Manage Rare Cardiomyopathies**
Cardiac involvement is part of several other rare neurological, metabolic, and storage diseases as well as primary muscular diseases. These include other mitochondrial diseases (eg, the carnitine transporter defect and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), several
primary muscular diseases (eg, myotonic dystrophy type 1 and 2 and Becker and Duchenne muscular dystrophy), and storage diseases (eg, Fabry disease, familial amyloidosis, and metabolic diseases), and pediatric syndromes (eg, Leopard and Noonan syndromes).

In most of these diseases, we have no clear recommendations for timing of initiation of screening, screening intervals, and screening content. The MICONOS study group adds to the awareness of the importance of genetic diagnostics in the future cardiology setting. Furthermore, this study should increase the awareness among cardiologists that several of our cardiac patients with well-known myocardial diseases may have involvement of other organ systems, necessitating a multidisciplinary approach. In this context, it is of major importance that journals dedicated to medical specialties invite articles with multidisciplinary approaches even when study populations are small.14 With FA as an example, the MICONOS study group illustrates the clear benefit of a multicenter approach to increase the level of evidence in rare cardiomyopathies.

In order to ensure proper and timely identification of rare cardiac disease entities, and especially those that are potentially reversible, the development of clinically applicable algorithms are urgently needed. Thus, after routine cardiac assessment, establishment of a cardiac phenotype, and the exclusion of common causes for a cardiomyopathy such as hypertension, ischemic heart disease, thyroid disease, alcohol abuse, and myocarditis, the major challenge is to identify the actual, rare cause. This requires the cardiologist to identify syndromes or multiorgan diseases but may also depend on the availability of advanced biochemistry testing (eg, in Fabry disease, connective tissue disorders, or familial amyloidosis) and genetic testing (eg, for sarcomere gene mutations and Lamin A/C mutations). Next-generation sequencing using cardiac platforms may prove to be a very important tool in such algorithms. Algorithms for clinical management should include documented treatment modalities and follow-up regimens that in many cases would include multidisciplinary teams. For inherited cardiac diseases, algorithms including presymptomatic cascade screening and genetic counseling are obligatory.15 Considerable efforts from cardiology societies are needed to reach these goals.

Interestingly, the European Union has decided that all European Union member states should have a national strategy for management of rare diseases in place by 2013. It is essential that such strategies facilitate the establishment of international multicenter approaches to registries and clinical trials.

Disclosures

None.

References


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