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

**Running title:** Jensen et al.; Cardiomyopathy in Friedreich’s ataxia

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Friedreich’s ataxia (FA) is an autosomal recessively inherited neurodegenerative disease that most often presents in childhood or in young adults. A substantial proportion of the patients with FA also develops a cardiomyopathy that mainly presents as left ventricular hypertrophy (FA-CM). The mean life expectancy is significantly reduced to approximately 40 years, and approximately 60% of patients with FA die from cardiac causes\(^1\),\(^2\). The prevalence of FA is 0.1-4.7:100,000 and estimated 9,000 Americans are affected\(^3\). The potential ability to reduce the disease progression or even reverse the 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 MICONOS study group investigated such markers\(^4\).

Early identification of FA as the etiology of a newly identified cardiomyopathy depends on the cardiologists’ ability to identify the extra-cardiac 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 pediatricians or neurologists’ 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 al.\(^6\) 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 the ATP repletion. In combination with decreased iron
chelating capacity in the mitochondria, iron overload may cause oxidative damage\textsuperscript{7}.
Correspondingly, in FA patients, abnormal cardiac energetics has been found by MR spectroscopy\textsuperscript{8} and by cMRI impaired myocardial perfusion reserve and fibrosis has been reported\textsuperscript{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\textsuperscript{1,3}. Similar to what has been observed in other rare diseases the clinical spectrum of FA has expanded considerably after family screening and genetic testing has enabled earlier diagnosis in asymptomatic or mildly symptomatic relatives.

**The FA-CM - diagnostic approach**

In patients with FA the standard cardiac evaluation of morphology and systolic and diastolic function is echocardiography, though cardiac magnetic resonance imaging (cMRI) has gained increasing availability and 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\textsuperscript{10}. However, to identify cardiac involvement based on 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 and/or body size (e.g. body surface area (BSA)). 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 the MICONOS study group representing 13 centres from 6 European countries presents a carefully performed cross sectional study of 205 patients with FA. Based on
cMRI and echocardiographic evaluation and applying the Henry’s nomogram they suggest a classification of severity of FA-CM. In agreement with previous studies they found that approximately two thirds of the patients had some degree of FA-CM.

The Henry’s nomogram used to adjust for age and BSA may be the best available reference data to apply when analyzing cardiac dimensions. However, considering that Henry’s nomogram was developed in 1980 and was based on approximately 200 subjects with the echocardiographic technology of that time, the use of this nomogram may have limitations. The natural history of FA includes in most cases mild to severe muscle wasting, resulting in reduced BSA. 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, e.g. in hypertrophic cardiomyopathy where obesity may affect the BSA and thus interfering 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.

The 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 supporting that the four 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 if it may represent different courses of the disease.

Clinical use of the present findings
The ICARS and the FARS scores are established as tools for monitoring of neurological state in
FA, but at present no criteria for identification and monitoring of cardiac involvement in FA has 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 the neurological scores and the 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 the FA-CM**

The basic pathophysiologic features in FA are mitochondrial iron accumulation due to reduced chelation by frataxin, formation of reactive oxygen species and oxidative damage. 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 Q10. However, reports on cardiac changes in response to idebenone treatment are inconsistent (See supplemental material). 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 (inter-ventricular septal diastolic thickness, (IVSd) or left ventricular posterior wall diastolic thickness (LVPWd) > 12 mm) in a double-blinded randomized clinical trial. They found a significant reduction of IVSd and left ventricular mass index (LVMI) after 12 months treatment with idebenone. This illustrates the potentially valuable treatment with idebenone and the importance of categorization of 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 LV dysfunction or arrhythmia, and may include conventional heart failure drugs, anti-arrhythmic drugs and device implantations.

**Future studies of the FA-CM**

The possible regression of myocardial hypertrophy during *idebenone* treatment may be a major step forward in treatment of patients with FA. However, due to the limited number of patients with FA available for clinical trials it will be difficult to definitely establish a survival benefit of *idebenone*. Clinical studies of FA cardiomyopathy may therefore focus on surrogate endpoints like arrhythmia, syncope, disease progression and heart failure, i.e. endpoints which 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 endpoint, when analyzing cardiac function. In conclusion, a broad range of classical cardiac investigations like ECG, Holter recordings and echocardiography, along with more advanced echocardiographic modalities and cMRI and in subgroups of patient maybe also electrophysiological studies and left/right sided catheterization may be of value for monitoring of FA patients in clinical praxis and clinical trials. Incorporating a wide range of cardiac investigations 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 are 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 development of morphological abnormalities\textsuperscript{10}. 
Considering the well-described FA cohort by The MICONOS study group, these authors have a unique possibility to follow the development of the FA cardiomyopathy over time, to enhance our knowledge of the natural history of FA as well as 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 regarding rate of progression, i.e. the rate of recommended screening interval. At the same time their multi-centre and multi-disciplinary approach offers the best possible potential to investigate new therapies.

**Need for clinical algorithms for management of 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 like e.g. the carnitine transporter defect (CTD) and MELAS (mitochondrial encephalomopathy, lactic acidosis, and stroke-like episodes), several primary muscular diseases like e.g. myotonic dystrophy type 1 and 2, Becker’s and Duchenne’s muscular dystrophy, and storage diseases like e.g. Fabry’s disease, and familial amyloidosis, metabolic diseases and pediatric syndromes like e.g. Leopard’s and Noonan’s syndromes etc.

In most of these diseases we have no clear recommendations for timing of initiation of screening, screenings 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 multi-disciplinary approach. In this context, it is of major importance that journals dedicated to medical specialties allow publications with multi-disciplinary scientific approaches, also despite low study populations. With FA as an example the MICONOS study group illustrates the clear
benefit of a multi-centre approach in order to increase the level of evidence in rare cardiomyopathies.

In order to ensure proper and timely identification of rare and not least the (few) potentially reversible cardiac disease-entities, the development of clinically applicable algorithms are urgently needed. Thus, after the routine cardiac assessment and establishing of a cardiac phenotype followed by the exclusion of the presence of a common etiology for the cardiomyopathy like hypertension, ischemic heart disease, thyroid disease, alcohol abuse, myocarditis etc., the major challenge is to identify the rare etiology. This calls for the cardiologists ability to identify syndromes or multi-organ diseases, but may also depend on the availability of advanced biochemistry testing, e.g. in Fabry’s disease, CTD or familial amyloidosis and genetic testing, e.g. for sarcomere gene mutations, Lamin A/C mutations etc. Next generation sequencing using cardiac platforms may prove to be very important tools in such algorithms. Algorithms for clinical management should include documented treatment modalities and follow-up regimens that in many cases include multidisciplinary teams. For the inherited cardiac diseases, algorithms including pre-symptomatic cascade screening and genetic counseling are obligate\textsuperscript{15}. Considerable efforts from the cardiac societies are needed to reach these goals.

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

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References:


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