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Brief Report

Cardiac features of a novel autosomal recessive dilated cardiomyopathic syndrome due to defective importation of mitochondrial protein

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Abstract Dilated cardiomyopathy as seen in children is clinically and genetically heterogeneous, with an increasing proportion of cases known to be caused by disorders of single genes. An autosomal recessive syndrome with a high incidence of dilated cardiomyopathy was recently described in the Canadian Dariusleut Hutterite population. It is caused by homozygous mutations in a novel gene, *DNAJC19*, presumed to play a role in importation of mitochondrial proteins. We discuss the cardiac features of this syndrome, and its relationship to cardiac mitochondrial function.

Keywords: Dilated cardiomyopathy; genetics; mitochondrial disorders

Dilated cardiomyopathy is an important cause of morbidity and mortality in children. One-third to one-half of dilated cardiomyopathy is monogenic, or due to an inherited defect in a single gene.[1,2] Most of these monogenic forms are inherited in an autosomal dominant fashion, although a few autosomal recessive, X-linked, and maternally inherited mitochondrial conditions have been described. Although the details are not completely understood, genetic defects affecting the cytoskeleton, sarcolemma, and sarcomere, as well in proteins involved in production of mitochondrial energy, are thought to cause dilated cardiomyopathy via a final common pathway of myocytic death due to impaired myocardial structural integrity and generation of force.[3]

An autosomal recessive syndrome characterized by dilated cardiomyopathy and cerebellar ataxia, known as the DCMA syndrome, was recently described in the Canadian Dariusleut Hutterite population[4]. This condition bears some similarity to the X-linked Barth syndrome. In addition to an early-onset of dilated cardiomyopathy with conduction defects and non-progressive cerebellar ataxia, the variable features of the multisystem disorder include failure of growth, mild developmental delay, male genital anomalies, and increased biochemical markers of mitochondrial dysfunction in the plasma and urine, specifically 3-methylglutaconic and 3-methylglutaric acids. This syndrome is due to homozygous mutations affecting post-transcriptional splicing in the novel *DNAJC19* gene, whose product localizes to mitochondria in cardiac myocytes. It is presumed, based on its homology to yeast proteins, to play a role in importation of mitochondrial proteins and intramitochondrial transport.

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Case series

Over thirty Hutterite patients affected by the DCMA syndrome have been identified. Of these, 17 individuals, including ten males and seven females, from seven sibships consented to participation in the clinical genetic study which led to the discovery of the causative gene.[4] A retrospective review of the clinical course, echocardiographic and electrocardiographic findings was undertaken for all of these patients, who have homozygous mutations of *DNAJC19*, as summarized in the Table.

Of the 17 patients, 13 (76%) had an echocardiographic or pathological diagnosis of dilated

cardiomyopathy, with onset at a mean age of 12 months, and a range from 1 to 36 months. The cardiomyopathy was characterized by increased left ventricular end diastolic dimensions, mural thinning, and poor systolic function, with mild to severe global hypokinesia. The variant with left ventricular noncompaction, which has been reported in Barth syndrome, was not seen in this series.

In 10 of the children, congestive heart failure and/or arrhythmias led to early death, at a mean of 22 months, and with a range from 4 to 48 months. Resolution of cardiomyopathy occurred in two males diagnosed at 16 months and two years, who are currently aged 13 and 23 years, respectively. At the time of writing, both have residual mild mitral regurgitation, but otherwise normal cardiac structure and function. Another male diagnosed at two years of age had improved at the age of five years, but has persistent but clinically stable mild cardiomyopathy at the age of 15 years. An additional 4 individuals, two male and two female, presented primarily with non-cardiac features, and have thus far failed to develop cardiomyopathy.

Electrocardiographic abnormalities were documented in each of the 13 patients for whom electrocardiograms were available for review. Prolongation of the QT interval was the most common finding, documented in 8 patients. Long QT was observed both in the presence and absence of dilated cardiomyopathy, in 6 and 2 patients respectively. Of 2 patients with isolated long QT, 1 died suddenly at the age of 14 months.

Discussion

We have described the cardiac features of a novel autosomal recessive syndrome associated with a high incidence of dilated cardiomyopathy. This condition, unfortunately, is marked by high mortality, with three-quarters having succumbed to cardiac complications. In three males, nonetheless, the cardiomyopathy improved or resolved. Upon retrospective review, no clinical or echocardiographic features at the time of diagnosis distinguished these three patients, although the small size of our sample precludes statistical analysis.

At a gross cardiac structural level, there are no unique features which differentiate the dilated cardiomyopathy seen in this syndrome from that due to other aetiologies. Overall, the rate of death due to cardiac complications is higher than those reported for dilated cardiomyopathy in general,[3] but similar to those reported for dilated cardiomyopathy associated with mitochondrial disease.[5]

Interestingly, the rate of cardiomyopathy among our population appears to be greater than that reported for

Table. Cardiac features of 17 Hutterite patients with homozygous mutations of *DNAJC19*.

Patient	Sex	Age at onset of cardiomyopathy	Dilated cardiomyopathy	Electrocardiographic abnormalities	Clinical state
1	Male		No	Long QT	Stable at 15 years
2	Male	1 month	Yes	Nonspecific ST/T changes	Deceased at 4 months
3	Male	2 years	Yes	Long QT	Cardiomyopathy improved; stable at 15 years
4	Male	8 months	Yes	Nonspecific ST/T changes	Deceased at 8 months
5	Male	17months	Yes	Long QT	Deceased at 4 years
6	Male	17 months	Yes	Not available	Deceased at 17 months
7	Female	9 months	Yes	Long QT	Deceased at 10 months
8	Male		No	Nonspecific ST/T changes	Stable at 24 years
9	Female		No	Nonspecific ST/T changes	Stable at 22 years
10	Male	2 years	Yes	Long QT	Cardiomyopathy resolved; stable at 23 years
11	Female	6 months	Yes	Long QT, first degree AV block	Deceased at 16 months
12	Female	15 months	Yes	Not available	Deceased at 15 months
13	Female	3 years	Yes	Not available	Deceased at 3 years
14	Male	16 months	Yes	Long QT	Cardiomyopathy resolved; stable at 13 years
15	Male	18 months	Yes	Nonspecific ST/T changes	Deceased at 18 months
16	Female	12 months	Yes	Not available	Deceased at 4 years
17	Female		No	Long QT	Deceased at 14 months

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mitochondrial disorders collectively.[5] This may be an artefact of the small size of the sample or bias in ascertainment. If true, this finding could be related to the susceptibility of cardiac myocytes, in particular, to the specific underlying molecular defect, although the mechanism is not clear. Also, nuclear gene defects, such as the mutation seen in DCMA syndrome, would affect all the mitochondria in every cell. In contrast, mutations in mitochondrially encoded genes are characterized by heteroplasmy whereby any given cell can have varying degrees of normal or mutant mitochondrial load resulting in greater variability in disease severity.

Disorders in the production of mitochondrial energy in general are extremely clinically heterogeneous, and can involve multiple organs and tissues, with symptoms presenting at different ages. Mitochondrial dysfunction is frequently associated with cardiomyopathy and conduction disturbances.[6,7] Presumably, this is a consequence of the dependence of the heart on aerobic metabolism. Some mitochondrial disorders directly affect genes which encode subunits of the respiratory chain.[6] Production of mitochondrial energy, however, involves the coordinated transport, assembly and functioning of hundreds of proteins, and can be more indirectly impaired. For example, patients with *SURF1* mutations have defective assembly of one of the five respiratory chain complexes, and present with dilated cardiomyopathy.[8] X-linked cardiomyopathy with neutropenia and 3-methylglutaric academia, known as the Barth syndrome, is caused by mutations in a mitochondrial inner membrane protein of unknown function, which affects cardiolipin, a molecule known to be necessary for proper functioning of the respiratory chain.[9]

DNAJC19 has strong homology to the yeast protein Tim14, which localizes to the inner mitochondrial membrane and functions as part of a multi-protein complex involved in the transport of mitochondrial-targeted proteins into the mitochondrial matrix.[10] Virtually all of the estimated 1000 mitochondrial proteins are encoded by nuclear genes, and therefore are synthesized in the cytosol and imported into the mitochondria.[6] Defective importation of protein, therefore, could prevent appropriate mitochondrial localization of both mitochondrial respiratory chain and matrix proteins. Although the exact mechanism is not clear, this seems a plausible explanation for the mitochondrial cytopathy seen in this disorder.

Individuals with this novel syndrome are being followed prospectively with clinical, echocardiographic and electrocardiographic assessment. This cohort now includes several children without cardiac disease, who are being monitored for the development of cardiomyopathy and long QT, in hopes that early identification and prompt treatment will retard the progression towards congestive heart failure and improve chances of survival. In addition, several patients with and without evidence of cardiomyopathy are being treated with a mitochondrial "cocktail" consisting of nonspecific enhancers of mitochondrial function in hopes of preventing, stabilizing or reversing dilated cardiomyopathy.

In the future, the introduction of a population-specific screening test, as well as the identification of non-Hutterite patients with mutations in DNAC19 in conjunction with longitudinal studies of outcome, will help further to delineate the cardiac phenotype and enable further predictions about prognosis and mortality. Further work is also being undertaken to elucidate the molecular processes involved. This will potentially contribute to the understanding of the multiple mechanisms of mitochondrial dysfunction in the pathogenesis of dilated cardiomyopathy, helping to define potential targets of therapy.

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