Published in final edited form as:

Congest Heart Fail. 2012 ; 18(3): 183–186. doi:10.1111/j.1751-7133.2011.00265.x.

Severe Dilated Cardiomyopathy in a Patient with Myotonic Dystrophy Type 2 and Homozygous Repeat Expansion in *ZNF9*

Teresa M. Lee¹, Mathew S. Maurer², Izabela Karbassi³, Corey Braastad³, Sat D. Batish³, and Wendy K. Chung¹

¹Columbia University Medical Center Department of Pediatrics 1150 St. Nicholas Avenue, RBI 620 New York, NY 10032 USA

²Columbia University Medical Center Department of Medicine 622 West 168th Street, PH 12-1291 New York, NY 10032 USA

³Athena Diagnostics, Inc. Four Biotech Park 311 Plantation Street Worcester, MA 01605 USA

Keywords

Dilated cardiomyopathy; Myotonic dystrophy

Introduction

Cardiomyopathy is a well-recognized association in skeletal myopathies such as Duchenne, Becker, and Emery-Dreifuss muscular dystrophy, sarcoglycanopathies, glycogenosis disorders, mitochondrial myopathies, and myotonic dystrophy type 1 and 2.¹ Myotonic dystrophy type 2 (DM2), also known as proximal myotonic myopathy, is an autosomal dominant disorder characterized by myotonia (90%) and muscle dysfunction (82%).² Other less common clinical manifestations include posterior subcapsular cataracts, insulin insensitive diabetes mellitus type 2, testicular failure, and a variety of cardiac abnormalities including supraventricular tachycardia, atrial fibrillation, ventricular ectopy, and heart failure.³ Dilated cardiomyopathy and non-compaction cardiomyopathy have been reported in DM2 as well.^{4,5}

Expansion of the CCTG within a complex repeat motif, (TG)_n(TCTG)_n(CCTG)_n, in the first intron of the gene Zinc Finger Protein 9, *ZNF9* (*CNBP*) causes DM2. The normal allele size of the complex repeat is between 104 and 176 bp. RNA transcribed from the expanded allele results in toxic effects within the cell. Specifically in DM1, RNA containing the abnormal repeat interacts with RNA-binding proteins that then lead to downstream effects that can disrupt regulation of alternative splicing, mRNA translation, or mRNA stability.⁶

Case Report

The patient presented at the age of 65 with a four-year history of worsening exercise intolerance. She was only able to walk for five minutes before developing dyspnea, chest discomfort, and angina. In addition, she had noted difficulty rising from the floor or a low chair without assistance, and had occasional diplopia, mild dysphagia, and skeletal muscle weakness.

Her medical history was significant for cataracts and multiple cardiac procedures. She was diagnosed with multi-vessel coronary artery disease and underwent a coronary artery bypass surgery four years prior to presentation. She had progressive symptoms compatible with heart failure and underwent mitral and tricuspid valve repairs for regurgitant valve disease a year later. At that time she also had removal of a papillary fibroelastoma from the aortic valve. She continued to have symptoms of chest fullness, shortness of breath, and fatigue. She underwent coronary angiography and had percutaneous stenting one year prior to this admission. After each intervention she only had temporary relief of her symptoms with subsequent recurrence. As well she developed atrial fibrillation and NYHA Class III heart failure. She was referred to our institution for additional management. Her medications included digoxin 0.125 mg po daily, metoprolol 12.5 mg po daily, lisinopril 10 mg po daily, furosemide 40 mg po daily, isosorbide mononitrate 30 mg po daily, rosuvastatin 2.5 mg po daily, aspirin 81 mg po daily, and coumadin 2.5 mg po daily. She was treated with milrinone which was discontinued due to lack of clinical benefit.

The family history was notable for a brother who died at age 33 after a heart transplant for cardiomyopathy and a sister who died at 42 after her second mitral valve replacement for what was thought to be rheumatic heart disease (Figure 1). There is also a sister who underwent ablation for an irregular heartbeat. Her two other brothers are alive; the oldest had a myocardial infarction in his 60s, and the other brother had a coronary stent in his 60s. Her father died in his 50s from an unknown cancer and her mother died at the age of 85 after hip surgery. Both of her children and all her nieces and nephews are alive and clinically asymptomatic.

On initial physical examination she was a thin woman with frontal balding. Her cardiac examination was significant for jugular venous distention noted to the jaw line. She had an irregularly, irregular heart beat with a S3 gallop and a left ventricular heave. Bibasilar rales were heard to the mid-chest. She had 3+ pitting edema to the thighs bilaterally. Her neurological examination showed mild weakness in the deltoids, biceps, finger extensors, finger flexors, and iliopsoas muscles. Reflexes were hypoactive and grip myotonia was present.

Surface ECG showed atrial fibrillation with a right bundle branch block, left anterior fascicular block, and a prolonged QTc of 497 ms. Transthoracic echocardiography showed a mildly dilated left ventricle with severely reduced left and right ventricular function and bi-atrial dilation with an ejection fraction of 20-25%. Right and left heart catheterization demonstrated patent grafts with elevated filling pressures (right atrial pressure of 18 mmHg, right ventricular pressure of 51/13 mmHg, pulmonary artery pressure of 50/23 mmHg with a mean of 32 mmHg, and pulmonary capillary wedge pressure of 20 mmHg). Her pulmonary artery saturation was 38% with a cardiac output of 2.4 L/min by Fick and a cardiac index of 1.5 L/min/m² (Figure 2).

Electromyography testing showed prominent myotonic discharges. Genetic testing for myotonic dystrophy type 1 was normal. Muscle biopsy revealed features of a chronic and active myopathy with the presence of peculiarly atrophic fibers and markedly increased internal nuclei consistent with myotonic dystrophy.

At the age of 67 the patient died of heart failure.

Results

DM2 genetic testing of the proband (II.2) showed that she had a 15,600 bp expansion on one allele of *ZNF9* and a 4,700 bp expansion on the other allele. Subsequent testing in the family showed that her asymptomatic brother (II.1) had a 3,600 bp expansion in one allele. Her

daughter (III.1) was found to have a 1,300 bp expansion, and her son (III.2) had a 900 bp expansion (Figure 1). Both children were asymptomatic. On echocardiogram the daughter had borderline left ventricular enlargement and the son had borderline left atrial enlargement.

Discussion

While there have been multiple reports of homozygosity in myotonic dystrophy type 1, homozygosity for the CCTG expansion in *ZNF9* is extremely rare due to the rarity of DM2 with only one published report from a large consanguineous family.⁷ In this report the oldest homozygote had the most severe DM2 phenotype within her family. She had leg weakness starting at age 40, cataracts at 46, diabetes mellitus, ventricular arrhythmia, and dilated cardiomyopathy. Her two homozygous affected sisters had milder symptoms at the time of the report. After comparison with six other heterozygous family members, the authors concluded that homozygotes within this family demonstrated a similar clinical course with no significant difference in muscle histology and brain imaging. However, in our family, bi-allelic expansions appear to demonstrate a more severe phenotype although we have limited genotypic information on other family members. Presumably both parents were carriers, yet neither demonstrated symptoms of DM although her father died early in his 50s of cancer. Her brother who is a proven carrier has no symptoms of DM2 in his 60s. The deceased brother (II.3) and sister (II.6) may both have been homozygotes like the proband and this hypothesis could explain the early symptoms and severity of disease. Unfortunately, a major limitation of our report is the inability to genotype these deceased individuals. Finally, although young, both of the proband's children who are carriers have been thoroughly evaluated and are currently disease free.

DM2 is generally thought to be less severe and to have less cardiac involvement than its related disorder myotonic dystrophy type 1. However, it is now becoming recognized that severe cardiomyopathy can occur in DM2 as well.⁴ Early recognition of cardiac manifestations is important as there are therapies available that can modify the clinical course. Surveillance for individuals with primary myopathies should include an electrocardiogram and echocardiogram. Ambulatory 24-hour Holter monitoring, exercise stress test, SPECT, cardiac MRI, PET, coronary angiography, or myocardial biopsy may be needed to diagnose the condition particularly if the neurological diagnosis is not definitive and to further define the phenotypic expression.¹ One study has suggested that cardiac MRI/MRS may be a more sensitive tool for evaluation for cases in which subclinical cardiomyopathy is suspected.⁸

Atrioventricular and intraventricular conduction delay is common in myotonic dystrophy. Arrhythmias can occur early on or often even before the onset of neuromuscular symptoms and can sometimes lead to sudden cardiac death.⁹ At the present time, cardiac manifestations are much better studied in myotonic dystrophy 1. Studies in these patients have shown that conduction disease and prolongation of the PR and QTc intervals are associated with a higher risk of sudden cardiac death.¹⁰ One DM2 case control study found that conduction defects were less frequent in DM2 patients when compared to age-matched type 1 patients but that supraventricular arrhythmias had a similar prevalence.¹¹

One study by Schoser et al. in 2004, found the frequency of sudden cardiac death before the age of 45 in DM2 patients to be 4/297. All four patients had dilated cardiomyopathy, and cardiac histopathology demonstrated pathogenic CCUG ribonuclear inclusions in the cardiac myocytes.¹² The efficacy of pacemaker/defibrillator implantation in this population is not well defined. Although an AICD will prevent sudden death, heart failure, respiratory failure due to diaphragmatic involvement, and skeletal muscle weakness are progressive and fatal.

In conclusion, physicians should be aware of the risk of cardiac complications in DM2 patients, especially those rare patients with two *ZNF9* repeat expansions. Close cardiac monitoring with biannual echocardiogram and ECG should be considered in all genetically at risk *ZNF9* carriers. Initiation of cardiac medications may slow the progression of disease or attenuate heart failure symptoms.

References

1. Finsterer J, Stöllberger C. Cardiac involvement in primary myopathies. *Cardiology*. 2000; 94:1–11. [PubMed: 11111138]
2. Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. *J Neurol Neurosurg Psychiatry*. 2010; 81:358–367. [PubMed: 20176601]
3. Day JW, Roelofs R, Leroy B, Pech I, Benzow K, Ranum LP. Clinical and genetic characteristics of a five-generation family with a novel form of myotonic dystrophy (DM2). *Neuromuscul Disord*. 1999; 9:19–27. [PubMed: 10063831]
4. von zur Mühlen F, Klass C, Kreuzer H, Mall G, Giese A, Reimers CD. Cardiac involvement in proximal myotonic myopathy. *Heart*. 1998; 79:619–621. [PubMed: 10078095]
5. Wahbi K, Meune C, Bassez G, Laforêt P, Vignaux O, Marmursztejn J, Bécane HM, Eymard B, Duboc D. Left ventricular non-compaction in a patient with myotonic dystrophy type 2. *Neuromuscul Disord*. 2008; 18:331–333. [PubMed: 18395448]
6. Lee JE, Cooper TA. Pathogenic mechanisms of myotonic dystrophy. *Biochem Soc Trans*. 2009; 37:1281–1286. [PubMed: 19909263]
7. Schoser BG, Kress W, Walter MC, Halliger-Keller B, Lochmüller H, Ricker K. Homozygosity for CCTG mutation in myotonic dystrophy type 2. *Brain*. 2004; 127:1868–1877. [PubMed: 15231584]
8. Schneider-Gold C, Beer M, Köstler H, Buchner S, Sandstede J, Hahn D, Toyka KV. Cardiac and skeletal muscle involvement in myotonic dystrophy type 2 (DM2): a quantitative ³¹P-MRS and MRI study. *Muscle Nerve*. 2004; 30:636–644. [PubMed: 15452841]
9. Verhaert D, Richards K, Rafael-Fortney JA, Raman SV. Cardiac involvement in patients with muscular dystrophies: magnetic resonance imaging phenotype and genotypic considerations. *Circ Cardiovasc Imaging*. 2011; 4:67–76. [PubMed: 21245364]
10. Breton R, Mathieu J. Usefulness of clinical and electrocardiographic data for predicting adverse cardiac events in patients with myotonic dystrophy. *Can J Cardiol*. 2009; 25:23–27.
11. Wahbi K, Meune C, Bécane HM, Laforêt P, Bassez G, Lazarus A, Radvanyi-Hoffman H, Eymard B, Duboc D. Left ventricular dysfunction and cardiac arrhythmias are frequent in type 2 myotonic dystrophy: a case control study. *Neuromuscul Disord*. 2009; 19:468–472. [PubMed: 19481939]
12. Schoser BG, Ricker K, Schneider-Gold C, Hengstenberg C, Dürre J, Bültmann B, Kress W, Day JW, Ranum LP. Sudden cardiac death in myotonic dystrophy type 2. *Neurology*. 2004; 63:2402–2404. [PubMed: 15623712]

Figure 1.

Pedigree from DM2 family with the proband indicated by an arrow. Numbers below the pedigree symbols represent repeat length in the four individuals who were genetically tested. Aside from the proband, the other genetically tested individuals with a single DM2 repeat expansion are asymptomatic for neuromuscular or cardiac symptoms. The proband had muscle weakness, cataracts, and dilated cardiomyopathy.

Figure 2.

A) Surface ECG showing atrial fibrillation, right bundle branch block, left anterior fascicular block, and a prolonged QTc of 497 ms. B) Transthoracic echocardiography in the apical 4 chamber and parasternal short axis views showing a mildly dilated left ventricle and dilated atria consistent with restrictive cardiomyopathy with concomitant severely reduced left and right ventricular function with an left ventricular ejection fraction of 20-25%. C) Right atrial pressure tracing showing elevated pulmonary capillary wedge pressure of 18 mmHg. D) Chest film showing mildly enlarged cardiac silhouette with small right pleural effusion and generalized haziness.