Editorial

Repeats and Survival in Myotonic Dystrophy Type 1

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The myotonic dystrophies are multisystem disorders characterized by progressive skeletal muscle weakness, myotonia, cataracts, endocrine abnormalities, cognitive impairment, and cardiomyopathy. Myotonic dystrophy type 1 (DM1) is the most common of the myotonic dystrophies. The cardiac-specific phenotypes of DM1 include progressive atrioventricular conduction delay, atrial and ventricular arrhythmias, impaired left ventricular diastolic and systolic dysfunction, impaired contractile reserve, and mesocardial fibrosis. Cardiac conduction abnormalities in patients with DM1 range from asymptomatic preclinical conduction system disease to complete heart block or ventricular arrhythmias leading to sudden death. In addition, DM1 patients are at increased risk for left ventricular dysfunction, ranging from impaired global longitudinal strain and impaired contractile reserve with preserved resting ejection fraction to overt left ventricular systolic dysfunction leading to overt heart failure.

See Article by Chong-Nguyen et al

Much concerning the pathogenesis of DM1 has been elucidated. Abnormal repeat expansion of a CTG triplet repeat in the 3′ untranslated region of the *DMPK* gene (dystrophia myotonica protein kinase)[1] leads to accumulation of mutant transcripts in the nuclei of cells that in turn lead to dysregulated splicing and altered transcription.[2,3] Sequestration of RNA-binding proteins including MBNL1 by *DMPK* mRNA CUG repeats and compensatory upregulation and activation of CUGBP1 (CUG-binding protein) lead to altered splicing of multiple transcripts.[4–6] In addition to splicing defects, reduction of the DM protein kinase itself may contribute to the cardiac conduction defect seen in patients with DM1.[7,8] Aberrant differential splicing of the *SCN5A* mRNA, with switching of exon 6 from the adult exon 6B to fetal 6A, is likely contributory to reductions in cardiomyocyte excitability and increased atrioventricular conduction delay.[9]

There is extensive evidence of a relationship between age-dependent neuromuscular dysfunction and *DMPK* CTG repeat length in DM1. Indeed, clinical phenotypes of late-adult-onset, classical-adult-onset, childhood-onset, and congenital-onset disease are differentiated in part by CTG repeat lengths of 50 to 100, 50 to 1000, >800, and >1000 CTG repeats, respectively.

There is conflicting evidence on the importance of CTG repeat length with regard to cardiac conduction, arrhythmias, and survival in DM1. Early analysis of the arrhythmias in DM1 multicenter registry[10] of 395 myotonic dystrophy patients, of whom 342 had confirmatory genotyping, found severity of muscular disability, conduction abnormalities, and likelihood of arrhythmia diagnosis each correlated with CTG repeat length treated as a continuous variable. The correlation of PR and QRS prolongation with repeat length was confirmed in additional studies.[11,12] Breton and Mathieu,[13] in a separate cohort of 428 patients followed up for a mean of 11.7 years, did not find an association between CTG repeat length and risk of sudden death or pacemaker implantation but did demonstrate a correlation of risk of sudden death or pacemaker placement with neuromuscular impairment. Invasive electrophysiology study determined that atrioventricular conduction disturbances were correlated with inducibility of atrial and ventricular arrhythmias but not with repeat length.[14] Bhakta et al[15] showed evidence for an association between left ventricular systolic dysfunction and clinical heart failure with all-cause and cardiac mortality but did not find an association with CTG repeat length. Groh et al,[16] in a seminal report of the Arrhythmias in DM1 study of 406 patients with genetically confirmed DM1 followed up for a median of 6.5 years, identified severe ECG findings at baseline (QRS duration of >120 ms, PR interval of >240 ms, second- or third-degree atrioventricular block, and rhythms other than sinus) and atrial tachyarrhythmias as independent risk factors for sudden death during follow-up, whereas age, heart failure, and neuromuscular impairment were associated with risk of death from respiratory failure. In this study, size of CTG expansion was not significantly associated with sudden death, death caused by respiratory failure, or death from any cause.

In this issue of *Circulation: Cardiovascular Genetics*, Chong-Nguyen et al[17] provides evidence to support an association between repeat expansion size and cardiac outcomes in DM1. Out of 1014 patients, 855 underwent genotyping at the time of baseline evaluation. These genotyped patients with DM1 were followed up for a median of 11.5 years. Chong-Nguyen et al confirm that total survival in myotonic dystrophy is associated with quartile of CTG expansion size, with larger expansion portending poorer prognosis during follow-up (37% mortality in the highest quartile of ≥830 CTG repeats versus 19% to 22% mortality in first to third quartiles). Pacemaker implantation and supraventricular arrhythmia during follow-up were also associated with CTG expansion size on multivariate analysis. Sudden death during follow-up was correlated with CTG expansion size only when age of onset was not included in the multivariate model. In contemporaneous work, Wahbi

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et al[18] had shown in 1388 consecutive patients with a diagnosis of DM1 that age, left bundle branch block, and family history of sudden death were independent predictors of sudden death. Major conduction defects were associated with a history of syncope, atrial fibrillation, and conduction abnormalities on ECG; association with repeat length was not addressed.

The 855 patient cohort included a significant proportion with cardiac disease at baseline, with almost half exhibiting conduction system disease and ≈1 in 10 having left ventricular dysfunction or supraventricular arrhythmia. During the study period, 181 patients (21%) underwent pacemaker implantation and 11 underwent implantable cardioverter defibrillator placement. During follow-up, nearly a quarter (210 patients) of patients died. Importantly, a plurality (68) of patients died because of respiratory failure, whereas 32 died suddenly and 12 died because of heart failure. The cause of death for the remaining 98 patients is not reported, reflecting a limitation of registry-based natural history studies. As in previous studies, noncardiac death was responsible for a significant majority of adjudicated events. Indeed, several of the sudden death events detailed by Wahbi et al were caused by pulmonary embolism and not primary arrhythmia. Ten of 19 patients with documented rhythm at time of sudden death presented with brady-arrhythmia, asystole, or pulseless electric activity. Although the event rates of total death were high, the frequency of sudden death was found to be relatively low, limiting the power to detect significant associations in this patient cohort.

In this study, those with left ventricular dysfunction were not aggressively treated at baseline, with only a slim majority receiving renin–angiotensin–aldosterone inhibitors and a quarter of those with left ventricular dysfunction receiving β-blockers, likely because of concerns of worsening conduction system disease. The use of neurohormonal blockade may alter the natural history of systolic dysfunction, arrhythmias, and heart failure in this population. Furthermore, the use of medications across all quartiles of triplet repeat was not significantly different at baseline, and medication use on follow-up is not detailed. Whether some of the subsequent outcomes would be preventable with medical therapy is not known. In a small crossover trial,[19] the class I antiarrhythmic mexiletine has been shown to reduce myotonia, whereas definitive trials of class I antiarrhythmics have consistently shown harm in patients with structural heart disease. The correlation between repeat length and increased arrhythmia risk could be confounded by excess mexiletine use in the highest risk subgroup. Additionally, because pacemaker implantation is likely to prevent bradycardia-mediated death in a proportion of patients, the appropriate use of pacemakers may attenuate the magnitude of association for other outcomes.

How do we reconcile the findings of this study with those before? Each of the aforementioned studies have a low event rate of sudden death and similarly frequent conduction abnormalities. The precise method by which triplet repeat length was tested for association with other parameters is likely contributory to conflicting results. Indeed, correcting for confounders and covariates, such as age and age of onset, attenuates or eliminates the significance of the association between triplet expansion size and clinical outcomes. Chong-Nguyen et al present multivariate models both including and excluding age of onset and, for the critical question of association with sudden death, find that sudden death is only associated with CTG repeat length when age of onset is not included in the multivariate analysis. Similarly, the findings of association with repeat length in earlier studies seem to be attenuated when age, age of onset, or correlates of age of onset such as neuromuscular symptom severity are included in the model.

Clinically, age of onset and repeat length may have different utilities. Indeed, in practice, cascade genetic testing in families known to have DM1 may lead to the identification of patients at risk for disease onset before overt manifestation of disease. Knowledge of repeat length at an early or preclinical stage of disease may lead to changes in screening strategy. Alternatively, age of onset may be more accurately demonstrated in patients who are followed up closely through the early stages of disease, whereas those identified post–symptom onset may be undiagnosed or misdiagnosed for years before presentation and present at a more advanced stage of cardiac disease.

These data suggest that knowledge of *DMPK* CTG repeat length can impact the approach to clinical care. Those with longer repeats are at higher risk of dying from any cause and are more likely to meet criteria for pacemaker implantation. Closer multidisciplinary care and treatment is likely warranted in patients with higher repeat count. A practical approach based on the currently available data would be to screen patients with longer repeat lengths at relatively frequent intervals while screening those with low repeat lengths less often, particularly earlier in life. These data are not sufficient, however, to restrict device implantation based on CTG repeat length nor to eliminate cardiac screening in DM1 patients harboring shorter CTG repeat expansions. Furthermore, prospective studies of larger, multinational cohorts are needed to determine the optimum approach to cardiovascular care in patients with myotonic dystrophy.

Disclosures

None.

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