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.

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) leads to accumulation of mutant transcripts in the nuclei of cells that in turn lead to dysregulated splicing and altered transcription. 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. In addition to splicing defects, reduction of the DM protein kinase itself may contribute to the cardiac conduction defect seen in patients with DM1. 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.

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 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. Breton and Mathieu, 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. Bhakta et al 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, 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 provide 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...
a small crossover trial,19 the class I antiarrhythmic mexiletine up is not detailed. Whether some of the subsequent outcomes significantly different at baseline, and medication use on follow-
and heart failure in this population. Furthermore, the use of renin–angiotensin–aldosterone inhibitors and a not aggressively treated at baseline, with only a slim major-
den death was found to be relatively low, limiting the power to
arrhythmia, asystole, or pulseless electric activity. Although
dmented rhythm at time of sudden death presented with brady-
and not primary arrhythmia. Ten of 19 patients with docu-
denied by Wahbi et al were caused by pulmonary embolism
adjudicated events. Indeed, several of the sudden death events
noncardiac death was responsible for a significant majority of
registry-based natural history studies. As in previous studies,
remaining 98 patients is not reported, reflecting a limitation of
12 died because of heart failure. The cause of death for the
remaining 98 patients is not reported, reflecting a limitation of
place...


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