Myotonic dystrophy: time for evidence-based therapy

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This editorial refers to ‘Cardiac involvement in myotonic dystrophy: a nationwide cohort study’, by M. Lund et al., on page 2158.

Lund and colleagues report on the association between cardiac disease and myotonic dystrophy using data derived from Danish patient registries.1 The major finding that myotonic dystrophy is strongly associated with cardiac disease throughout life emphasizes the importance of continuous cardiac follow-up and the urgent need for prevention and treatment of cardiac complications in this disease. The study also illustrates the value of research based on routinely collected healthcare data.

Myotonic dystrophy is the most common muscular dystrophy in adults (incidence 1 in 8000 live births).2 There are two genetically distinct forms; myotonic dystrophy type 1 (DM1 or Steinert’s disease) and the rarer myotonic dystrophy type 2. DM1 is caused by expansion of a repetitive trinucleotide sequence (CTG) in the 3’-untranslated region of the myotonic dystrophy protein kinase (DMPK) gene which, when transcribed into CUG-containing RNA, forms aggregates of mutant transcripts that sequester RNA-binding proteins and cause abnormal splicing of downstream effector genes. In addition to this ‘RNA toxicity’ mechanism, other effects on protein translation and turnover and activation of cellular stress pathways have been observed3–5 (Figure 1).

Clinically, DM1 is characterized by myotonia, progressive myopathy, and multiorgan involvement including cataracts, diabetes, thyroid dysfunction, hypogonadism, cognitive impairment, and gastrointestinal abnormalities.2 Pathological studies have shown that the heart in patients with DM1 is characterized by fibrosis and fatty replacement in the specialized conduction system and in both ventricles,8 and numerous clinical studies have reported progressive conduction disease, atrial and ventricular arrhythmia, and ventricular dysfunction.3,9,10 Yet, in spite of decades of study, three questions continue to trouble clinicians caring for patients with the disease. (i) What is the frequency of heart abnormalities in DM1? (ii) What is their impact on prognosis? (iii) Is it possible to treat and prevent cardiac complications and thereby improve survival.

The answers to these questions are elusive because of the rarity of the disease and the lack of prospective data from large unselected patient populations. To date, the most informative data have come from a few large referral centres and systematic reviews of the literature. In a pooled analysis (comprising 1828 cases), the most frequent cardiac abnormalities were prolongation of the PR and QT intervals.7 With the exception of ventricular premature beats, atrial and ventricular arrhythmia were reported in <10% of cases and left ventricular systolic impairment in only 7.2%. The estimated annual risks for pacemaker or implantable cardioverter defibrillator (ICD) implantation during follow-up were 1% and 0.2%, respectively.

The study by Lund and colleagues is the first to use a National Patient Registry (NPR) to ascertain cases. The authors identified a cohort of >1000 patients diagnosed between 1977 and 2011 using the International Classification of Diseases 8 and 10 coding systems. These data were linked to various Danish health registers and the Civil Registration System (CRS) and were cross-referenced with information on genetic testing obtained directly from diagnostic laboratories. Information on incident cardiac disease and implantation of pacemakers and ICDs were also obtained from the NPR.

During follow-up, 22.3% of the cohort died. The standardized incidence ratio (SIR) for any cardiac disease was 3.42 (95% confidence interval (CI) 3.01–3.86), rising to 6.91 (95% CI 5.93–8.01) for any cardiac disease in the selected subgroups. The risk was particularly high in the first year after the diagnosis of myotonic dystrophy but remained elevated in subsequent years in all age categories. The results were similar in separate analyses of genetically confirmed DM1 patients.

Unfortunately, the authors were unable to examine in detail the relationship between cardiac disease and survival or the impact of therapy on outcomes. Previous studies have reported an overall mortality more than seven times higher than that of an age-matched reference population, with a mean age at death of 53 years.11 In most reports, respiratory failure and cardiovascular disease are the most common causes of death, accounting for ~40% and 30% of fatalities.
Figure 1 Summary of pathophysiological pathways that may be involved in the cardiac manifestations of myotonic dystrophy type 1. The current disease paradigm for myotonic dystrophy type 1 is based on a toxic RNA gain-of-function hypothesis that results in gene missplicing, dysregulation of transcription, abnormal protein translation and turnover, and the activation of cellular stress pathways. Mutant \((\text{CTG})_n\) expansions in non-coding regions of DMPK (myotonic dystrophy protein kinase) are transcribed into CUG-containing transcripts that fold into an imperfect double-stranded hairpin structure that forms RNA foci in the nucleus. These sequester members of the MBNL RNA-binding protein family, such as MBNL1, in ribonuclear foci, resulting in loss of function and dysregulation of MBNL splice and transcription targets and microRNA metabolism. DMPK-CUGn RNA also activates protein kinase C (PKC), resulting in phosphorylation, stabilization, and up-regulation of CUG-binding protein 1 (CUGBP1 or CELF1) that leads to alternative splicing and abnormal translation, and protein turnover. Sequestration of transcription factors and other nuclear factors also contributes to dysregulation of gene expression. Cardiac genes that are affected in animal models are shown, together with the possible clinical effects of gene dysfunction.
respectively. Disease-related cardiac mortality results from progressive left ventricular dysfunction, pulmonary embolism, or unexpected sudden death. In the study by Lund et al., 12% of the main cohort had a device implanted either before or after diagnosis of myotonic dystrophy.

For most patients with myotonic dystrophy, arrhythmias and left ventricular dysfunction are managed in accordance with current practice guidelines for common cardiac conditions, although there is little, if any, evidence to support this. There is considerable debate on the management of occult conduction disease in asymptomatic DM1 patients, particularly in relation to the use of invasive measurement of HV intervals. An interval of >70 ms has been suggested as an indication for prophylactic pacemaker implant, but data on the rate of progression to complete atioventricular block are contradictory and the prognostic benefit of pacing uncertain. The role of ICDs is even less clear. In a recent non-randomized comparison of an invasive electrophysiological testing strategy vs. standard clinical assessment, individuals with evidence of conduction disease on a 12-lead electrocardiogram (ECG) had a poorer overall survival than those with normal conduction, whether or not they underwent electrophysiological study to measure the HV interval. There was a significantly lower incidence of sudden cardiac death in patients that underwent the invasive testing strategy, but patients in the non-invasive testing group underwent permanent pacing, suggesting that they already had disease sufficiently advanced to indicate the need for device implantation without recourse to electrophysiological study. Importantly, sudden cardiac deaths were observed in patients with both pacemakers and ICDs.

In essence, the paper by Lund et al. shows us the need to work collaboratively to solve important clinical questions in this and other rare diseases. We can take it as a fact that patients with myotonic dystrophy are prone to cardiac complications; the collective challenge is to use this knowledge as the basis of a concerted effort to demonstrate conclusively the benefit (or harm) of established and emerging therapies. This can only be done through the tried and tested methods of randomized clinical controlled trials.

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References