Cardiac involvement in myotonic dystrophy type 1: an electrophysiological perspective

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Abstract

Myotonic dystrophy type 1 (DM1) is the commonest neuromuscular condition, presenting with a constellation of systemic findings secondary to CTG triplet expansion of the non-coding region of the DMPK gene. Cardiac involvement is frequent, with conduction disease, supraventricular and ventricular arrhythmias being the most prevalent manifestations, often developing from a young age. The development of cardiac arrhythmias has been linked to increased morbidity and mortality, with sudden cardiac death having been well described. Strategies to mitigate risk of arrhythmic death have been developed. In this review, we sought to outline the current knowledge on the pathophysiology of rhythm abnormalities in this population and summarize available knowledge on arrhythmic risk stratification. We also review management strategies from an electrophysiological perspective, attempting to underline the substantial unmet need to address residual arrhythmic risks for this population.

Introduction

Myotonic dystrophy type 1 (DM1 – Steinert disease) is the commonest inherited multisystem disorder with a prevalence of 1/10000 patients, characterized by clinical features of striated muscle weakness, early myotonia, ocular, cutaneous, central nervous system, metabolic abnormalities, and cardiac manifestations [1]. The genetic basis of DM1 is expansion of the 3' non-coding region of the DMPK gene, located in chromosome 19q13.3, by more than 35 CTG trinucleotides [2]. Inheritance is autosomal dominant. The onset of phenotypic expression varies significantly, from a more severe congenital form to mild late onset disease. Disease severity and age of onset seem to correlate with expansion size [3]. Anticipation is well recognized in this population, as phenotypical severity tends to increase in sequential generations [2].

Cardiac involvement has been a well-recognized driver of mortality in myotonic dystrophy. It is manifested mainly with conduction disease and has the propensity to supraventricular and ventricular arrhythmias. Younger patients exhibit higher risks for cardiac disease [4-7]. A minority of patients may develop systolic dysfunction that is associated with increased risk for life threatening arrhythmias. In this setting, the role of electrophysiology in the management of this population becomes increasingly relevant.

Pathophysiologic basis of cardiac disease in DM1

Although cardiac disease is a well-recognized complication of DM1 in humans and knock-out mice, the mechanism by which CTG expansions lead to cardiac manifestations is not entirely clear. It is postulated that increasing size of CTG repeats affects splicing, either by reducing transcription, or more likely resulting in abnormal DMPK isoforms, with consequent impaired localization in specific tissue cytoplasm [8].

DMPK gene translation produces an 80 kD serine/threonine protein kinase, that is highly expressed in smooth, striated and cardiac muscle, but the full extent of interactions with other proteins still remains unclear. This protein has been detected both in a soluble form and interacting with G receptors in cardiomyocyte membranes in cardiac samples [9]. In DMPK knock-out mice, reduced phosphorylation of phospholamban (PLN) has been demonstrated, with the latter resulting in reduced calcium uptake in the sarcoplasmic reticulum [10]. In vitro co-

localization with Lamin A/C (LMNA/C) in the nuclear envelope has also been established, with loss of DMPK resulting in disruption of nuclear integrity [11].

An increasing number of studies suggest abnormal sodium (Na) handling as the underlying mechanism of conduction disease in DM1. Knock-out DMPK mice exhibited reduced skeletal muscle Na+ channel amplitudes, as well as fewer and delayed activated ion channels, resulting in abnormal calcium handling and abnormal excitation-relaxation coupling. Additionally, the degree of abnormal channel activation was associated with increasing mice age, similar to the progression of DM1 in human patients [12]. Delayed Na channel activation was reversed by Na channel blockers lidocaine in this study and tetradotoxin in another one [12, 13]. A further study performed in a transgenic mouse with human DM1 CTG expansions showed rapid inactivation of Na channels after intravenous administration of the Na channel blocker flecainide, resulting in impaired conduction and contractility [14]. Although this model was not found to carry any SCN5A mutations or demonstrate relevant functional alterations, a subsequent study from the same group found evidence of abnormal splicing in exon 6 of the SCN5A gene in explanted heart samples of a transplanted DM1 patients with history of ventricular arrhythmia and electrocardiographic pattern in keeping with Brugada syndrome. Interestingly, sequencing of the SCN5A gene was normal in this patient, suggesting splicing may have been affected post-translation by the concurrent DMPK mutations [15]. Further research has shown that abnormal SCNA5A splicing leads to loss-of-function of the Nav1.5 voltage gated cardiac channel, resulting in similar conduction abnormalities to those seen in Brugada syndrome [16].

A spontaneous type 1 Brugada pattern was found in 7 patients of a cohort of 914 patients with DM1, 5 of which had a prior history of ventricular tachycardia (VT) or sudden death (SD) [15]. Ajmaline testing unveiled a type 1 Brugada pattern in further 3 of 12 patients with DM1, presenting no evidence of electrical or structural disease and no evidence of HV interval prolongation on electrophysiological testing. None of the patients included in this small cohort was found to be a carrier of SCN5A mutations, providing further evidence on the link between DMPK mutations and abnormalities in the Brugada syndrome spectrum as a potential driver of arrhythmia in DM1. Furthermore, early histopathological studies as well as later studies utilizing cardiac magnetic resonance (CMR) in DM1, demonstrated findings similar to those in Brugada syndrome (interstitial fibrosis, fatty replacement and myocyte degeneration), despite no macroscopically apparent abnormalities [17-23].

The above findings suggest that DM1-related cardiomyopathy could be considered a form of ion channel disorder but the majority of mechanisms implicated in cardiac pathogenesis still remains obscure. However, this observation has found therapeutic applications in the use of class I antiarrhythmic medications, more prominently Mexiletine, for the treatment of myotonia in DM1 patients [24]. Caution is nonetheless advised as use of class Ic antiarrhythmic has been associated with increased prevalence of Brugada pattern ECG abnormalities on surface ECG, albeit with no known prognostic implications [25].

Whether cardiac disease follows a concurrent natural course with neuromuscular involvement is yet unclear. It has been well established that both neuromuscular and cardiac abnormalities exhibit progression with age and CTG repeat length [26-28]. Young age and small CTG expansion size do not preclude the development of cardiac disease as shown in a study of 127 patients with CTG length of <200 repeats. During a follow up of 11.7 +/- 7.6 years, almost a third of patients developed severe conduction disturbances in the form of ECG PR and QRS prolongation, advanced AV block, supraventricular arrhythmia or need for device implantation, with events being associated with more advanced neuromuscular impairment as assessed by the Muscular Impairment Rating Scale (MIRS) [29]. CTG length, nonetheless, is independently associated with more rapid progression and increased severity of cardiac involvement in multiple patient cohorts, possibly related to the earlier onset of clinically evident disease observed in carriers of long CTG repeats [30-35]. Although these observations increase vigilance for more severe cardiac phenotype in DM1 carriers of large CTG expansions, there is no evidence to support that these patients should be managed more aggressively with more frequent EPS and earlier device implantations, solely on the basis of their genetic background.

Conduction disease in DM1

The observation that patients with DM developed conduction abnormalities was made early in the 20th century, with researchers highlighting advanced degree AV block as the principal feature in DM1-related cardiac involvement [36]. Electrophysiological testing was employed early in the investigation of DM1 patients, and demonstrated high prevalence of His Purkinje abnormalities, as reflected by HV interval prolongation, albeit not suggesting any specific threshold over which pacemaker implantation should be considered [37]. The progressive nature of conduction defects was confirmed in small cohorts, utilizing longitudinal monitoring of both ECG and electrophysiologic studies (EPS) derived indices [38-40]. These studies suggested that neither

148 severity of peripheral muscle disease, nor ECG indices correlated well with severity of findings on
149 EPS, emphasizing its value as the mainstay of assessing cardiac risks in DM1 [38, 40]. Of all EPS
150 derived parameters, the only measure correlating with progressive conduction disease was found
151 to be the HV interval [41].
152
153 The currently used threshold of HV interval for prophylactic pacemaker implantation was first
154 suggested by Lazarus et al., following a study enrolling 49 patients with EPS derived HV>70 ms,
155 in whom devices programmed in VDI mode were implanted [42, 43]. This allowed for assessment
156 of bradyarrhythmias and discrimination between underlying sinus bradycardia and AV block.
157 Almost half of patients (46.7%) developed high-degree AV block requiring backup pacing, with a
158 diurnal pattern suggestive of impaired infra-hisian conduction. On the contrary, sinoatrial block
159 and sinus bradycardia followed a nocturnal pattern that was more consistent with a functional
160 substrate, with potential contribution of nocturnal sleep apnoea and concurrent hypoxia. None of
161 the 10 recorded deaths was attributed to bradyarrhythmia as all but one events were adjudicated
162 clinically and on pacemaker interrogation.
163
164 Adding more weight to the hypothesis that an HV interval >70 ms can predict development of
165 high-grade AV block, another study of 100 patients with DM1 assessed outcomes with
166 pacemaker implantation in 49 fulfilling this criterion on EPS. During a follow-up period of 74 ± 39
167 months, 20 occurrences of complete AV block were recorded, 19 of which in the pacemaker
168 implanted patients. Ten deaths occurred mainly secondary to respiratory causes, apart from one
169 sudden cardiac death related to VT in a patient with a pacemaker [44].
170
171 Nonetheless, invariable performance of EPS in all DM1 patients is clinically problematic, taking
172 into account the complexity in anesthetic management, higher expected risks following
173 complications and limited mobility of this population. In an effort to assess the efficiency of non-
174 invasive markers to predict which patients warranted an EPS, Wahbi et al. suggested resting ECG
175 PR duration >200 ms and/or QRS duration >100 ms as markers of severe conduction disease.
176 Out of 914 patients, 486 fulfilled this criterion, 70% of which underwent an EPS. Pacemaker
177 implantation was undertaken in those with HV interval >70 ms. This invasive strategy was
178 retrospectively analyzed against the remaining patients not undergoing an EPS. Over a median
179 follow-up of 7.4 years, the invasive strategy was associated with a 36% reduction in the risk for
180 mortality, which was attributed to a substantially reduced risk for sudden cardiac death [hazard
181 ratio with invasive strategy 0.24 (95% CI, 0.10-0.56; P = .001)].
182

In terms of alternative non-invasive modalities to assess the integrity of the conduction system in DM1, few studies employed Holter monitoring to assess for transient high-degree AV block. In a retrospective analysis of 49 genetically confirmed DM1 patients followed up for a mean period of 95 +/- 22 months, Holter parameters were not associated with either the primary all-cause mortality or secondary sudden death endpoints, including the composite of all-cause mortality, device implantation, arrhythmia and heart failure [45]. Nevertheless, the inclusion of Holter monitoring in the assessment of another cohort comprising of 129 DM1 patients showed conduction disturbances even in subjects with normal surface ECG tracings. This finding suggests that ECG alone is not accurate in assessing risk for conduction disease in this population [46]. The use of Holter monitoring has provided some further insight in the assessment of autonomic tone in this populations, with studies showing reduced heart rate variability suggestive of impaired vagal tone [46-48]. Current guidelines advocate the use of Holter monitoring on initial assessment and as adjunct for the detection of sublinical supraventricular and ventricular arrhythmias. For the time being there is no consensus with regards to its utility in predicting advanced conduction disease, particularly in patients with otherwise normal investigations [49].

Data on the utility of implantable loop recorders is currently scarce deriving mainly from case reports and a small case series. In this limited experience, loop recorders unveiled mainly tachyarrhythmias. Only one patient required device implantation due to an asystolic event of 12 seconds [50-52].

Supraventricular arrhythmias in DM1

Supraventricular tachyarrhythmias represent the second most frequent heart rhythm abnormality in DM1 patients, and are considered to substantially contribute to cardiac mortality and morbidity [53]. In a cohort of 161 DM1 patients, only 4 of which exhibited cardiac symptoms, 17% developed atrial flutter/fibrillation during a follow-up period of 5 +/- 4 years [54]. The advent of atrial fibrillation and flutter was associated with a 3-fold increase in the risk of death, and was an independent predictor of this endpoint alongside age >40 years. In a large cohort of 929 patients, prevalence of atrial flutter was 8.5%, and was associated with older age and more severe neuromuscular and cardiac involvement, but not left atrial size [55]. Only 2 patients suffered an ischemic stroke during follow-up of 53 +/- 28 months, raising the possibility that cardiac morbidity related to atrial flutter was not exclusively driven by thromboembolism.

Management of tachyarrhythmia in this population poses a major challenge as antiarrhythmic treatment is limited due to the predilection for advanced AV block and the risk of developing Brugada spectrum abnormalities. Similarly, decision making on antithrombotic treatment needs to take into account the frequency of falls these patients suffer, that potentially increase the risk of traumatic intracranial bleeding. Few case reports suggest that supraventricular tachycardia ablation can be a feasible alternative in DM1 patients [52, 56]. Only one study investigated the feasibility and long-term efficacy of atrial flutter ablation performed in 22 patients. Compared to 28 patients undergoing cardioversion only, atrial flutter ablation was performed with no increased complication rates and resulted in an 87% increased chance of freedom of recurrence, with the procedure being the only predictor of this on multivariate analysis [55]. To date, there is no information on the efficacy of atrial fibrillation ablation in this population. The contribution of comorbid conditions, namely obstructive sleep apnoea which is highly prevalent in the DM1 population, has been considered, but the effect of supportive measures such as CPAP non-invasive ventilation on arrhythmic burden has not been established [57]. Atrial overdrive pacing in patients with dual chamber devices has been postulated as an efficient method of reducing atrial fibrillation burden via suppression of atrial ectopy in a single centre study [58, 59].

Ventricular arrhythmia and sudden cardiac death

The observation that a portion of DM1 patients still died suddenly despite cardiac pacing raised the suspicion that ventricular tachyarrhythmias underlie this residual risk [60, 61]. In the study by Lazarus et al. on the efficacy of pacemaker implantation for the prevention of sudden death, 4 such events (two non-arrhythmic according to post mortem device interrogation) occurred in a population of 49 device recipients [42].

A multitude of studies sought to determine predictors for sudden cardiac death, however only two studies provided information on predictors of ventricular tachyarrhythmia-related death. Groh et al. enrolled 406 patients with genetically confirmed DM1 from multiple US centres, followed up for a median of 6.5 years, during which 81 patients died. The mode of death was deemed sudden in a third of patients (27 patients, rhythm undetermined in 10). On multivariate analysis, severe ECG abnormalities, representing a composite of PR and QRS prolongation and presence of atrioventricular block, and atrial tachyarrhythmias were found to be independent predictors of sudden death. In the 10 of the 17 sudden deaths in which the rhythm was reported, VT/VF was found to be the underlying arrhythmia, with the authors concluding that patients with such

characteristics may benefit from implantable cardioverter defibrillator (ICD) implantation. Notably, 3 of these patients were pacemaker recipients [62].

A large multicentre French registry study is currently the only study that investigated the incidence on ventricular tachyarrhythmia-related sudden death and sought to determine risk factors for this. A population of 1388 adult patients with DM1 were retrospectively reviewed over a median period of 10.3 years. Ventricular tachyarrhythmias were detected in 26 patients, with 8 occurrences of VF, resulting in a total of 9 sudden deaths. In the remaining 27 cases of sudden death (total of 36, incidence of 3.6%) the cause was undetermined in 17, non-cardiac causes and bradyarrhythmias were found in the rest. Notably, pacemakers had been implanted in almost a third of patients, and this may have accounted for the differences in incidence and causality of sudden death in this cohort compared to other studies. Although left ventricular dysfunction was frequently detected in patients with VT, the only risk factor for sustained ventricular tachyarrhythmias on multivariate analysis was a personal history of non-sustained VT [63]. The actual prognostic benefit of primary prevention ICD implantation in the DM1 population remains unknown.

A small subset of patients with DM1 develop systolic dysfunction which seems to pertain worse prognosis, despite the absence of overt heart failure symptoms [21, 64]. Taking into account the high prevalence of concurrent conduction abnormalities, with LBBB developing in 5-25% of patients and predilection to AV block translating in increased pacing requirements, cardiac resynchronization therapy could be considered for patients presenting with these features. Nonetheless, the decision on cardiac synchronization needs to take into account the presence of comorbidities and their effect on patient prognosis, particularly with regards on pacing only versus defibrillator implantation [43]. Isolated case reports have demonstrated benefits from cardiac resynchronization suggesting this could be a viable option in DM1 patients fulfilling criteria on an individual basis [65-67].

It is considered that the pathological substrate involving myocyte degeneration with fibrofatty replacement constitutes a favourable arrhythmogenic substrate, even in the absence of systolic dysfunction [68, 69]. The underlying mechanism of ventricular tachyarrhythmias in DM1 was shown to be bundle-branch re-entry in ventricular stimulation studies of 6 patients, all of whom were successfully treated with pacemaker implantation due to significant HV prolongation following bundle branch ablation [70]. Other mechanisms, such as increased automaticity and re-entry not involving the His bundle with positive results of VT ablation have been described in

isolated case reports [69, 71-73]. Inducibility of VT has been exhibited in myotonic dystrophy and although the prognostic value of such a finding in predicting sudden death has not been established, induction of a monomorphic sustained VT on EPS may constitute a favourable substrate for VT ablation [41, 74].

Conclusions

Despite its relatively high prevalence, DM1 still remains a rather poorly understood clinical entity from the cardiac perspective. Its propensity to affect young patients, its progressive nature and potentially lethal consequences of cardiac involvement raise the need for increased awareness amongst cardiologists. Electrophysiology holds a distinct role in the management of this population, addressing the multitude and complexity of conduction and arrhythmia-related issues these patients will develop throughout their lifetime, taking into account the fact that DM1 patients' lives are now improved thanks to advances in respiratory and pharmacological support. The impact of such supportive measures in cardiac function has not been assessed. Notwithstanding advances made in mitigating arrhythmic risk, there are still numerous issues that remain unresolved in terms of electrophysiological management to effectively reduce cardiac mortality.

In terms of bradyarrhythmic risk, little progress has been made in understanding the role of non-invasive markers as adjuncts to the risk stratification according to EPS parameters. While population studies have demonstrated a rationale for repeated EPS, on an individual patient basis it still remains undecided how frequently this should take place and whether non-invasive monitoring is reliable in determining the need for repeat invasive HV interval measurement. Additionally, to this point there are no studies reporting the incidence of sudden death in patients with intermediate prolongation of HV interval between 55 ms and 70 ms. Although pacemaker implantation has demonstrated a meaningful reduction in sudden death rates, ventricular tachyarrhythmia still poses a significant residual risk. Accurate stratification of patients who would benefit from ICD over pacemaker implantation becomes particularly relevant taking into account the high prevalence of atrial tachyarrhythmias and the associated higher risk of inappropriate device shocks [75]. Little progress has been made on defining the risk of thromboembolism in this population and more importantly assessing the risk-benefit balance for anticoagulation therapy given the risk of traumatic intracranial bleeding.

In this environment of multiple unanswered questions, electrophysiology can serve as the driver for further improvements with innovative research translating in much needed better clinical outcomes for the DM1 population.

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522

Table 1. Studies reporting on incidence of severe conduction abnormalities, tachyarrhythmias and device implantation.

Author(s) \ref	Patients (n)	Age*	Follow up*	CTG repeat length	Severe conduction disease+	AT/AF	Sustained VT	SCD at end of F/U	PPM	ICD
29	127 (82 at end of F/U)	48.6 (16.6 - 80.5)	11.7±7.6	95	1 (26 with PR>240, QRS>120)	2	0	0	6	1
31	73	35±14	4.8±1.8	673+371	4 (PR>200 25 (34%, QRS>100 16 (22%)	5	0	2 (highest CTG)	4	0
33	855	37 (27-49)	11.5 (8.2–14.7)	530 (IQR 300-830)	423 (49%) at start of F/U	166 (19%)	17 (6%)	32 (8 of which with VT)	181 (21%)	11 (1%)
34	151	28.1±15.9	7.8±6.2	467.4±333.1	8 (39 with resting ECG conduction abn.)	19		9		
42	49	45.5±8.9	53.5±27.2 months	921±441	21	25	13	4 (2 non-arrhythmic)	42	0
44	100	40±13.8	74±39 months	2.65+/-1.58 kb	20	21	13 (1 with sustainedVT)	1	49	1
62‡	406	5.7	5.7±2.3 vs 5.5±2.2	606+ 379 vs 704+399	96 with severe ECG abn	29	8	27 (VT/VF in 10, 4 asystole/CHB, 3 PEA)	41	14
63	1388	39.9 ± 13.3	10.3 (6.7–13.0)	2.68±0.36 kb	145	173	26 (all sustained)	39	275	13

**Values are reported as mean values in years, unless otherwise stated*

+Defined as 2nd degree antrioventricular block or higher and asystole

‡Values reported separately for patients with absence versus presence of severe ECG abnormalities, defined as at least one of the following features: rhythm other than sinus, PR interval of 240 msec or more, QRS duration of 120 msec or more, or second-degree or third-degree atrioventricular block

523