Workshop report

107th ENMC International Workshop: the management of cardiac involvement in muscular dystrophy and myotonic dystrophy. 7th–9th June 2002, Naarden, the Netherlands

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1. Introduction

Sixteen participants from Austria, France, Germany, Italy, the Netherlands and the UK met to discuss the cardiac implications of the diagnosis of muscular dystrophy and myotonic dystrophy. The group included both myologists and cardiologists from nine different European centers. The aims of the workshop were to agree and report minimum recommendations for the investigation and treatment of cardiac involvement in muscular and myotonic dystrophies, and define areas where further research is needed. During the workshop, all participants contributed to a review and assessment of the published evidence in each area and current practice amongst the group. Consensus statements for the management of dystrophinopathy, myotonic dystrophy, limb-girdle muscular dystrophy, Emery Dreifuss muscular dystrophy, facio-scapulo-humeral muscular dystrophy and congenital muscular dystrophy were produced. The need for further research to extend the evidence-base in certain key areas was also highlighted and outline proposals to resolve these deficiencies put forward. A summary of the cardiac implications of the disorders discussed is presented in Table 1.

2. Dystrophinopathy [Duchenne and Becker muscular dystrophy (DMD and BMD) and carriers of DMD and BMD]

There is strong evidence of frequent progressive cardiac involvement in these disorders, characterized ultimately by the development of dilated cardiomyopathy [1–12]. Abnormalities on investigation are more common than symptomatic presentation [13,14]. Although evidence in these rare conditions of the effect of treatment is lacking [15], extrapolation from other conditions causing heart failure with dilated cardiomyopathy means that there is a strong case for the use of ACE inhibitors and potentially also beta blockers, certainly in the presence of detectable abnormalities and possibly preventatively [16–25].

The recommendations of the group are as follows.

2.1. DMD

- Patients should have a cardiac investigation (echo and electrocardiogram (ECG)) at diagnosis.
- DMD patients should have cardiac investigations before any surgery, every 2 years to age 10 and annually after age 10.
- Respiratory failure is also common in DMD and assessment and treatment of respiratory function should be performed in parallel with the cardiological investigations [26].
- Patients should be treated with angiotensin-converting enzyme (ACE) inhibitors initially in the presence of progressive abnormalities [15–19]. Subsequently the addition of beta blockers should be considered [20–23].
- There is no evidence that the currently used steroid treatment regimes have a detrimental effect on cardiac involvement or are a contraindication for the concurrent use of ACE inhibitors [27].
- The multiple other complications of DMD including scoliosis and respiratory failure mean that these patients are rarely fit for cardiac transplantation.
- There is an urgent need for multi-centre clinical trials to determine whether treatment of patients with cardiomyopathy, prior to the onset of symptoms, improves prognosis and quality of life. There is also unpublished evidence to suggest that treatment even before any...
Table 1
Frequency, type and implications of cardiac involvement in different forms of muscular dystrophy and myotonic dystrophy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cardiac involvement (in increasing order of severity)</th>
<th>% of patients in whom abnormality likely</th>
<th>Age range</th>
<th>Morbidity/mortality</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>ECG abnormalities: HCM and DCM</td>
<td>Abnormal ECG &gt;90%; abnor mal Echo &gt;90%</td>
<td>ECG abnormalities detectable from age 6, progressive thereafter</td>
<td>Cardiac death in approx 10–20%, usually in teens</td>
<td>de Kermadec et al. [2]; Corrado et al. [3]; Farah et al. [4]; Backman et al. [6]</td>
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<tr>
<td>Becker muscular dystrophy</td>
<td>ECG abnormalities: HCM and DCM</td>
<td>ECG abnormal – 90%, Echo abnormal – 65%</td>
<td>Variable, may be disproportionate to skeletal involvement</td>
<td>Cardiac death in up to 50%</td>
<td>Melachini et al. [7]; Saito et al. [9]; Nigro et al. [8]; Hoogerwaard et al. [10]</td>
</tr>
<tr>
<td>Manifesting carriers of DMD/BMD</td>
<td>ECG abnormalities: HCM and DCM</td>
<td>Variable estimates 21–90%</td>
<td>Variable, may be out of proportion to skeletal muscle involvement</td>
<td>DCM in 7–11%. Several reports of successful cardiac transplantation</td>
<td>Politano et al. [33]; Hoogerwaard et al. [34]; Grain et al. [35]</td>
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<tr>
<td>XL-EDMD</td>
<td>AV block; atrial paralysy; atrial flutter and fibrillation</td>
<td>&gt; 95% by age 30 years</td>
<td>10–39</td>
<td>SCD common in non-paced individuals (mean age at pacing 24 years, range 14–35) Approx 5% require pacemaker insertion. Risk of SCD.</td>
<td>Emery et al. [52]; Merli et al. [55]; Bione et al. [53]; Funakoshi et al. [54]</td>
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<tr>
<td>Myotonic dystrophy</td>
<td>AV-conduction disturbances; atrial flutter and fibrillation, ventricular tachy-arhythmias</td>
<td>Approximately 65% of the adult myotonic dystrophy population have abnormal ECG</td>
<td>Earliest age at which abnormalities become clinically relevant is unclear. Greatest risk is in middle adulthood</td>
<td>Impact on overall prognosis unclear</td>
<td>Hayashi et al. [38]; Olofsson et al. [36]; Hawley et al. [43]; Antonini et al. [46]; Clarke et al. [44]</td>
</tr>
<tr>
<td>Sarcoglycanopathies (LGMD2C-2F)</td>
<td>ECG abnormalities; HCM and DCM</td>
<td>18.7%</td>
<td>Not established</td>
<td>Over whole spectrum of LGMD2I/MDC1C relates to severity of overall disease</td>
<td>Van der Kooi et al. [72]; Politano et al. [71]; Gnechi-Ruscone et al. [76]</td>
</tr>
<tr>
<td>LGMD2I</td>
<td>ECG abnormalities, DCM</td>
<td>1/3 of adult onset cases</td>
<td>1/3 of adult cases have symptomatic cardiomyopathy. Further data needed on natural history</td>
<td>Dilated cardiomyopathy Vascular and clinically significant</td>
<td>Brockington et al. [74]; Poppe et al. [73]</td>
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<tr>
<td>MDC1C</td>
<td>Dilated cardiomyopathy</td>
<td>Invariable and clinically significant</td>
<td>Present from early childhood in most severe cases May be a major contributory factor to early death</td>
<td>Dilated cardiomyopathy Invariable and clinically significant</td>
<td>Brockington et al. [74]</td>
</tr>
<tr>
<td>Laminopathies (including AD-EDMD, LGMD1B)</td>
<td>AV block; atrial paralysy; atrial fibrillation/flutter</td>
<td>&gt; 95% by age 30 years</td>
<td>15–52</td>
<td>Mean age at pacing 32 (range 19–57) years; 50% of deaths are sudden despite pacing or transplantation</td>
<td>Bonne et al. [57]; van der Kooi et al. [60]; Fatkin et al. [61]; Becane et al. [62]</td>
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<tr>
<td>Laminopathies (including AD-EDMD, LGMD1B)</td>
<td>Dilated cardiomyopathy</td>
<td>35% of all cases</td>
<td>19–55</td>
<td>Death from heart failure common if not transplanted</td>
<td>Graham et al. [67]; Davies [68]; Becane et al. [62]; Fatkin et al. [61]</td>
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<tr>
<td>Facioscapulohumeral muscular dystrophy</td>
<td>Conduction defects, atrial arrhythmias</td>
<td>Minor ECG changes in up to 30%</td>
<td>Further work needed to establish prevalence of cardiac involvement in severe childhood onset disease Few reports of clinically relevant cardiac involvement</td>
<td>Reduced ejection fraction No reports to date of clinically significant cardiomyopathy</td>
<td>Stevenson et al. [83]; De Visser et al. [77]; Laforet et al. [81]</td>
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<tr>
<td>MDC1A</td>
<td>Reduced ejection fraction</td>
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* DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; and SCD = sudden cardiac death.
impairment of ventricular function is detectable on echocardiogram may delay the onset and progression of cardiomyopathy [28]. Concerns about the possible impact of ACE-inhibition on left ventricular development in very young children, means that treatment in the very young should only be undertaken in the context of a formal clinical trial, at the present time.

- There is a case for continued evaluation of more sophisticated tools (echo tissue Doppler imaging, cardiac magnetic resonance imaging (MRI), etc.) for earlier detection of abnormalities, but these are not required for routine management [29].

2.2. BMD

Cardiac involvement in BMD is common and is frequently out of proportion to the skeletal muscle involvement [7–10].

- BMD patients should have cardiac evaluation (ECG and echo) at diagnosis.
- BMD patients should be screened for the development of cardiomyopathy at least every 5 years.
- They should be seen more regularly and treated with ACE inhibitors and, if indicated, beta blockers when progressive abnormality is found [15–25].
- Cardiac transplantation may be a viable treatment in this group of patients [30,31].

2.3. Female carriers of DMD and BMD

There is unequivocal evidence that approximately 10% of female carriers of dystrophin mutations, either DMD or BMD develop overt cardiac failure even in the absence of any skeletal muscle involvement [32–35].

- All carriers of DMD or BMD should have echo and ECG at diagnosis or after the age of 16 years and at least every 5 years thereafter, or more frequently in patients with abnormalities on investigation.
- Carriers manifesting severe skeletal muscle symptoms or cardiac symptoms require more frequent investigation.
- Once significant abnormalities are detected patients may benefit from treatment with ACE inhibitors and additional medication as indicated.
- Ultimately cardiac transplantation may be appropriate.

2.4. Myotonic dystrophy type 1

There is clear evidence of conduction disease in myotonic dystrophy, but not of ischaemic heart disease or of impaired myocardial function [36–41]. In many patients, conduction defects progress in a predictable way over time [42–44]. Surface ECG may be normal despite the presence of important intra-Hisian conduction delay but the role of electrophysiological testing in patients with normal ECG is not established [45]. This could be addressed in a trial setting.

When invasive electrophysiology testing is performed in patients with abnormal ECGs, it typically detects more widespread conduction abnormalities that that suggested by the surface recording [45,46]. Electrophysiological tests and MRI may help to predict those at particular risk of severe arrhythmia [45,47,48]. Ventricular arrhythmias are likely to explain some cases of sudden death. However, in patients with pacemakers implanted, the best predictor of death is deteriorating respiratory function.

Cardiac investigation in these patients should include.

- Annual ECG from diagnosis.
- Holter monitoring may also be valuable at diagnosis in adult patients.
- Echocardiogram should be performed at diagnosis in congenital myotonic dystrophy.
- Additional investigations should include Holter monitoring, if annual ECG shows increasing PR interval or other evidence of increased risk of bradycardia. Invasive measurement of the HV interval (infra-nodal conduction delay: HV >70 ms) may help decide the need for pacing in borderline cases.
- Atrial tachyarrhythmias (atrial flutter, fibrillation) are common and, if symptomatic, may justify antiarrhythmic treatment. However, antiarrhythmic drugs may aggravate any preexisting tendency to bradycardia or ventricular tachy-arrhythmias.
- Treatment with pacemaker is indicated when a progressive arrhythmia is detected even prior to symptoms.
- Despite reports of ventricular tachy-arrhythmias the incidence is not sufficiently high to justify implanteable defibrillator therapy routinely when permanent pacing is indicated.
- There is a need to collect data on cardiac involvement in young patients to determine the incidence of cardiac complications in this group [49,50].

3. Congenital muscular dystrophy

The congenital muscular dystrophies are a heterogeneous group of disorders, and cardiac involvement depends on the type [49,50]. In congenital muscular dystrophy therefore it is necessary to define the genetic basis of the disease as the different types carry different cardiac risks. MDC1C (due to fukutin-related protein gene (FKRP) mutations) needs to be followed closely as cardiac involvement is common [51].

There are reports of cardiomyopathy in primary merosin deficient congenital muscular dystrophy (CMD) but to date this has been non-progressive. In other types of CMD, echo and ECG is recommended at diagnosis and thereafter prior to surgery or as clinically indicated.

4. Emery Dreifuss muscular dystrophy (EDMD)

EDMD is a genetically heterogeneous condition. X linked EDMD is due to mutations in the STA gene encoding the
protein emerin [52–56]. Autosomal dominant EDMD is due to mutations in the lamin A/C gene [57–65]. Lamin A/C mutations are also found in a range of other conditions including autosomal recessive EDMD [66], LGMD1B, familial dilated cardiomyopathy [67,68], partial lipodystrophy and peripheral neuropathy (AR CMT2). Variable phenotypes may be seen in the same family.

Because of the different implications of laminopathy and emerinopathy both from the point of view of management and genetic counseling, a precise diagnosis should be sought in all patients.

4.1. XLEDMD

There is strong evidence for cardiac involvement in XLEDMD and in this condition long term prognosis is entirely dependent on cardiac status [52–56]. The major problem is that of atrioventricular (AV) conduction defects and there are only very rare reports of development of dilated cardiomyopathy, congestive heart failure or death after pacemaker insertion.

Recommended investigations in this group include.

- Follow up by a cardiologist as ECG changes may be subtle and difficult to interpret.
- Twelve lead ECG (preferably at 50 mm/s) at diagnosis and annually thereafter.
- Holter monitoring for tachy- or brady-arrhythmias annually.
- Echocardiography on a less regular basis.
- Permanent pacemaker implantation is justified, even in asymptomatic patients, when ECG begins to show abnormalities of sinus node or AV node disease. However, nocturnal AV-Wenkebach may be a normal finding in young people.
- In the presence of sino-atrial or AV-nodal conduction abnormalities on surface ECG, the role of electrophysiology is unclear. Invasive electrophysiology testing probably adds little to the decision to or timing of pacemaker implantation. However, such testing may have a role in determining the optimum mode of and sites for pacing.

As with DMD, there may be some female carriers of this X-linked disease who manifest cardiac disease. Published cases of manifesting carriers may have been diluted by cases of dominant disease. Carrier status should be established in females at risk. These women should be offered periodic ECG surveillance to detect atrial or AV-nodal conduction disease. There is a need for more systematic study of the natural history of cardiac involvement in XLEDMD carriers.

4.2. Laminopathies

Apart from the partial lipodystrophy and CMT phenotypes, there is strong evidence for cardiac involvement in laminopathy and this is progressive with age [57–65]. As with XLEDMD, long term prognosis is directly related to cardiac status, and investigation of these patients should be performed as outlined above. However, the cardiac management of this group is more complex than XLEDMD. Dilated cardiomyopathy may develop as well as conduction defects [58–61]. Sudden death is seen in patients even after pacing [61–65]. As a result of accumulating evidence of sudden death even in patients who have been paced, the consensus recommendation at present is that implantable defibrillators may be a more appropriate form of management than pacemakers in this group. However, management of these cases is complex and the complications of implantable defibrillators may be greater than with pacemakers. These patients should be managed in specialized centers and their data collated to contribute to further evidence in the future. In the meantime there is a strong indication for defibrillator implantation to be considered when anti-bradycardia pacing is indicated [62]. This interim recommendation needs to be validated over time through the collection of high quality prospective data.

4.3. The role of anticoagulation

In both XLEDMD and ADEDM atrial fibrillation/flutter and atrial standstill occur frequently, even after pacemaker implantation, and this carries a substantial risk of thromboembolic events, including ischaemic stroke. When atrial fibrillation or atrial standstill are recognised, antithrombotic prophylaxis with warfarin should be considered.

5. The limb-girdle muscular dystrophies (LGMD)

The limb-girdle muscular dystrophies are a very heterogeneous group of disorders with variable underlying genetic abnormalities [69,70]. Cardiac involvement may be present in any type of sarcoglycanopathy (LGMD2C-F) [70–72]. For example, LGMD2I due to mutations in the FKRP gene appears to have a frequent association with cardiomyopathy [73,74]. In contrast, there is no evidence that cardiac involvement occurs commonly in calpainopathy (LGMD2A) or dysferlinopathy (LGMD2B) [75]. Cardiac involvement has not been described to date in the rarer LGMD2H (TRIM 32), LGMD2G (telethoninopathy) or LGMD2J (titin) nor in the dominant forms of LGMD, LGMD1A (myotolin) and LGMD1C (caveolin). Therefore, the recommendations for cardiac surveillance in this group depend very much on the particular type of LGMD.

- There is evidence to suggest that cardiac surveillance is not indicated routinely in LGMD2A, 2B, 2G, 2H, 2J, 1A, 1C. Occasional cardiac review might be useful, for example at diagnosis and when patients lose independent ambulation.
- Sarcoglycanopathy patients should be investigated with the same intensity as in patients with DMD/BMD (see above).
LGMD2I patients are at risk of cardiomyopathy and should be assessed as for DMD/BMD. The severity of cardiomyopathy may be out of proportion to that of skeletal muscle involvement.

- ECG and echo appear to be appropriate investigative tools for standard initial clinical assessment and follow-up.
- Present perception is that the incidence of tachy- or brady-arrhythmias in sarcoglycanopathies is low but the issue is not fully resolved. Some arrhythmia surveillance with Holter ECG or similar recordings is still justified.
- Standard therapy should be effective in these patients with evidence of cardiomyopathy, but trial-based evidence of efficacy is lacking.
- Cardiac transplantation may be indicated in selected patients with cardiac failure progressing despite anti-failure therapy.
- Further research studies are needed to determine:
  - Whether prophylactic therapy will prevent or delay the onset of cardiomyopathy in patients with LGMD2I.
  - The natural history of cardiac involvement in LGMD2I and genotype-phenotype correlations.
  - Involvement of smooth muscle in coronary artery walls contributes to the development of cardiomyopathy in patients with sarcoglycanopathy. Data from mouse models of the condition suggest a role for calcium antagonists as a specific treatment to reduce abnormalities of coronary artery flow and the development of related myocardial damage [76]. Given the rarity of this condition, evidence of benefit from any treatment in humans could only come from a well coordinated multi-centre collaborative study.

6. Facioscapulohumeral muscular dystrophy (FSHD)

FSHD is probably not a major cause of cardiac disease [77,78]. The older literature reporting atrial paralysis in FSHD may have represented cases of probably misdiagnosed EDMD [79]. There are few large series and few papers with secure genetic data [80,81]. Severe cardiac involvement is exceptional (or not related to the FSHD). There appears to be a low incidence of conduction defect and atrial arrhythmia potentially complicated by embolism [82,83]. Data are lacking on the prevalence of cardiac problems in severe childhood disease, and these data should be collected on a collaborative basis.

For classical FSHD, echocardiography and ECG should be performed as a baseline investigation at diagnosis. Further cardiac follow up should be dictated by the clinical situation.

7. Future work

There are a number of questions which were identified as the basis for further studies. Anyone interested in taking part in such studies are encouraged to contact the workshop organisers.

1. When and how to treat cardiac abnormalities in dystrophinopathy.
2. The prevalence of cardiac abnormalities or cardiac symptoms in young patients with myotonic dystrophy.
3. The pathogenesis of cardiomyopathy in sarcoglycanopathies – the role of smooth muscle involvement.
4. The natural history of cardiac involvement in LGMD2I and response to therapy.
5. The natural history of cardiac involvement after implantable defibrillator in laminopathy.
6. Cardiac involvement in young patients with severe FSHD.

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