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Published in:
Current Opinion in Rheumatology

DOI:
10.1097/BOR.0000000000000753

Publication date:
2020

Document version:
Accepted manuscript

Citation for published version (APA):

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Download date: 09. Oct. 2023
CARDIAC INVOLVEMENT IN INFLAMMATORY MYOPATHIES AND INHERITED MUSCLE DISEASES

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ABSTRACT
Purpose of review:
To examine recent developments relating to cardiac involvement in the adult idiopathic inflammatory myopathies (IIM) and those inherited muscle diseases which may present in adulthood and mimic IIM.

Recent findings:
Cardiac involvement is a common feature of IIM and inherited muscle diseases. Frequency according to disease subtype varies, with serotype having particular influence in IIM, and genotype in the inherited muscle diseases. Innovative techniques for examining cardiac function have been investigated further, including speckle-tracking echocardiography and cardiac magnetic resonance tomography. This work has highlighted a likely underestimate of the burden of cardiac disease to date. The complex relationship between IIM, atherosclerosis, and traditional cardiovascular risk factors has been further elucidated. Consensus recommendations for managing patients with inherited muscle diseases and prominent cardiac involvement have been recently published. In addition to supportive care, disease modifying treatments are increasingly becoming available for inherited muscle diseases which may also improve cardiac outcomes.

Summary:
Cardiac involvement is associated with significant morbidity and mortality. We suggest having a low threshold for considering the possibility of cardiac involvement in all patients with muscle disease.

KEY WORDS
Idiopathic inflammatory myopathy
Inherited muscle disease
Myopathy
Muscular dystrophy
Cardiac disease
KEY POINTS

- Cardiac involvement in the adult idiopathic inflammatory myopathies and inherited muscle diseases is associated with increased morbidity and mortality
- There should be a low threshold for considering the possibility of cardiac involvement in all patients with muscle disease
- In the inherited muscle diseases, the risk and type of cardiac involvement is primarily determined by genotype
- In the adult idiopathic inflammatory myopathies, complex relationships between cardiac involvement, atherosclerotic risk factors, and serotype are observed.
- Basic investigations such as electrocardiography and echocardiography, as well as advanced techniques such as cardiac magnetic resonance tomography, can be used to identify and monitor cardiac involvement.

INTRODUCTION

This review will focus on recent developments relating to cardiac involvement in adult idiopathic inflammatory myopathies (IIM) and those inherited (genetic) muscle diseases which primarily affect adults, may occasionally mimic IIM, and where a general rheumatologist could potentially be involved in patient care. It is noted however that cardiac involvement may occur in other inherited muscle diseases, including Emery Dreifuss muscular dystrophy, several of the limb girdle muscular dystrophies, and the myofibrillar myopathies, but the rarity and heterogeneity of these conditions makes discussion beyond the scope of this manuscript.1,2

The occurrence of cardiac involvement in IIMs and inherited muscle disease is associated with significantly increased morbidity and mortality.3 Despite this, the true incidence is underappreciated due to manifestations being subtle in some cases, or because the clinical focus is on the often more obvious skeletal muscle manifestations of disease. Furthermore, the severity of cardiac involvement is usually not associated with the severity of skeletal muscle involvement.

Cardiac involvement may be categorised as affecting the conducting system, manifesting with conduction defects or arrhythmia, or the myocardium, manifesting as dilated, hypertrophic, or restricted cardiomyopathy and heart failure. Whilst there is overlap, each inherited muscle disease tends to manifest in one of these categories from a cardiological perspective.1 In the IIMs cardiac manifestations are more heterogeneous and may additionally include pericardial involvement (figure 1) and atherosclerotic disease, which is increasingly recognised across autoimmune rheumatic diseases (ARDs).4
CARDIAC MANIFESTATIONS IN IIM

The IIMs are a heterogeneous group of autoimmune connective tissue diseases, with cardiac manifestations demonstrated in all major subsets (except inclusion body myositis, IBM) as revealed in classic autopsy studies. Whilst occasionally manifesting with overt cardiac symptoms, in many cases cardiac involvement in the IIMs can only be detected on testing, usually with electrocardiography (ECG), echocardiography and serum muscle damage markers (cardiac troponin I [cTnI] and T [cTnT]).

Disease subtypes in IIM are defined according to clinical manifestations (e.g. presence of rash in dermatomyositis) and serology, with myositis-specific autoantibodies (MSAs) linked to defined clinical phenotypes. However, associations with cardiac involvement according to serotype is variable. For example, anti-SRP disease was initially reported to be associated with heart involvement, but this has not been confirmed in more recent studies.

Rhythm and conduction disturbances

Electrographic abnormalities are common in patients with IIM, with one recent cross-sectional study demonstrating abnormalities in 18% of IIM patients compared to 10% of healthy controls. Whilst usually subclinical, such rhythm and conduction disturbances may have serious implications in some cases. For example, IIM patients in this study also had significantly longer QTc intervals compared with healthy controls. Whilst this may indicate an increased risk of ventricular arrhythmias, no significant difference in the frequency of pathologically prolonged QTc intervals (defined as >450ms) was demonstrated. Importantly, ECG changes have been shown to be more pronounced in new-onset untreated IIM, with abnormal findings in 43% compared to only 14% in healthy controls, suggesting clinicians should be particularly vigilant in this scenario. Finally, a large retrospective study on atrial fibrillation (AF) in 20,772 Korean patients with ARDs included 317 patients with IIM. This revealed a significantly higher prevalence of AF in IIM patients compared to all other ARDs studied (3.5% versus 1.1% overall), with all-cause mortality significantly higher in those with AF, compared to non-AF patients.

Systolic and diastolic cardiac dysfunction

The true prevalence of systolic dysfunction in IIM remains uncertain, particularly as systematic screening is often not undertaken or because the techniques used are insensitive. Recent work has described sensitive markers of subclinical systolic dysfunction using novel speckle-tracking echocardiography (e.g. diminished left ventricular global longitudinal systolic strain [GLS]). When applied to those with preserved left ventricular ejection fraction according to conventional echocardiography, significantly worse indices, including a lower GLS, are demonstrated in those with IIM compared to health controls. Diastolic dysfunction is also noted to occur in IIM with case-
control studies demonstrating diastolic dysfunction on echocardiography as determined by Tissue Doppler Imaging (TDI) in up to 77% of adult IIM patients.\textsuperscript{10,15}

Myocarditis has been proposed as one of the possible mechanisms causing systolic dysfunction, while fibrosis of the left ventricle secondary to the inflammatory process could lead to diastolic dysfunction. This potential sequence of events is supported by a study demonstrating subclinical systolic dysfunction in new-onset IIM restored after three months of immunosuppressive treatment, but in the same period development of diastolic dysfunction was seen corresponding to initial inflammation replaced with myocardial fibrosis.\textsuperscript{16} Thus, it is possible that early identification and aggressive treatment of inflammatory myocarditis in IIM will reduce the burden of subsequent fibrosis and improve outcomes, but this has not been confirmed in controlled studies.

**Coronary atherosclerosis**

A systematic review including 2,585 patients with IIM found an increased risk of coronary artery disease\textsuperscript{17}, later confirmed in population-based studies.\textsuperscript{18}\textsuperscript{*} Beyond five years from IIM diagnosis the cardiovascular risk appears to return to that of the general population, according to a recent large UK study.\textsuperscript{19}\textsuperscript{**} Traditional risk factors contribute to the development of atherosclerosis in IIM, with a higher burden of hypertension, diabetes, dyslipidaemia and obesity in these patients, perhaps indicating shared aetiological factors.\textsuperscript{20,21}

**Cardiac magnetic resonance tomography**

Studies using cardiac magnetic resonance (CMR) scans in patients with IIM are being performed with increasing frequency and this technique is becoming part of standard clinical practice in many settings. Several recent case-control studies describe myocarditis detected using CMR in IIM patients with and without cardiac symptoms.\textsuperscript{22–24}\textsuperscript{**} Whilst it is assumed that this highlights the high sensitivity of this technique, uncertainties do remain, particularly as comparison to a gold standard (i.e. myocardial biopsy) is rarely forthcoming (figure 1).

Inclusion body myositis is an IIM subgroup which has a later age of onset and is unresponsive to immunosuppression. In contrast to the other IIM subtypes, cardiac involvement is scarcely identified. Despite this, a recent CMR study in IBM patients without cardiac symptoms and normal echocardiograms demonstrated abnormalities in 16 of 17 subjects. This included significantly reduced stroke volumes and increased early myocardial enhancement in IBM patients compared to age- and gender-matched controls. However, late gadolinium enhancement did not differ between the groups, suggesting that the higher proportion of hypertension seen in the IBM group explained the CMR changes. The need to carefully place results of highly sensitive studies in the correct context is highlighted.
CARDBIAC MANIFESTATIONS IN INHERITED MUSCLE DISEASES

Inherited muscle diseases compromise a vast array of conditions including dystrophic and non-dystrophic myopathies, mitochondrial disease, storage/metabolic myopathies, and skeletal muscle channelopathies. In general, genetic defects lead to sarcolemmal membrane fragility due to impaired function of the structural and/or regulatory proteins required for normal muscle function. Genotype-phenotype correlations are often observed which can help to guide the intensity of cardiac surveillance undertaken.

Whilst this is a highly heterogeneous disease area, typical patterns of cardiac involvement are seen in the different inherited muscle diseases, with each tending to manifest with one of conduction defects or arrhythmia, or dilated-, hypertrophic-, or restricted cardiomyopathy. Here we focus on three inherited muscle diseases which can manifest in adulthood and in the authors experience have been shown to occasionally mimic IIM.25

Becker muscular dystrophy

Becker muscular dystrophy (BMD) is an X-linked progressive disease caused by decrease in the function of dystrophin protein. This contrasts to the more severe Duchenne muscular dystrophy (DMD) where functioning dystrophic protein is absent. However, the separation of DMD from BMD is viewed as increasingly arbitrary, especially with the recognition of intermediate phenotypes (i.e. genetic change predictive of DMD, but with a clinical phenotype more in keeping with BMD). In addition, female carriers of DMD-type mutations can present with BMD or intermediate phenotypes, including with prominent cardiomyopathy (figure 1).

Around 2/3 of BMD patients will develop cardiomyopathy with the age of onset generally corresponding to mutations in different regions of the dystrophin gene.26 Dilated cardiomyopathy is the most common cardiac manifestation of BMD, with onset usually after the second decade of life, although arrhythmia can also occur.1 Overall, malignant arrhythmia or heart failure accounts for 50% deaths in BMD.27

Whilst BMD is milder in severity than DMD, with most patients remaining ambulant into adulthood, cardiac manifestations may be more prominent when viewed in contrast to the severity of skeletal muscle involvement, potentially due to the increased workload and cumulative mechanical stresses affecting the former. In a recent imaging study, the severity of cardiac involvement in BMD showed an inconsistent relationship with severity of skeletal muscle involvement determined by thigh MRI.28 Some patients in this study were found to have cardiomyopathy in the absence of skeletal muscle involvement, consistent with the X-linked dilated cardiomyopathy phenotype.28
Myotonic dystrophy

The myotonic dystrophies are autosomal dominant multi-system disorders characterised by progressive muscle weakness and myotonia. Myotonic dystrophy type 1 (DM1, Steinhert disease) occurs in the context of expanded CTG repeats the DMPK gene. Much rarer, and with a lower incidence of cardiac dysfunction, myotonic dystrophy type 2 (DM2, also known as proximal myotonic myopathy), is caused by a tetranucleotide repeat expansion (CCTG) in the CNBP (ZFN9) gene.29

In DM1, larger CTG repeat expansions are associated with a more severe disease course. This is mirrored in terms of the cardiac involvement, which typically involves cardiac conduction and rhythm abnormalities, as well as left ventricular diastolic dysfunction in some cases.30,31 Most patients with DM1 will develop cardiac abnormalities, with arrhythmia accounting for 25% of deaths, the second leading cause after respiratory complications.32 A recent UK registry study has shown that approximately 1/3 of DM1 patients require some form of cardiac implant (e.g. permanent pacemaker) during their life.33

Recent CMR studies in DM1 have focussed on investigating the relationship of MR findings with cardiac conduction defects and arrhythmia. In one study, myocardial fibrosis defined according to the presence of late gadolinium enhancement (LGE) was found in 42% of DM1, but with occurrence independent of cardiac conduction defects meeting indications for pacing.34* In another study, LGE was found to be the only CMR marker associated with the occurrence of atrial fibrillation, but again no association with conduction abnormalities was found.35

Pompe disease

Pompe disease (glycogen storage disease type 2) is an autosomal recessive disorder caused by deficiency of the lysosomal glycogen-hydrolysing enzyme acid α-glucosidase (GAA). The late-onset form of Pompe disease (LOPD), where patients have some residual GAA function, is characterized by weakness of the proximal limb girdle and respiratory muscles. Whilst conventionally grouped with the metabolic myopathies, LOPD clinically resembles a limb girdle dystrophy – but is unique in that disease modifying enzyme replacement treatment is available.

Clinically important cardiac involvement in LOPD is much less commonly seen than in childhood onset forms where no measurable GAA activity is found.36 One recent retrospective analysis of 83 LOPD cases found cardiac abnormalities at rates comparable with the general population37. A further smaller observational study published in 2019 also showed similarly low rates, but in those were cardiomyopathy did occur (3/18), it appeared to respond to enzyme replacement therapy.38* Finally, a detailed CMR study in 2016 showed only infrequent, mild and non-specific abnormalities on CMR of 17 LOPD patients.39
SCREENING FOR CARDIAC INVOLVEMENT

The rarity and heterogeneity of IIMs has made specific screening recommendations difficult to produce. Screening paradigms for cardiac involvement are perhaps best defined for the myotonic dystrophies, as described in the recent consensus based care recommendations. Recommendations for other inherited muscle diseases have been produced by the American Heart Association. When considering screening programmes, the modality of investigation used must be carefully chosen, balancing clinical, technical, and financial/resource considerations. Simple clinical tools and bedside tests such as ECG or blood-based cardiac biomarkers are more likely to be feasible than CMR, given the relatively time consuming and expensive nature of the latter.

Targeting efforts towards specific high-risk groups is also more likely to yield useful results. Recent analysis of data from a cohort of 1,296 DM1 patients has led to production of a scoring tool to predict prognosis. Whilst not yet integrated into the consensus care recommendations, personalised approaches using data-driven risk prediction systems such as this are likely to be more widely used in the future.

Serum muscle damage markers such as cardiac troponin I (cTnI) have been shown to be highly specific for cardiac involvement in IIM and show promise as a potential way of screening for subclinical cardiac manifestations in high risk patients. Similar work has also been performed in the inherited muscle diseases, with serum BNP and cTnI shown to be useful in recent studies. However, where these different assays might fit in to clinical practice, and how one determines if the abnormalities found are due to the disease itself rather than a consequence of traditional cardiovascular risk factors, remains to be fully determined.

TREATING CARDIAC INVOLVEMENT

Presently, there are no consensus guidelines for treatment of heart involvement in IIM. Immunosuppression is the mainstay of treatment, but evidence is limited to case reports and small series, including several recent publications. We suggest a low threshold for early and aggressive treatment to reduce myocardial inflammation and subsequent potential transformation to irreversible myocardial fibrosis and heart failure.

Whilst disease modifying therapies are scarcer for the inherited myopathies, prompt identification of cardiac involvement remains important as several supportive measures can be undertaken. These include pharmacological treatments, pacemaker implants or even ventricular assist devices and cardiac transplantation, as summarised by Feingold et al. In the dystrophinopathies, glucocorticoids and genetic therapies are generally reserved for those with DMD. However, angiotensin converting
enzyme inhibitors, anti-mineralocorticoid (e.g. epleronone) and beta blockade all have potential efficacy in terms of reducing the rate of progression of cardiomyopathy.\textsuperscript{2,47,48} In those with respiratory failure, use of home mechanical ventilation has also been shown to potentially have a protective effect on cardiac function, presumably by reducing pulmonary pressures and outflow resistance.\textsuperscript{49}

In myotonic dystrophy, implantation of permanent pacemakers or cardioverter-defibrillators should be considered in those found to be at high risk of cardiac arrest from abnormalities detected on cardiac surveillance tests. Enzyme replacement treatment is used in Pompe disease according to agreed starting and stopping criteria.\textsuperscript{50} Overall we would emphasise having a low threshold for screening for this treatable condition using acid $\alpha$-glucosidase enzyme activity testing.

CONCLUSIONS

Cardiac involvement in IIM and inherited muscle disease is associated with significant morbidity and mortality. Early detection through systematic screening and commencement of either disease modifying treatments or interventions targeted at reducing the risk of future harm are likely to improve outcomes. We suggest having a low threshold for considering the possibility of cardiac involvement in patients with muscle disease, even where disease manifestations might otherwise be limited. Close working with cardiologists is mandatory for those with suspected cardiac involvement.
FIGURE LEGEND

Figure 1. Various manifestations of cardiac involvement in inflammatory myopathies and inherited muscle diseases.
A: Post contrast cardiac magnetic resonance imaging in a manifesting female carrier of Duchenne muscular dystrophy. A dilated left ventricle and diffuse myocardial late gadolinium enhancement are shown, indicative of extensive fibrosis.
B: Echocardiographic image showing pericarditis (arrow) in a patient with idiopathic inflammatory myopathy. *(Courtesy of Mikkel Hougaard, MD, PhD, Odense University Hospital, Denmark)*
C: Myocardial biopsy demonstrating cardiomyocytes (middle arrow) surrounded by fibrosis (left arrow) and inflammatory infiltrates (right arrow) in a patient with myocarditis occurring in the context of idiopathic inflammatory myopathy (Hematoxylin and eosin stain). *(Courtesy of Professor Ulrik Baandrup, Vendsyssel Hospital, Aalborg University, Denmark)*
Acknowledgements
The authors are grateful to Prof. Federico Roncaroli and Dr Redi Pecini for reviewing draft versions of this manuscript.

Financial support and sponsorship.
JBL holds a NIHR Clinical Lectureship in Neurology (NWN/006/025/A). The views expressed are those of the authors and not necessarily of the NHS, NIHR, or Department of Health.

Conflicts of interest
JBL has undertaken consultancy work for Roche and received speakers bureau from Sanofi Genzyme.
REFERENCES


A large Taiwanese study finding that IIM is associated with an increased risk of coronary heart disease. An important demonstration of using large healthcare databases to investigate rare diseases.


An important study of 603 patients with IIM using the UK Clinical Practice Research Datalink (CPRD). IIM was shown to be associated with an increased risk of cardiovascular events in the first five years after diagnosis, similar to that of RA.


Cardiac magnetic resonance study of IIM patients without cardiac symptoms. Myocardial fibrosis was frequently found, highlighting a potential under recognition of cardiac involvement in IIM.


In this study cardiac magnetic resonance imaging is used to investigate a potential link between fibrosis and conduction abnormalities. In agreement with other studies, myocardial fibrosis was highly prevalent, but not related to conduction abnormalities. The relevance of this finding in terms of prognostication requires further investigation.


This observational cohort describes outcomes in 18 LOPD patients treated with enzyme replacement therapy, three of whom had cardiomyopathy which appeared to improve. The authors suggest that whilst cardiomyopathy appears rare in LOPD, regular surveillance for it should be undertaken.


Consensus-based care recommendations are now available for myotonic dystrophy type 1 and 2. These documents provide a useful resource for those managing patients with these
conditions.


