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MD Sine Søndergaard Korsholm[* 1,2], MD PhD Daniel C. Andersson[3, 4], MD John Bonde Knudsen[2], MD PhD Maryam Dastmalchi[5], MD PhD Axel CP Diederichsen[6], PhD Oke Gerke[7], MD PhD Nanna Witting[8], MD DSc Søren Jacobsen[1], MD PhD Redi Pecini[9], Cand.Scient. PhD Tina Friis[10], MD Markus E. Krogager[9], MD PhD Prof. Ingrid E. Lundberg[# 5], MD PhD Louise Diederichsen[# 1,2]

* Corresponding author: Sine Søndergaard Korsholm, MD, Center for Rheumatology and Spine Diseases Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark; e-mail: sinekorsholm@gmail.com; ORCID iD: https://orcid.org/0000-0003-3947-9111

# These authors contributed equally

[1]Center for Rheumatology and Spine Diseases, Copenhagen University Hospital (CUH), Rigshospitalet, Copenhagen, Denmark, [2]Dept of Rheumatology, Odense University Hospital (OUH), Odense, Denmark, [3]Dept of Physiology and Pharmacology, Karolinska Institute, Solna, Stockholm, Sweden, [4]Heart, Vascular and Neurology Theme, Cardiology Unit, Karolinska University Hospital, Stockholm, Sweden, [5]Division of Rheumatology, Dept of medicine, Solna, Stockholm, Karolinska Institutet and Rheumatology, Karolinska University Hospital, Solna, Stockholm, Sweden, [6]Dept of Cardiology, OUH, Odense, Denmark, [7]Dept of Nuclear Medicine, OUH, Odense, Denmark, [8]Dept of Neurology, CUH, Copenhagen, Denmark, [9]Dept of Cardiology, CUH, Copenhagen, Denmark, [10]Dept of Autoimmunology and Biomarkers, Statens Serum Institut, Copenhagen, Denmark

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Keywords:

Myositis, idiopathic inflammatory myopathy, heart, cardiac involvement, electrocardiogram, autoantibodies

Key messages:

- Presence of myositis-specific autoantibodies anti-Mi2 and anti-Pl-7 are associated with QTc abnormalities
- Associations between elevated CRP and QTc alterations may suggest a role for inflammatory mechanisms in the pathogenesis of QTc prolongation in IIM
- Findings from this study imply further investigations for future IIM-specific cardiac screening guidelines

Abstract

Objectives

The aim of this study was to investigate cardiac involvement detected by electrocardiography (ECG) in patients with idiopathic inflammatory myopathies (IIM) and to evaluate possible associations between autoantibody profile and ECG changes in these patients.

Methods

In a Scandinavian cross-sectional study, patients were included from two Danish centres and one Swedish centre. Resting 12-lead ECG was investigated in 261 patients with IIM compared to 102 patients with systemic sclerosis (SSc) and 48 healthy controls (HCs). ECG changes were correlated to clinical manifestations and myositis-specific (MSAs) and myositis-associated (MAAs) autoantibodies.

Results

Patients with IIM had longer mean QTc duration and more frequently presented with prolonged QTc (≥ 450 ms; P = 0.038) compared to HCs. Longer QTc duration was recorded in SSc compared to IIM (433 ± 23 ms vs. 426 ± 24 ms, P = 0.011), yet, no significant difference in the fraction with prolonged QTc (SSc: 22%, IIM: 16%; P = 0.19). In multivariable regression analyses, anti-Mi2 (P = 0.01, P = 0.035) and anti-Pl-7 (P = 0.045, P = 0.014) were associated with QTc duration and prolonged QTc in IIM. Elevated CRP was associated with prolonged QTc (P = 0.041).

Conclusion

Presence of QTc abnormalities was as common in patients with IIM as in patients with SSc, including prolonged QTc seen in almost one fifth of the patients. Anti-Mi2, anti-Pl-7, and elevated CRP may serve as biomarkers for cardiac disease in IIM, but needs to be confirmed in a larger prospective study.

Introduction

Idiopathic inflammatory myopathies (IIMs) are rare inflammatory diseases sharing symptoms of symmetric muscle weakness and inflammation of skeletal muscle (1). The most common subgroups are polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), antisynthetase syndrome (ASS), and immune mediated necrotizing myopathy (IMNM) (2). IIM is characterized by multisystem involvement which is associated with a poor outcome (1, 3). Heart involvement is a significant cause of death in patients with PM or DM, already in the first year after diagnosis of IIM, yet, cardiac symptoms are often subclinical and may be overlooked (3, 4).

Cardiac abnormalities have been reported in 6%-75% of PM and DM patients, depending on patient selection, definition of and methods used to detect heart involvement (5). Conduction defects and arrhythmias are frequently reported in PM and DM patients. ECG findings include among others ST-segment deviations, atrial arrhythmias, and life-threatening ventricular tachycardia (5-7). Prolonged QTc has been shown in patients with juvenile DM (8). QTc duration reflects the ventricular repolarization period and a prolonged QTc indicates a slowed ventricular repolarization, which is linked to increased risk of ventricular arrhythmias and sudden death (9-11). We have shown longer mean QTc intervals and more frequently left ventricular diastolic dysfunction in a cohort of patients with PM/DM compared to healthy controls (HCs) (3). Presence of myositis-specific autoantibodies (MSAs) or myositis-associated autoantibodies (MAAs) was associated with diastolic dysfunction, although no relationship between any specific autoantibody and cardiac function was found, probably due to the low number of patients with each autoantibody. Systemic sclerosis (SSc) is another connective tissue disease (CTD) that frequently involves cardiac dysfunction (12), including prolongation of QTc (13). Cardiac monitoring, including ECG, was recently recommended in the management of patients with SSc (14). Similar recommendations do not yet exist for patients with IIM.

Autoantibodies are important biomarkers to identify subgroups of myositis and can be subdivided into MSAs and MAAs (15, 16). While MAAs can be detected in other autoimmune disorders, MSAs are specific for IIM (15). One of the most frequent MSAs is anti-Jo1 which is associated with the clinical subset ASS characterized by interstitial lung disease, arthritis, and muscle inflammation (17, 18). Anti-signal recognition particle (SRP) autoantibody has been reported to be associated to cardiac involvement (19, 20). Recently one MAA, anti-mitochondrial autoantibody (AMA), was reported to be associated with severe heart disease in IIM (21). Whether other MSAs or MAAs could serve as biomarkers for ECG changes in patients with IIM is unknown.

The aim of this study was to compare QTc durations in a large cohort of patients with IIM to patients with SSc and HCs. In addition, we aimed to evaluate possible associations between autoantibody profile and ECG changes with focus on QTc duration in patients with IIM.

Materials and Methods

Study design and participants

This study was designed as a Scandinavian cross-sectional study. Patients were identified and included from two centres in Denmark and one centre in Sweden. Patients were of age ≥ 18 years and diagnosed with PM or DM according to the classification criteria by Peter and Bohan (22, 23), IBM according to Griggs criteria (24), and ASS according to criteria by Connors et al (25). Exclusion criteria were myositis associated with another defined autoimmune disease (25).

Patients were identified and included from two Danish centres; Department of Rheumatology, Odense University Hospital (OUH) from December 2016 to September 2018 and Department of Neurology, Copenhagen University Hospital (CUH) from August to September 2017. Of 139 invited Danish patients with IIM, 113 participated (OUH 88, CUH 25). Additionally, existing data from a former study of Danish patients with PM or DM (n = 79) included from May 2011 to January 2012 was included (3).

Consecutive patients in the out-patient clinic at Division of Rheumatology, Karolinska University Hospital (KUH), Sweden, were invited and participated in the study from December 2016 to June 2017 (n = 69).

As a comparator group consecutive patients of age ≥ 18 years, diagnosed with systemic sclerosis (SSc) according to the 2013 Classification Criteria for Systemic Sclerosis (26), coming in the out-patient clinic from December 2016 to September 2018 at Department of Rheumatology, OUH, were identified and invited to participate. Of 139 invited patients with SSc, 102 participated.

Data from Danish HCs (n = 48), who had participated in a former cardiovascular (CV) screening project, was used and previously described in detail (3). HCs were of age ≥ 18 years, had no history of rheumatic or CV diseases, and did not receive any medication. HCs were included from March to June 2012.

The study was approved by The Regional Committees on Health Research Ethics for Southern Denmark and the Stockholm Ethical Committee. The study was approved by the Danish Data Protection Agency. Verbal and written informed consent according to the Declaration of Helsinki II were obtained from all participants.

Assessments of disease activity and damage

Participating patients were examined by experienced physicians with extensive knowledge of IIM and SSc at study visit. Basic patient characteristics were drawn from medical records (age at diagnosis, gender, duration of disease, and present medications). Disease activity was recorded according to International Myositis Assessment & Clinical Studies Group (IMACS) by the Health Assessment Questionnaire (HAQ), patient/physician global disease activity and extra-muscular disease activity using a 10 cm visual analogue scale (VAS 0-10), manual muscle test including eight muscle groups (MMT-8) with each muscle scored 0-10, yielding a maximal score at 80. Disease damage was measured by patient/physician global disease damage using VAS 0-10. Serum levels of creatine kinase (CK) and C-reactive protein (CRP) were measured at the time of study visit (27). Due to different upper limits and analysis methods, CK and CRP were each categorized as increased according to each hospitals' standards for upper limits. For patients with SSc, a modified Rodnan skin score was performed at study visit.

Autoantibody analysis

For the Danish patients with IIM, blood samples were analysed for autoantibodies at time of diagnosis and/or time of study visit at Statens Serum Institut or at OUH according to the manufacturer instructions (Euroimmun, Lübeck, Germany). EDTA-plasma samples were analysed by line immunoblot (EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (24)) for MSAs (anti-Jo-1, anti-Pl-7, anti-Pl-12, anti-OJ, anti-EJ, anti-SRP) and MAAs (anti-PM/Scl75, anti-PM/Scl100, anti-Ro52/SSA, anti-Ku). EDTA-plasma samples were analysed for MSAs against HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) antigens by the QUANTA Lite HMGCR ELISA (Inova Diagnostics/ILS Denmark, Allerød, Denmark). EDTA-plasma samples were analysed for MAAs against cN-1A (cytosolic 5'-nucleotidase 1A) antigens by the Anti-cN-1A ELISA (24) (Euroimmun, Lübeck, Germany). MSAs and MAAs of the Swedish patients were tested by the same line blot as above in Uppsala Academic Hospital, by immunoprecipitation, kindly provided by Professor Mimori, Kyoto, Japan, or by ELISA as part of the clinical routine at KUH. Information on SSc specific autoantibodies was retrieved from medical records. Autoantibodies were noted if the patient had ever been positive for the given autoantibody.

Cardiovascular assessments

At study visit, weight (kg), height (m), and body mass index (BMI) was noted. Systolic and diastolic blood pressures (S-BP and D-BP) were measured three times with a minute in between. An average of the last two values was calculated. Hypertension was defined as presence of either S-BP ≥ 140 mmHg, D-BP ≥ 90 mmHg, or medical antihypertension treatment. Diabetes was defined by current antidiabetic therapy (orally or insulin). Patients responded to a basic CV questionnaire concerning medical conditions including CV disease, current medication, smoking habits, cardiac symptoms (reported if the patient ever had an episode of dyspnea, palpitations, chest pain, or syncope), and family history of premature CV events

(stroke, acute myocardial infarction, deep venous thrombosis, or aorta dissection) within the nearest family (parents, siblings, and children) in men younger than 55 years and in women younger than 65 years of age.

Electrocardiographic assessments

A standard ambulatory resting 12-lead ECG at 25 or 50 mm/s was recorded and analysed according to standard published criteria (10, 28-31). ECGs were read by a trained medical student with supervision from three clinical cardiologists. PQ, QRS, and QT durations given by the automated ECG algorithm were manually validated. The corrected QT (QTc) interval was calculated using Bazett's formula i.e. QT duration divided by square root of RR interval.

Prolonged intervals were defined as PQ interval ≥ 220 ms in majority of beats in any of leads I, II, III, aVL, aVF, QRS duration ≥ 120 ms in any of leads I, II, III, aVL, aVF, and QTc duration ≥ 450 ms in any leads of V2, V3 or aVR (10, 28, 29).

Statistical analyses

Descriptive statistics for continuous variables comprised mean ± SD for normally distributed data and median (range) for non-normally distributed data. Distribution of data was visually evaluated by histograms. Comparisons between patients with IIM and patients with SSc and HCs, respectively, were carried out using two-sample t-test for continuous normally distributed data and Wilcoxon rank-sum test for non-normally distributed data.

As for categorical data, comparisons between patients with IIM and patients with SSc and HCs, respectively, were conducted using chi-square test or Fisher's exact test depending on the distribution of data in the 2x2 tables. If data was small (less than five) in either of the cells in the 2x2 tables, Fisher's exact test was used.

Patient variables were included in a multivariable linear regression analysis of QTc duration; here, backward variable elimination was applied to identify possible risk factors for QTc duration. Patient characteristics such as patient/physician assessed global damage, extra-muscular assessment, and presence of anti-HMGCR and anti-cN-1A were not included due to missing data. Variables in the final multivariable linear regression analysis for QTc duration were starting point for the multivariable logistic regression analyses of prolonged QTc to which backward variable selection was applied. For multivariable linear and logistic regression analyses, a predefined p-value threshold of 0.3 was chosen indicating variables to stay within the models. Known predictor variables (age at inclusion, gender, hypertension, and smoking status) were kept in the multivariable linear and logistic regression analyses irrespective of p-values.

The level of statistical significance was set to 0.05 with a two-sided p-value. Data was analysed in Stata/IC 16.0 (StataCorp LLC, College Station, Texas 77845 USA).

Results

A total of 261 patients with IIM participated in the study. During data analysis, patients with IIM were re-classified with the definitions 'definite/probable/possible' IIM according to the new EULAR/ACR classification criteria (2). Eighty patients had definite PM/DM, 51 probable PM/DM, and 11 possible PM/DM. Fifty-six patients had ASS, 38 patients definite IBM and nine possible IBM. Results from patients with IIM were compared to patients with SSc (n = 102) and HCs (n = 48).

Patient characteristics and autoantibody profile

Patient characteristics and autoantibody status are summarized in Table 1 and Table 2. Disease activity depicted as HAQ, MMT-8, CRP, and CK in Table 1 showed low to moderate disease activity. Patients with IBM had the highest mean HAQ score (1.38) and lowest CRP (1.5 mg/L). Patients with ASS had the highest median CRP (4 mg/L), and 26 patients with ASS (46%) had an elevated CRP. Two hundred and seven IIM patients (79%) were positive for presence of either MSAs or MAAs, MSAs were present in 146 patients (56%), and MAAs in 137 patients (52%) (Table 2). Immunosuppressive medication is shown in Supplementary Material (Table A).

Cardiovascular characteristics

Cardiovascular (CV) characteristics in patients with IIM compared to patients with SSc and HCs are presented in Table 3. More patients with IIM experienced dyspnea (New York Heart Association II-IV) compared to patients with SSc (P = 0.012) and HCs (P < 0.001). Patients with IIM more often had palpitations at rest compared to HCs (P = 0.01). Patients with IIM had a significantly higher BMI compared to patients with SSc (P < 0.001). Sixty-nine percent of patients with IIM had hypertension, which was significantly more than 42% of HCs (P < 0.001), but not different to patients with SSc (65%). Twenty-three patients with IIM had diabetes, which was significantly more than patients with SSc (P = 0.02) and HCs (P = 0.032).

Electrocardiographic assessments

Mean QTc duration in patients with IIM was longer compared to HCs (P < 0.001), and patients with IIM more often displayed prolonged QTc than HCs (P = 0.038) (Table 3). Patients with IIM had shorter mean QTc interval compared to patients with SSc (P = 0.011). Prolonged QTc was found in 39 patients with IIM (16%) which was similar to patients with SSc (21/102, 22%) (P = 0.19).

Factors associated with QTc duration and prolonged QTc

In a multivariable linear regression analysis, presence of MSAs/MAAs (P = 0.025), anti-Mi2 (P = 0.01) or anti-Pl-7 autoantibodies (P = 0.045), age at inclusion (P = 0.011), and BMI (P = 0.03) correlated to QTc duration in patients with IIM (Table 4). QTc duration was inversely associated to male gender (P = 0.003).

Multivariable logistic regression analysis revealed that presence of MSAs/MAAs (P = 0.019), anti-Mi2 (P = 0.035) or anti-Pl-7 autoantibodies (P = 0.014), and elevated CRP (P = 0.041) were significantly associated with prolonged QTc (Table 5). Centre (Danish versus Swedish) was not associated to QTc duration or prolonged QTc. Former smoking (P = 0.05), dyspnea (P = 0.016), and abnormal heart rate (P = 0.013) were associated with prolonged QTc in patients with SSc.

Discussion

In this cross-sectional observational study, we found that patients with IIM displayed longer mean QTc duration than HCs, and that a prolonged QTc was more frequently seen in patients with IIM compared to HCs. Patients with IIM and patients with SSc showed similar ECG patterns, including prolonged QTc, which was found in approximately one fifth of patients with IIM (16%) and SSc (22%). Notably, presence of MSAs/MAAs and anti-Mi2 and anti-Pl-7 autoantibodies were associated with longer mean QTc duration and prolonged QTc in patients with IIM. Elevated CRP was associated with prolonged QTc in patients with IIM.

Cardiac abnormalities have been detected by ECG in up to 75% of adult patients with IIM. In this study, ECGs were quantitatively analysed according to the Minnesota ECG codes (31). Especially QTc abnormalities is of clinical relevance as it increases the risk of serious ventricular arrhythmias (9). The definition of prolonged QTc differ for men (> 440 ms) and women (> 450 ms) according to standard criteria (10). In this study, the cut-off value for prolonged QTc was set to 450 ms for both men and women to simplify analysis and allow comparability to other studies. Our slightly higher limit for prolonged QTc in men might have underestimated the number of males with prolonged QTc.

Prolonged QTc in patients with SSc has been hypothesized to partly be due to myocardial fibrosis (32). ECG alterations in patients with IIM are thought to be caused mainly by inflammation and fibrosis in the conduction system of the heart associated with the myositis disease process (33, 34). Several case series on cardiac imaging in IIM has revealed signs of myocardial inflammation and fibrosis, unfortunately without including ECG description (35, 36). In the present study, cardiac imaging was not part of the set-up.

Older age was significantly associated with an increased risk of longer mean QTc duration, but male gender was inversely correlated to longer mean QTc duration, which is in line with previous reports on healthy elderly individuals (9, 37). In this study, the cardiovascular factors diabetes, abnormal heart rate, and history of AMI showed no association to QTc duration or prolonged QTc in IIM patients.

Patients with IIM were subgrouped according to autoantibody profile. Presence of MSAs/MAAs was found in 79% of patients with IIM, and MSAs were present in 56% of patients with IIM in accordance with a study arising from the Euromyositis Registry (19).
We found that presence of MSAs/MAAs, anti-Mi2 and anti-Pl-7 were independent risk factors for QTc abnormalities. Anti-Mi2 is mainly seen in patients with clinical features of DM, often with severe muscle disease. Only a single case with anti-Mi2 positive DM with underlying clinical cardiac involvement consisting of arrhythmia has been reported (39). After treatment with rituximab and prednisolone, ECG and Holter monitoring normalized.
Anti-Pl-7 is one of the ASS autoantibodies and has been associated with extra-muscular involvement, e.g. interstitial lung disease, arthritis, and Raynaud's phenomenon (18, 40). Anti-Pl-7 has previously been associated with pericarditis, yet, it has never been linked to ECG changes (40, 41). In a recent Dutch study, eight patients were anti-Pl-7-positive (4.3%), of which two had cardiac involvement (42). Our data reveals for the first time a significant association between anti-Pl-7 and QTc alterations, implying that anti-Pl-7 – in addition to anti-Mi2 – may be a risk marker for cardiac involvement in IIM.

Cardiac involvement has previously been associated to several MSAs or MAAs. Anti-SRP positive IIM patients had an OR of 4.15 for cardiac involvement (pericarditis, myocarditis, arrhythmia, or sinus tachycardia) in the Euromyositis Registry study (19). A retrospective study described myocarditis in two of 60 anti-SRP positive IIM patients (9%) (43). None of these studies reported ECG results, which makes comparison difficult. A large prospective study on patients with IIM and SSc found echocardiography or ECG abnormalities in two of 16 anti-SRP positive PM patients (13%) (44), a finding we could not replicate. Arrhythmias has been found in three of 12 patients with anti-SRP positive PM, though method of diagnosing cardiac involvement is not described (20).
Anti-Ro/SSA has been associated to cardiac involvement in patients with CTD, though clear consensus lacks (13, 45, 46). To our knowledge, no former studies have investigated correlations between anti-Ro/SSA and ECG changes in IIM, and neither did our results reveal such associations.

Blood CRP elevation mirrors the systemic inflammatory activity. We found that elevated CRP in IIM patients was associated to prolonged QTc. A link between the inflammatory burden of rheumatoid arthritis and cardiac mortality has been suggested (47, 48). One study showed shortened QTc duration correlating with decreased serum level of CRP (48), while elevated CRP had a positive correlation with prolonged QTc in another study (47). Such associations between inflammation in IIM and ECG changes have not been studied previously, though our study implies that elevated CRP indicates higher risk of cardiac involvement.

The strengths of this study include the large sample size and a comparator group of HCs and patients with SSc, though the cross-sectional study design carries a risk for volunteer bias. Consecutive patients were

invited to participate and no randomization was performed which could be considered a limitation. Some of the most severely ill patients may not have been invited to participate or were too ill to participate. As the mean duration was 74 months since diagnosis of IIM we may have missed some patients that have already died from cardiac involvement, as the risk for cardiac death is highest the first year after diagnosis. Another limitation is that we did not have up-to-date information that would permit the diagnosis of IMNM although 10% of our patients presented with anti-SRP and 13% with anti-HMGCR antibodies, most of these patients were subgrouped into PM patients. Another limitation is the limited number of patients when subgrouping according to the autoantibody profiles. We need to be cautious with the interpretation of anti-Mi2 and anti-Pl-7 autoantibodies as potential risk factors for QTc abnormalities, and data needs to be confirmed in a larger and preferentially prospective cohort. The MSA anti-HMGCR and the MAA anti-cN-1A are included in the factor of presence of MSAs/MAAs, anti-HMGCR in the factor of presence of MSAs, and anti-cN-1A in the factor of presence of MAAs in multivariable analyses. Due to missing values, we were not able to conduct multivariable analyses with anti-HMGCR and anti-cN-1A as individual explanatory factors for ECG changes. The rare MAA AMA was not analysed in this study, as it is not included in the assays MSAs/MAAs used for patients in the study. Autoantibody analyses were performed in specialised clinical immunology laboratories, though the same methods were not used in Denmark and Sweden, which is a weakness of the study. Centre (Danish versus Swedish) showed no significant association to QTc alterations, which indicates that methods of autoantibody analysis probably did not influence the results. Another limitation is that current immunosuppressive medications were not included in multivariable regression analyses. Prednisolone and rituximab have been reported with possible side effects on the heart, though this is not known for ciclosporin A, methotrexate or azathioprine. Furthermore, we did not have full information on all other agents, which potentially could cause QTc abnormalities.

In conclusion, ECG changes are more frequently present in IIM compared to HCs. Importantly, one fifth of patients with IIM had prolonged QTc, indicating a risk for ventricular arrhythmias.
The frequency was comparable to SSc patients supporting the importance of screening IIM patients with ECG to detect changes that should alert for a more thorough work up of cardiac involvement. Presence of anti-Mi2 and anti-Pl-7 autoantibodies was associated with QTc abnormalities. These novel findings support the notion that specific autoantibodies may predict cardiac involvement in IIM. Additional longitudinal studies including cardiac imaging will be required to further investigate the clinical significance of QTc abnormalities and to understand the underlying mechanisms of ECG abnormalities in IIM.

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Conflicts of interest

IE Lundberg has served on advisory boards for Corbus Pharmaceutical, EMD Serono Research & Development Institute, Argenx, Octapharma, Kezaar, Orphazyme, Janssen and Pfizer, and has received grant support from Astra Zeneca and from Bristol Myers Squibb and has stock shares in Roche and Novartis.

Data availability statement

The data that supports the findings of this study is available on request from the corresponding author. The data is not publicly available due to patient privacy.

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Table 1. Characteristics of patients with polymyositis, dermatomyositis, inclusion body myositis, antisynthestase syndrome, and systemic sclerosis.

Patient characteristics	**Patients, PM n = 89**	**Patients, DM n = 60**	**Patients, IBM n = 56**	**Patients, ASS n = 56**	**Patients, SSc n = 102**
Age at inclusion, years, mean ± SD	62.4 ± 12.0	57.1 ± 13.7	72.5 ± 7.0	59.0 ± 14.7	59.5 ± 12.4
Female	56 (63)	41 (68)	21 (38)	35 (63)	78 (76)
Age at diagnosis, years, mean ± SD	55.0 ± 12.9	51.4 ± 13.8	67.5 ± 8.6	52.6 ± 16.4	53.1 ± 13.6
Disease duration, years, median (range)	6.0 (0-63.5)	4.4 (0-32.2)	4.4 (0.04-21.8)	5.0 (-0.04-42.3)	4.3 (0-29.3)
HAQ (0-3), median (range)	0.8 (0-3)	0.4 (0-2.8)	1.4 (0-3)	0.6 (0-2.6)	0.1 (0-2)
MMT-8 (0-80), median (range)	75 (47-80)	76 (37-80)	67 (14-78)	77 (58-80)	NA
Global activity, patient, median (range)	33 (0-100)	21.5 (0-100)	2 (0-100)	33 (0-100)	27 (0-100)
Global activity, physician, median (range)	10 (0-89)	11 (0-85)	2 (0-20)	18 (0-80)	19 (0-64)
Global damage, patient, median (range)	50 (0-100)	27 (0-93)	55 (2-100)	47 (0-89)	35 (0-100)
Global damage, physician, median (range)	24.3 (0-78)	17 (0-54)	42 (5-93)	31 (1-82)	28 (0-86)
Extra-muscular assessment, physician, median (range)	1 (0-20)	5 (0-68)	1 (0-13)	23 (0-50)	NA
Modified Rodnan skin score	NA	NA	NA	NA	4 (0-16)
CRP, mg/L, median (range)	2.3 (0.6-195)	2 (0-51)	1.5 (0.2-49.78)	4 (0-83)	2.1 (0.6-40)
Increased	25 (28)	12 (20)	11 (20)	26 (46)	21 (21)
CK					
Increased	46 (52)	10 (17)	21 (38)	12 (21)	1 (1)
Increased x 3	23 (26)	4 (7)	2 (4)	6 (11)	0 (0)

Values are expressed as n (%) unless otherwise noted. PM: polymyositis, DM: dermatomyositis, IBM: inclusion body myositis, ASS: antisynthetase syndrome, SSc: systemic sclerosis, HAQ: health assessment questionnaire, MMT8: manual muscle test of 8 muscles, NA: not available, CRP: C-reactive protein, CK: creatine kinase.

Table 2. Autoantibodies in patients with polymyositis, dermatomyositis, inclusion body myositis, antisynthestase syndrome, and systemic sclerosis.

Autoantibodies	**Patients, PM n = 89**	**Patients, DM n = 60**	**Patients, IBM n = 56**	**Patients, ASS n = 56**	**Patients, SSc n = 102**
SSc specific autoantibodies					
Anti-centromer (n = 102)	NA	NA	NA	NA	41 (40)
Anti-Scl70/topoisomerase I (n = 102)	NA	NA	NA	NA	11 (11)
Anti-RNA-polymerase III (n = 102)	NA	NA	NA	NA	4 (4)
Presence of MSAs or MAAs (n = 261)	72 (81)	45 (75)	34 (61)	56 (100)	NA
Presence of MSAs (n = 261)	51 (57)	35 (58)	5 (9)	55 (98)	NA
Anti-SRP (n = 253)	18 (21)	4 (7)	2 (4)	1 (2)	NA
Anti-Jo-1 (n = 261)	9 (10)	10 (17)	0 (0)	40 (71)	NA
Anti-EJ (n = 252)	1 (1)	0 (0)	0 (0)	4 (8)	NA
Anti-OJ (n = 252)	1 (1)	0 (0)	0 (0)	1 (2)	NA
Anti-Pl-7 (n = 253)	1 (1)	0 (0)	1 (2)	9 (17)	NA
Anti-Pl-12 (n = 253)	2 (2)	0 (0)	0 (0)	3 (5)	NA
Anti-HMGCR (n = 211)	19 (24)	5 (13)	1 (2)	3 (8)	NA
Anti-Mi2 (n = 253)	1 (1)	2 (3)	0 (0)	4 (8)	NA
Anti-SAE1 (n = 241)	0 (0)	5 (9)	0 (0)	0 (0)	NA
Anti-NXP2 (n = 240)	4 (5)	2 (4)	0 (0)	1 (2)	NA
Anti-MDA-5 (n = 241)	2 (2)	9 (16)	0 (0)	0 (0)	NA
Anti-TIF1-γ (n = 241)	4 (5)	7 (12)	2 (4)	0 (0)	NA
Presence of MAAs (n = 261)	40 (45)	25 (42)	32 (57)	40 (71)	NA
Anti-Ro-52/SSA (n = 261)	23 (26)	18 (30)	10 (18)	35 (63)	NA
Anti-Pm/Scl-75 (n = 249)	7 (8)	6 (10)	2 (4)	3 (6)	NA
Anti-Pm/Scl-100 (n = 248)	5 (6)	5 (8)	0 (0)	4 (8)	NA
Anti-Ku (n = 253)	3 (3)	2 (3)	1 (2)	2 (4)	NA
Anti-cN-1A (n = 170)	18 (30)	4 (13)	25 (49)	1 (4)	NA

Values are expressed as n (%) unless otherwise noted. PM: polymyositis, DM: dermatomyositis, IBM: inclusion body myositis, ASS: antisynthetase syndrome, SSc: systemic sclerosis, MSAs: myositis specific-autoantibodies, MAAs: myositis-associated autoantibodies, NA: not available.

Table 3. Cardiovascular characteristics of patients with myositis compared to patients with systemic sclerosis and healthy controls.

CV characteristics	Patients, IIM n = 261	Patients, SSc n = 102	P-value	HCs n = 48	P-value
Age at inclusion, years, mean ± SD	62.6 ± 13.3	59.5 ± 12.4	**0.039***	59.4 ± 8.6	0.10*
Female	153 (59)	78 (76)	**0.001†**	32 (67)	0.30†
Cardiac symptoms					
Dyspnea (NYHA II-IV)	92 (35)	22 (22)	**0.012†**	2 (4)	**<0.001#**
Palpitations at rest	59 (23)	32 (32)	0.066†	3 (6)	**0.010#**
Angina	1 (0)	0 (0)	0.99#	0 (0)	0.99#
Syncope	5 (3)	2 (2)	0.99#	0 (0)	0.99#
Smoking			0.30†		0.73†
Current smoker	36 (14)	20 (20)		8 (17)	
Former smoker	90 (34)	29 (29)		14 (29)	
Never smoker	135 (52)	52 (51)		26 (54)	
Family history of CV events	27 (11)	18 (19)	0.067†	5 (10)	0.89†
BMI (kg/m^2), mean ± SD	26.9 ± 5.7	24.7 ± 4.4	**<0.001***	26.0 ± 3.1	0.31*
Hypertension	181 (69)	66 (65)	0.39†	20 (42)	**<0.001†**
Diabetes	23 (9)	2 (2)	**0.020#**	0 (0)	**0.032#**
History of AMI	17 (7)	5 (5)	0.56†	0 (0)	0.085#
ECG					
Heart rate, mean ± SD	70 ± 123	71 ± 14	0.54*	67 ± 10	0.14*
Heart rate, abnormal < 50 ms or > 100 ms	5 (2)	5 (5)	0.12†	0 (0)	0.99#
PQ (ms), mean ± SD	164 ± 27	160 ± 23	0.21*	164 ± 20	0.99*
> 220 ms	7 (3)	1 (1)	0.45#	0 (0)	0.60#
QRS (ms), median (range)	90 (62-182)	90 (68-126)	0.24‡	87 (69-118)	**<0.001‡**
> 120 ms	22 (9)	3 (3)	0.10#	0 (0)	**0.032#**
QTc (ms), mean ± SD	426 ± 24	433 ± 23	**0.011***	404 ± 28	**<0.001***
> 450 ms	39 (16)	21 (22)	0.19†	2 (4)	**0.038#**

Values are expressed as n (%) unless otherwise noted. Significant differences (P-value < 0.05) in bold. † Chi-squared test, # Fisher's exact test, * Two-sample t test, ‡ Wilcoxon rank-sum test.

CV: cardiovascular, IIM: idiopathic inflammatory myopathy, SSc: systemic sclerosis, HCs: healthy controls, NYHA: New York Heart Association, BMI: body mass index, AMI: acute myocardial infarction, ECG: electrocardiogram.

Table 4. Multivariable linear regression analyses of QTc duration (ms) on possible risk factors.

	Patients, IIM (n = 231; R^2 = 0.20)			**Patients, SSc (n = 91; R^2 = 0.21)**			**Healthy controls (n = 48; R^2 = 0. 0.25)**		
Risk factor	**Coef.**	**95% CI**	**P-value**	**Coef.**	**95% CI**	**P-value**	**Coef.**	**95% CI**	**P-value**
Gender (male)	-8.89	-14.77;-3.01	**0.003**	-1.02	-13.71;11.68	0.87	-16.62	-34.14;0.91	0.062
Age at inclusion (years)	0.33	0.08;0.58	**0.011**	-0.20	-0.65;0.25	0.37	0.55	-0.44;1.54	0.27
Smoking status									
Former (no vs. yes)	1.01	-5.27;7.28	0.75	9.24	-2.78;21.27	0.13	16.88	-1.36;35.13	0.069
Current (no vs. yes)	5.17	-3.31;13.65	0.23	5.74	-7.07;18.56	0.38	14.04	-8.34;36.42	0.21
Dyspnea (NYHA II-IV) (no vs. yes)			NA	7.86	-4.88;20.59	0.22			NA
Palpitations at rest (no vs. yes)			NA	-9.19	-20.70;2.32	0.12	-22.23	-56.14;11.67	0.19
Family history of CV disease (no vs. yes)			NA	-8.76	-21.61;4.09	0.18			NA
BMI (kg/m^2)	0.61	0.06;1.16	**0.030**	-1.01	-2.21;0.20	0.10	1.68	-1.11;4.46	0.23
Hypertension (no vs. yes)	2.03	-4.85;8.90	0.56	3.70	-6.86;14.25	0.49	2.40	-15.10;19.90	0.78
Diabetes (no vs. yes)	-8.50	-18.56;1.56	0.097	-28.18	-63.49;7.14	0.12			NA
HAQ (range 0-3)			NA	13.65	0.70;26.60	**0.039**			NA
MMT-8 (range 0-80)	-0.28	-0.59;0.03	0.080			NA			NA
CRP (mg/L)			NA			NA	-0.98	-2.81;0.86	0.29
Increased CRP (no vs. yes)	5.36	-1.30;12.02	0.11			NA			NA
Heart rate, abnormal (no vs. yes)			NA	21.25	-3.25;45.76	0.088			NA
Anti-Scl70/topoisomerase I (no vs. yes)			NA	-12.30	-29.60;5.00	0.16			NA
Anti-RNA-polymerase III (no vs. yes)			NA	19.67	-8.01;47.34	0.16			NA
Presence of MSAs or MAAs (no vs. yes)	14.00	1.75;26.26	**0.025**			NA			NA
Presence of MSAs (no vs. yes)	-8.83	-17.74;0.08	0.052			NA			NA
Anti-Pl-7 (no vs. yes)	13.86	0.29;27.43	**0.045**			NA			NA
Anti-Mi2 (no vs. yes)	22.00	5.32;38.69	**0.010**			NA			NA
Anti-Ro-52/SSA (no vs. yes)	6.67	-1.99;15.34	0.13			NA			NA
Presence of MAAs (no vs. yes)	-6.90	-17.25;3.46	0.19			NA			NA
Anti-Ku (no vs. yes)	-10.74	-28.73;7.24	0.24			NA			NA

Significant differences (P-value < 0.05) in bold. IIM: idiopathic inflammatory myopathy, SSc: systemic sclerosis, HCs: healthy controls, CV: cardiovascular, BMI: body mass index, HAQ: health assessment questionnaire, MMT-8: manual muscle test of 8 muscles, CRP: C-reactive protein, MSAs: myositis-specific autoantibodies, MAAs: myositis-associated autoantibodies, NA: not available.

Table 5. Multivariable logistic regression analyses of prolonged QTc (above 450 ms) on possible risk factors.

	Patients, IIM (n = 238; R^2 = 0.15)			Patients, SSc (n = 92; R^2 = 0.18)		
Risk factor	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Gender (male)	-0.24	-1.06;0.58	0.56	-0.20	-1.60;1.20	0.78
Age at inclusion (years)	0.03	-0.01;0.07	0.10	-0.02	-0.07;0.03	0.39
Smoking status						
Former (no vs. yes)	-0.55	-1.50;0.39	0.25	1.43	0.0004;2.86	**0.05**
Current (no vs. yes)	0.80	-0.25;1.86	0.14	0.46	-1.19;2.12	0.59
Dyspnea (NYHA II-IV) (no vs. yes)			NA	1.65	0.31;2.99	**0.016**
Family history of CV disease (no vs. yes)			NA	-1.17	-3.09;0.74	0.23
Hypertension (no vs. yes)	-0.12	-1.08;0.84	0.80	0.04	-1.25;1.33	0.95
BMI (kg/m^2)	0.04	-0.03;0.12	0.24			NA
Increased CRP (no vs. yes)	0.88	0.04;1.73	**0.041**			NA
Heart rate, abnormal (no vs. yes)			NA	3.41	0.73;6.09	**0.013**
Anti-Scl70/topoisomerase I (no vs. yes)			NA	1.68	-1.21;4.57	0.25
Presence of MSAs or MAAs (no vs. yes)	2.10	0.34;3.86	**0.019**			NA
Presence of MSAs (no vs. yes)	-1.57	-2.81;-0.33	**0.013**			NA
Anti-Pl-7 (no vs. yes)	1.78	0.36;3.20	**0.014**			NA
Anti-Mi2 (no vs. yes)	1.93	0.14;3.73	**0.035**			NA
Presence of MAAs (no vs. yes)	-1.47	-3.05;0.11	0.068			NA
Anti-Ro-52/SSA (no vs. yes)	0.92	-0.35;2.19	0.15			NA

Significant differences (P-value < 0.05) in bold. IIM: idiopathic inflammatory myopathy, SSc: systemic sclerosis, CV: cardiovascular, BMI: body mass index, CRP: C-reactive protein, MSAs: myositis-specific autoantibodies, MAAs: myositis-associated autoantibodies, NA: not available.

Table A. Current medical history of patients with polymyositis, dermatomyositis, inclusion body myositis, antisynthestase syndrome, and systemic sclerosis.

Medical history	**Patients, PM n = 89**	**Patients, DM n = 60**	**Patients, IBM n = 56**	**Patients, ASS n = 56**	**Patients, SSc n = 102**
Present immunosuppressive					
Prednisolone	43 (52)	32 (58)	15 (27)	36 (65)	24 (24)
Non-prednisolone immunosuppressive	56 (68)	33 (60)	12 (21)	35 (64)	48 (47)
Methotrexate	13 (25)	16 (41)	7 (13)	8 (22)	28 (27)
Azathioprine	10 (19)	2 (5)	2 (4)	3 (8)	4 (4)
Ciclosporin A	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Mycophenolate mofetil	12 (23)	6 (15)	0 (0)	12 (33)	13 (13)
Cyclophosphamide p.o.	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Cyclophosphamide i.v.	0 (0)	0 (0)	0 (0)	1 (3)	2 (2)
Immunoglobulins i.v.	3 (6)	1 (3)	2 (4)	0 (0)	0 (0)
Anti-malaria	0 (0)	3 (8)	0 (0)	1 (3)	1 (1)
Rituximab	2 (4)	4 (1)	0 (0)	5 (14)	0 (0)
Other anti-inflammatory	3 (6)	1 (3)	0 (0)	0 (0)	0 (0)

Values are expressed as n (%). PM: polymyositis, DM: dermatomyositis, IBM: inclusion body myositis, ASS: antisynthetase syndrome, SSc: systemic sclerosis, p.o.: peroral, i.v.: intravenous.