ORIGINAL COMMUNICATION

The heart in sporadic inclusion body myositis: a study in 51 patients

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Abstract The purpose of this study was to explore the prevalence and nature of cardiac abnormalities in sporadic inclusion body myositis (sIBM). Fifty-one sIBM patients were cross-sectionally studied using history-taking, physical examination, measurements of serum creatine kinase activity, the MB fraction (CK-MB), cardiac troponin T (cTnT) and I (cTnI), a 12-lead electrocardiogram (ECG) and 2-dimensional echocardiography. Present cardiac history was abnormal in 12 (24%) out of 51 patients, 12 (24%) patients had abnormalities on ECG, mostly aspecific, and in 12 (24%) patients the echocardiograph showed abnormalities. Elevated CK-MB was present in 42 (82%) patients and 40 (78%) had an elevated cTnT in the absence of acute cardiac pathology. In contrast, in one patient (2%) cTnI was elevated. There was no apparent association between elevated biomarkers, ECG or echocardiographic abnormalities. The prevalence of cardiac abnormalities in sIBM does not seem to be higher than would be expected in these elderly patients. Elevated CK-MB and cTnT levels are common, in contrast to cTnI, but do not reflect cardiac pathology.

Keywords Inclusion body myositis · Creatine kinase · Troponin · Electrocardiography · Echocardiography

Introduction

Sporadic inclusion body myositis (sIBM) is a slowly progressive inflammatory myopathy of striated skeletal muscle, particularly affecting the quadriceps muscles, forearm flexors and pharyngeal muscles. Symptoms usually occur after the age of forty [4, 20].

Muscle biopsy specimens show predominantly endomysial inflammation, with CD8+ T-cells invading nonnecrotic muscle fibers. These infiltrates resemble those in polymyositis (PM). Essential differences with PM are the presence of rimmed vacuoles and intracellular deposits of a host of proteins, including β-amyloid and hyperphosphorylated tau in sIBM.

Cardiovascular studies in PM and dermatomyositis (DM), cross-sectional or retrospective, reported abnormalities in 32.5–85% of the patients, comprising congestive heart failure, conduction abnormalities, myocarditis, arrhythmias and cardiomyopathy [13, 14, 21, 26]. At the time these studies were done, sIBM was not yet considered a distinct disease entity, and the Bohan and Peter criteria then used resulted in the inclusion of sIBM patients into the PM groups [8, 9]. Cardiovascular case series in sIBM have not been published as far as we know.

The present study explored the possible involvement of the heart in sIBM patients using non-invasive techniques.

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Methods

Study population

The study comprised 51 patients diagnosed with sIBM, selected from a national cohort of 86 sIBM patients. The recruitment procedure has been previously described in detail [3]. In short, a database of sIBM patients was started through a national survey in all large neurologic and rheumatologic centers in the Netherlands in order to identify as many sIBM patients as possible. Clinical data and biopsy specimens of all patients previously coded with a diagnosis of sIBM, a chronic or refractory myositis or progressive myopathy of unknown origin, with an onset after the age of 45 years were reevaluated for sIBM characteristics. Included patients fulfilled the ENMC criteria for definite or probable sIBM [28]. The study protocol included a cross-sectional clinical evaluation, blood sample analysis, 12-lead electrocardiography (ECG) and transthoracic echocardiography. The studies were done at Leiden University Medical Center after approval by the Ethics committee and after attaining informed consent of all patients. From the remaining 35 patients who were not included in the present study, 13 refrained from participation, 5 could not be located, 6 died before starting the protocol (1 patient due to adenocarcinoma of the lung, one due to gastric bleeding, and 4 to causes unknown) and 11 did not undergo cardiac evaluation due to logistic difficulties.

Clinical evaluation

History-taking focussed on the presence of cardiovascular risk factors and previous history of ischemic heart disease, heart failure, cardiac arrhythmias and pericardial disease.
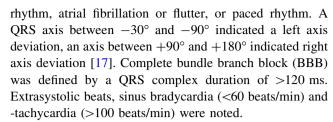
The physical examination comprised 12 automated blood pressure and pulse rate measurements taken within 30 min while seated, and a heart examination.

Blood sample analysis

Serum creatine kinase activity (sCK), the MB fraction (CK-MB) and cardiac Troponin T (cTnT) and Troponin I (cTnI) were analyzed. Normal values for sCK were ≤170 U/L in women and ≤200 U/L in men and for CK-MB ≤ 10 μg/L. The cut off value for cTnT was 0.03 μg/L and for cTnI > 0.2 μg/L.

Electrocardiography

The presence of any conduction disturbance, arrhythmia, myocardial ischemia or infarction was evaluated by ECG (25 mm/s) as follows: heart rhythm was classified as sinus rhythm, atrial fibrillation or flutter, or paced rhythm. A QRS axis between −30° and −90° indicated a left axis deviation, an axis between +90° and +180° indicated right axis deviation [17]. Complete bundle branch block (BBB) was defined by a QRS complex duration of >120 ms. Extrasystolic beats, sinus bradycardia (<60 beats/min) and -tachycardia (>100 beats/min) were noted.

ST-segment depression >1 mm and abnormal negative T-waves in two consecutive leads suggested myocardial ischemia. Pathological Q-waves in at least two consecutive leads, with a duration >0.04 s and a depth >25% of the R-wave voltage, indicated previous myocardial infarction.

Left ventricular (LV) hypertrophy was assessed using the Sokolow index [24]. The corrected QT-interval (QTc) was calculated according to Bazett's formula [5].

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system Vivid-5; General Electric-Vingmed, Milwaukee, WI, USA). Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber, long-axis) views. The images were stored for off-line analysis (EchoPac 6.0.1, General Electric Vingmed Ultrasound, Milwaukee, USA).

Both ECG and echocardiography were analyzed by one independent cardiologist blinded with regard to the clinical status of the patient, but aware of the sIBM diagnosis.

LV dimensions and function were measured from M-mode images. LV wall motion was classified as abnormal when hypokinesia was observed. LV mass was calculated by the cube formula and using the correction formula proposed by Devereux et al. [10]. LV mass index (LVMI) was calculated after correction for body surface area. A value of $LVMI > 110 \text{ g/m}^2$ in women and $>135 \text{ g/m}^2$ in men defined LV hypertrophy [27].

LV diastolic function was evaluated by the pulsed wave Doppler recordings of the transmitral inflow velocity [22]. Diastolic transmitral peak velocities (E-wave and A-wave), the E/A ratio and the E-deceleration time were measured. Valvular function was evaluated with color Doppler echocardiography and standard continuous and pulsed wave Doppler examinations.

Statistical analysis

Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the Fisher exact test. Laboratory data are stated as median

(range), other data are presented as mean ± standard deviation.

Results

Study population and clinical evaluation

All 51 sIBM patients (67 ± 9 years, 34 men) completed the study protocol. Mean disease duration was 11 ± 6 years. The investigated group did not differ significantly from the original population group of 86 patients with regard to sex distribution, age (at onset) and disease duration. The cardiovascular history profile up to inclusion is summarized in Table 1.

The majority of the patients ($n = 39$, 76%) reported no cardiovascular symptoms at the time of history taking. The remaining 12 patients (24%) disclosed exertion-induced chest pain, dyspnea, nycturia or palpitations. None of the patients had had a myocardial infarction within 3 months prior to evaluation. The mean systolic and diastolic blood pressures at examination were 133 ± 19 and 77 ± 12 respectively. A cardiac murmur was noted in 7 (14%) patients.

Table 1 Cardiovascular profile

Cardiovascular risk factors	
Hypertension	12 (24%)
Hypercholesterolemia	1 (2%)
Diabetes mellitus	1 (2%)
Obesity (BMI > 30 kg/m²)	5 (10%)
Cigarette smoking	
Present	5 (10%)
Previous	15 (29%)
Previous cardiac history	
Myocardial infarction	8 (16%)
Coronary revascularisation	3 (6%)
Conduction abnormalities	5 (10%)
Requiring pacemaker	2 (4%)
Pericarditis	1 (2%)
Heart failure	1 (2%)
Mitral valve abnormalities	2 (4%)
Requiring valve replacement	1 (2%)
Cardiovascular medications	
β-blockers	10 (20%)
Calcium-antagonists	4 (8%)
ACE-inhibitors	7 (14%)
Diuretics	8 (16%)

Multiple items possible per patient

BMI body mass index, *ACE-inhibitors* angiotensin converting enzyme inhibitors

Laboratory data

Elevated sCK levels were observed in 42 (82%) patients, 506 U/L (64–3,360) in men, 246 U/L (44–802) in women. Elevated CK-MB levels were measured in 42 (82%) patients, 18 μg/L (2–124). Elevated cTnT levels were observed in 40 (78%) patients, 0.08 μg/L (0.01–0.99), and an elevated cTnI level of 0.22 μg/L was found in one patient. CK-MB was elevated in four patients with a normal sCK.

Electrocardiographic data

Most patients were in sinus rhythm ($n = 47$, 92%). Three (6%) patients had atrial fibrillation and 1 (2%) a paced rhythm. Mean heart rate was 69 ± 15 beats/min.

The mean QRS duration was 91 ± 20 ms. Thirty-four (67%) patients showed a normal QRS axis, 2 (4%) a right axis deviation and 13 (25%) a left axis deviation. Two (4%) patients had complete BBB whereas 5 (10%) patients had incomplete BBB. Seven (14%) patients had signs of previous myocardial infarction whereas 4 (8%) had signs corresponding to our definition of myocardial ischemia.

Nine (18%) patients had LV hypertrophy. Mean QTc duration was normal.

Echocardiographic data

Most patients had a non-dilated LV with preserved function. Impaired systolic function (LV ejection fraction <50%) was observed in 4 (8%) patients. Fourteen (27%) patients met the echocardiographic criteria of LV hypertrophy. The LV diastolic function could be reliably assessed in 45 patients. The mean E/A ratio was 0.9 ± 0.6, which is in the normal range above the age of fifty.

The majority of the patients had normal valvular function. Mild mitral ($n = 7$, 14%), aortic ($n = 8$, 16%), and tricuspid ($n = 7$, 14%) regurgitation were infrequently found and only 1 (2%) patient had moderate tricuspid regurgitation.

Myocardial damage evaluation by combining serum levels of cardiac biomarkers, ECG and echocardiographic findings

To evaluate the clinical significance of the raised biomarkers, we compared the values of biomarkers between patients with and without abnormalities on ECG and echocardiography. For this purpose, pathologic ECG ($n = 12$, 24%) was defined by the presence of any conduction abnormality, pathologic ST-segment depression or

pathologic Q waves, whereas pathologic echocardiography (*n* = 12, 24%) was defined by the presence of impaired systolic LV function or wall motion abnormalities.

Of the patients with a normal ECG or echocardiography, 79% had raised CK-MB levels versus 100% in patients with a pathologic ECG or echocardiography (*p* = 0.2). For cTnT, these numbers were 79 and 85% respectively (*p* = 0.8). CK-MB and cTnT levels did not differ between the groups with and without pathologic ECG or echocardiography either (*p* = 0.8 and 0.09, respectively).

The only patient with an elevated cTnI had pathologic findings on ECG and echocardiography, including a wall motion abnormality with an ejection fraction of 18%.

Thus, raised cardiac biomarkers were not associated with pathologic findings on ECG or echocardiography and, furthermore, the majority of the patients with raised cardiac biomarkers had a normal ECG or echocardiography.

Discussion

The present study showed that the vast majority of sIBM patients were asymptomatic with regard to cardiac symptoms at the time of investigation. The frequencies of ECG and echocardiography abnormalities approximate those from large epidemiological studies in several cohorts from general populations with a similar age distribution as the present study [2, 11, 16, 25]. Therefore, the prevalence and nature of the found abnormalities are considered to be unrelated to sIBM. Consequently, standard cardiac evaluation in sIBM is not considered mandatory. This is different from previous findings in polymyositis and dermatomyositis.

In the last decade, cardiac troponins (cTnT or cTnI) have emerged as more specific biomarkers of cardiac damage as compared to sCK or CK-MB, and particularly acute myocardial ischemia is based upon raised troponin levels [15, 29]. Elevation of cTnT has been described in PM, DM and sIBM patients without apparent cardiac ischemia [12, 19]. In addition, one study and one case report described normal cTnI levels in the presence of elevated cTnT in myositis [12, 23]. In contrast to the present study, possible cardiac involvement was not studied by ECG, nor by echocardiography.

It has been hypothesized that CK-MB and cTnT, both expressed in fetal muscle, but down-regulated during development, are re-expressed in regenerating muscle fibers [7, 18, 19]. These fibers are common in PM, DM and sIBM muscle biopsies. Consequently, CK-MB and cTnT elevations arise in the absence of cardiac ischemia. Contrarily, cTnI, exclusively expressed in cardiac muscle, remains normal [6].

In the present study, CK-MB and cTnT were commonly elevated in the absence of cardiac pathology. The only patient with an elevated cTnI had a severe cardiomyopathy, explaining this elevation [1]. These outcomes support the hypothesis that elevated CK-MB and cTnT levels in sIBM are not of cardiac origin, but originate from skeletal muscle tissue.

The present study does not show evidence for cardiac involvement in sIBM, and therefore we do not recommend routine comprehensive cardiac evaluation in sIBM patients without cardiac symptoms. Increased cardiac biomarkers, i.e., CK-MB and cTnT in sIBM, do not necessarily suggest cardiac damage. To detect cardiac ischemia in sIBM patients, cTnI is likely the most informative and recommended biomarker.

Appendix

Authors and investigators of the Dutch IBM Study Group include, from the Departments of Neurology: M.L.C. Maat-Schieman (*Leiden University Medical Center*); P.A. van Doorn (*Erasmus Medical Center, Rotterdam*); B.G.M. van Engelen (*Radboud University Nijmegen Medical Center*); C.G. Faber (*Maastricht University Medical Center*); J.E. Hoogendijk (*University Medical Center Utrecht*) and M. de Visser (*Academic Medical Center Amsterdam*).

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