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ORIGINAL RESEARCH

Could C-reactive protein and erythrocyte sedimentation rate support monitoring of dermatomyositis and polymyositis activity?

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OBJECTIVES: To evaluate serum levels of C-reactive protein and erythrocyte sedimentation rates in patients with untreated newly diagnosed dermatomyositis or polymyositis and their correlation with clinical and laboratory parameters.
METHODS: A cross-sectional study including 48 consecutive patients with untreated newly diagnosed dermatomyositis and polymyositis reviewed between 2002 and 2015 was conducted. Fifty healthy subjects were enrolled as controls.
RESULTS: Patients with dermatomyositis and polymyositis had higher levels of C-reactive protein and erythrocyte sedimentation rate than healthy controls, but these values were not associated with clinical or laboratory parameters of disease activity either for dermatomyositis or for polymyositis. Additionally, erythrocyte sedimentation rate values correlated with pulmonary involvement as evidenced through computer tomography imaging (OR 1.15; 95%CI 1.01-1.31) only in patients with polymyositis.
CONCLUSIONS: Although elevated, C-reactive protein and erythrocyte sedimentation rate are not sensitive parameters for measuring clinical and laboratory activity of dermatomyositis nor for polymiositis. However, erythrocyte sedimentation rate may be a valid parameter for screening pulmonary involvement, particularly in patients with polymyositis.

KEYWORDS: Dermatomyositis; polymyositis; C-reactive protein; erythrocyte sedimentation rate.

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INTRODUCTION

Dermatomyositis (DM) and polymyositis (PM) are rare systemic autoimmune inflammatory myopathies that primarily affect skeletal muscle.[1-4] Moreover, cutaneous, cardiac, pulmonary, joint and gastrointestinal tract involvement may also occur in these inflammatory myopathies.[1-7]

The International Myositis Assessment & Clinical Studies Group (IMACS) has developed and validated a set of instruments for measuring DM and PM activity which includes the serum level of muscle enzymes: creatine phosphokinase, aldolase, aspartate aminotransferase, alanine aminotransferase and lactic dehydrogenase.[8,9] However, the IMACS does not include erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), which have been used indiscriminately as possible markers of DM and PM activity.[10-24]

High ESR levels have been correlated with neoplasia risk[11-16] and pulmonary involvement[17-22] in inflammatory myopathies. Likewise, high CRP levels seem to be associated with neuropathy risk in this population.[23,24] However, these studies[11-24] are limited by the fact that ESR and/or CRP were analyzed in patients who had been submitted to chronic use of glucocorticoids and/or immunosuppressants.

Therefore, the aim of the present study was to evaluate the relevance of ESR and CRP in treatment naive patients with newly diagnosed DM or PM.

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MATERIALS AND METHODS

A cross-sectional, single-center study was conducted in which 48 consecutive patients with defined DM or PM (Bohan and Peter criteria)[25] were systematically reviewed between 2002 and 2015.

All patients had been initially admitted to our tertiary center, to investigate progressive muscle weakness of the limbs, associated with high serum levels of muscle enzymes. The patients were treatment naive (glucocorticoids and/or immunosuppressants) and had had symptoms for less than one year. Some patients also had typical cutaneous lesions, characterized by heliotrope and/or Gottron's papules. The diagnosis of DM or PM was later confirmed by complementary examinations: electroneuromyography with evidence of myopathy and/or muscle biopsy (vastus lateralis or brachial biceps muscle) compatible with inflammatory myopathy. Fifty healthy volunteers (patients' relatives and employees of our Institution) were selected as a control group.

Patients with clinically amyopathic DM, inclusion body myositis, neoplasia associated myopathies, myositis overlap syndromes were excluded.

The present study was approved by the Institutional Ethics Committee.

The subjects in the patient and control groups were over 18 years of age and had no infectious processes (acute or chronic, including tuberculosis), uncompensated hypothyroidism, previous use of statins or tobacco, acute myocardial infarction, chronic obstructive pulmonary disease or fibromyalgia.

The clinical and laboratory data of patients with DM and PM were obtained from a systematic review of electronic medical records, previously parameterized and standardized, including the parameters of interest for the present study.

The following initial parameters were analyzed: age at disease diagnosis; time between symptom onset and disease diagnosis; gender; ethnicity; laboratory abnormalities, such as serum creatine phosphokinase (CPK: reference value 24 - 173 U/L), aldolase (1.0 - 7.5 U/L), lactic dehydrogenase (240 - 480 U/L), alanine aminotransferase (< 31 U/L), aspartate aminotransferase (< 31 U/L) performed by the automated kinetic method; ESR (6.2 - 13.2 mm/1 hour) by the automated Westergren method; CRP (< 5.0 mg/L) by the immunoturbidimetric method; constitutional symptoms; skin lesions (heliotrope rash, Gottron's papules, facial rash, "V-neck" sign, "shawl" sign, vasculitis, calcinosis, Raynaud's phenomenon); joint involvement (arthritis or arthralgia); pulmonary involvement (confirmed by computed tomography: presence of interstitial pneumopathy or honeycomb lesions) and presence of dyspnea; muscular strength of the limbs (degree 0: absence of muscle contraction, degree I: signs of mild contractility, degree II: normal amplitude movements but not enough to overcome the action of gravity, degree III: normal amplitude movements against the action of gravity; degree IV: integral mobility against the action of gravity and some degree of resistance, degree V: complete mobility against severe resistance and against the action of gravity);[26] antinuclear factor evaluated by indirect immunofluorescence using Hep-2 cells as a substrate; anti-Jo-1 antibody by the immunoblotting method.

Statistical analysis. Data were expressed as mean ± standard deviation (SD), median (25^{th} - 75^{th} interquartile) or percentage (%) and were assessed for normal distribution using Kolmogorov-Smirnov's test. Student's *t*-tests and the Mann-Whitney test were used for analysis of continuous data. Categorical data were analyzed the chi-square test or Fisher's exact test. Odds ratios (OR) and 95% confidence intervals (CIs) between the CRP values, as well as the ESR values and the different parameters analyzed in the present study were reassessed by multivariate logistic regression adjusted for patient sex and age (Spearman or Pearson correlation). These calculations were performed with the SPSS Statistics software program (version 15.0, USA). Values of $P < 0.05$ were considered statistically significant.

RESULTS

We evaluated 48 consecutive patients (29 DM and 19 PM). Fifty healthy subjects were included as the control group. The individuals in the groups had a mean age of around 40 years, and were predominantly female and Caucasian (Table 1).

Median time between symptom onset and disease diagnosis was 3.0 months (DM and PM). Approximately two-thirds of the patients had constitutional symptoms, whereas one-fifth had joint and pulmonary involvement. Cutaneous involvement was found mainly in patients with DM. Dysphagia was present in 69.0% and 31.6% of patients with DM and PM, respectively. Most patients had muscle strength of III and IV degrees, in both limbs.

The antinuclear factor was present in more than half of the patients (DM and PM), whereas the anti-Jo-1 autoantibody was detected in 20.7% and 15.8% of DM and PM patients, respectively.

Three out of 19 patients with PM had anti-Jo-1 antibody. Moreover, only one out of these three patients had pulmonary involvement (honeycomb lesions), joint involvement, fever, Raynaud's phenomenon and "mechanic's hands" and, therefore, antisynthetase syndrome.

Six out of 29 patients with DM had anti-Jo-1 antibody. Additionally, only one out of these six patients presented pulmonary involvement (interstitial pneumopathy). None of them had antisynthetase syndrome.

Table 1 - General characteristics of patient groups with dermatomyositis or polymyositis and of control group.

Parameters	Group		
	DM (N=29)	PM (N=19)	CTR (N=50)
Age* (years)	41.5±17.8	37.9±12.4	41.6±11.9
Female*	21 (72.4)	18 (94.7)	41 (82.0)
Ethnicity* (Caucasian)	25 (86.2)	14 (73.7)	40 (80.0)
Symptoms - diagnosis (months)	3.0 (1.5-5.5)	3.0 (2.0-4.0)	-
Constitutional symptoms	19 (65.5)	12 (63.2)	-
Cutaneous involvement			-
Heliotrope rash	29 (100.0)	-	-
Gottron's papules	28 (96.6)	-	-
Facial rash	22 (75.9)	-	-
"V-neck" sign	13 (44.8)	-	-
"Shawl" sign	7 (24.1)	-	-
Vasculitis	4 (13.8)	-	-
Calcinosis	0	-	-
Raynaud's phenomenon	16 (55.2)	3 (15.8)	-
Joint involvement	6 (20.7)	6 (31.6)	-
Pulmonary involvement			
Changes on computer tomography	7 (24.1)	5 (26.3)	-
Dysphagia	20 (69.0)	6 (31.6)	
Muscle strength			
Upper limbs			
Degree V	1 (3.5)	0	-
Degree IV	2 (75.8)	12 (63.1)	-
Degree III	6 (20.7)	6 (31.6)	-
Degree II	0	1 (5.3)	-
Degree I	0	0	-
Lower limbs			
Degree V	1 (3.5)	0	-
Degree IV	23 (79.2)	12 (63.1)	-
Degree III	5 (17.3)	6 (31.6)	-
Degree II	0	1 (5.3)	-
Degree I	0	0	-
Antinuclear factor	17 (58.6)	12 (63.2)	-
Anti-Jo-1	6 (20.7)	3 (15.8)	-

Data expressed as mean ± standard deviation, median (25^{th} and 75^{th} interquartile) or percentage (%). CTR: control, DM: dermatomyositis, PM: polymyositis. * Age, sex and color: DM x CTR, and PM x CTR (P> 0.05).

As expected, serum levels of creatine phosphokinase, aldolase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, ESR and CRP were significantly elevated in patients with DM and PM relative to the control group (Table 2).

As an additional evaluation, for each disease (DM and PM), an association analysis was performed between the ESR and CRP values and the different parameters analyzed in the present study. Neither ESR nor CRP correlated with anti-Jo-1 antibody. The only association found was between ESR and pulmonary involvement (changes on thoracic computed tomography) (OR 1.15; 95% CI: 1.01 - 1.31), and solely in patients with PM. Nevertheless, it was not possible to analyse the association between ESR and pulmonary involvement (interstitial pneumopathy or honeycomb lesions), because of the limited number of final samples.

Table 2. Laboratory characteristics of patient groups with dermatomyositis or polymyositis and of control group.

Parameters	Group			P value	
	DM (N=29)	PM (N=19)	CTR (N=50)	DM x CTR	PM x CTR
Creatinophosphokinase (U/L)	2892 (567-9283)	7197 (3010-14243)	109 (84-158)	<0.001	<0.001
Aldolase (U/L)	16.6 (8.6-58.8)	81.3 (23.1-124.2)	3.9 (3.2-4.4)	<0.001	<0.001
LDH (U/L)	794 (418-1759)	1394 (878-2590)	328 (341-383)	<0.001	<0.001
AST (U/L)	130 (51-361)	160 (83-395)	20 (17-23)	<0.001	<0.001
ALT (U/L)	90 (41-322)	189 (80-272)	17 (14-22)	<0.001	<0.001
ESR (mm/1st hour)	15 (10-23)	16 (7-33)	6 (3-11)	<0.001	<0.001
C-reactive protein (mg/L)	7.2 (3.2-12.3)	4.6 (2.8-11.6)	1.3 (0.8-2.9)	<0.001	0.001

Data expressed as mean ± standard deviation, median (25^{th} and 75^{th} interquartile %) or percentage (%). ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTR: control, LDH: lactic dehydrogenase; DM: dermatomyositis, PM: polymyositis; ESR: erythrocyte sedimentation rate.

DISCUSSION

The present study evaluated the relevance of ESR and CRP in newly diagnosed and treatment naive patients with DM or PM. ESR and CRP were elevated in patients with DM and PM compared to healthy individuals, but did not correlate with clinical or laboratory activity. However, ESR was found to be a predictor of pulmonary involvement in patients with PM.

In contrast to other studies available,[11-24] in this study ESR and CRP were assessed in newly diagnosed patients, with clinical and laboratory activity. In addition, the study did not include patients with factors that might have interfered with ESR and CRP values, such as infections, neoplasia associated myositis, overlap myositis syndromes, and patients submitted to glucocorticoid and/or immunosuppressant treatment regimes.

ESR can reflect the extent of a systemic inflammatory process and thus high levels are often observed in infections, neoplasms and other autoimmune diseases.[26-28] Moreover, since the ESR value may vary according to gender and age, patients and controls were also matched for these parameters.

The ESR and CRP values were elevated in our patients with DM and PM compared to control subjects. Nonetheless, the values were next to the upper limit value of normality in the patients. Therefore, additional studies will be necessary to confirm these high ESR and CRP values as well as their relevance in the clinical practice of patients with DM and PM. However, these levels did not correlate with increased serum levels of muscle enzymes, nor with the degree of muscular weakness. Thus, increases detected on these tests of inflammatory activity do not seem to be valid for measuring muscle activity of the disease, reinforcing the importance of the parameters evaluated by IMACS.[9]

Although newly diagnosed, a quarter of the patients analyzed in the present study already exhibited pulmonary involvement, with symptoms of dyspnea upon moderate or major efforts and changes on thoracic computed tomography. ESR was found to correlate with this involvement, but only in patients with PM. The analysis of the evaluation of the pulmonary function test was not performed, since the patients who underwent the test, did so after some time of treatment and diagnosis.

Other studies point to the association of ESR with pulmonary involvement in patients with classic DM[17,21,22] and amyopathic DM.[20,22] Marie et al.[10] have demonstrated that high levels of ESR and CRP, the presence of polyarthritis, anti-Jo-1 antibody, and microangiopathic changes on periungual capillaroscopy are associated with this involvement in both DM and PM.[19] In the present study, it was not possible to analyse the association between levels of ESR/CRP and anti-Jo-1 antibody and also type of pulmonary involvement, because of the reduced number of final samples. Therefore, further investigation with large samples will be necessary to better clarify these analyses.

Unlike other studies,[19,23] the increases in CRP found in the present investigation did not correlate with disease activity or pulmonary disease. Ideura et al.[24] suggested a prognostic value for elevated CRP level correlating with interstitial lung disease in amyopathic DM.

As a limitation of the present study, a specific analysis of correlation between possible features findings in histological muscle biopsies (fiber necrosis, fiber regeneration, inflammatory cell infiltration) and laboratory parameters (ESR and CPR) was not performed. However, previous studies have already shown the dissociation between the presence and the degree of inflammatory cell infiltration findings in muscle biopsies and clinical, laboratory and therapeutic parameters.[29,30] This occurs because the inflammatory infiltrated cells occur in "patches" in the muscle tissue.[31]

SUMMARY

In summary, CRP and ESR are not sensitive parameters for measuring clinical and laboratory activity of DM and PM. However, ESR may be valid for screening pulmonary involvement, particularly in patients with PM.

AUTHOR CONTRIBUTION

Miossi R: planning, reviewing literature, executing and writing the present article. De Souza FHC: planning, reviewing literature, executing and writing the present article. Shinjo SK: planning, reviewing literature, executing and writing the present article.

CONFLICT OF INTEREST

All authors declare no conflict of interest

É POSSÍVEL SUPOR QUE A PROTEÍNA C REATIVA E A HEMOSSEDIMENTAÇÃO POSSAM SER USADAS PARA MONITORAR A ATIVIDADE DA DERMATOMIOSITE E DA POLIMIOSITE?

OBJETIVOS: Avaliar os níveis séricos da proteína C reativa (PCR) e da velocidade de hemossedimentação (VHS) em pacientes recém-diagnosticados com dermatomiosite (DM) e polimiosite (PM), sem tratamento prévio, correlacionando-os com parâmetros clínico-laboratoriais.

MÉTODOS: Estudo transversal que incluiu 48 pacientes consecutivos com DM e PM (critérios de Bohan e Peter) recém-diagnosticados, sem tratamento medicamentoso, no período de 2002 a 2015. Foram incluídos 50 indivíduos saudáveis como grupo controle.

RESULTADOS: Os pacientes apresentaram níveis mais elevados de VHS e PCR comparativamente aos controles saudáveis. Estes valores, porém, não se correlacionaram com os parâmetros clínicos e laboratoriais da atividade da doença (DM e PM). Somente em pacientes com PM a VHS apresentou relação com acometimento pulmonar na tomografia computadorizada [OR 1,15 (IC 95% 1,01-1,31)].

CONCLUSÕES: Apesar de aumentadas, a PCR e a VHS não são parâmetros sensíveis para a mensuração da atividade clínica e laboratorial de DM e PM., No entanto, a VHS pode ter validade no rastreio do acometimento pulmonar, particularmente em pacientes com PM.

PALAVRAS-CHAVE: Dermatomiosite; polimiosite; proteína C reativa; velocidade de hemossedimentação.

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