Arterial Events in Persons with Dermatomyositis and Polymyositis

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ABSTRACT. ***Objective.*** To assess arterial events in dermatomyositis (DM) and polymyositis (PM), and associated factors.

Methods. We studied a cohort of persons with DM and PM, assembled from provincial administrative databases. New cases of ischemic heart disease, cerebrovascular accidents (CVA), and peripheral arterial disease were ascertained from billing and hospitalization data. We performed case-control analyses to assess the effects of clinical factors and medication exposures.

Results. Incident arterial events occurred in 80 subjects, including 34 acute myocardial infarctions (13.8/1000 person-years) and 13 CVA (5.1/1000); these rates are higher than available Canadian figures. Nested case-control analyses, with risk-set sampling, revealed an increased incidence of arterial events associated with hypertension [adjusted rate ratio (RR) 2.6; 95% confidence interval (CI) 1.2–5.5] and lipid disorders (adjusted RR 2.6, 95% CI 1.0–6.5), whereas nonsteroid immunomodulators (methotrexate, azathioprine, antimalarial agents, or cyclophosphamide) were inversely associated with arterial events (adjusted RR 0.5, 95% CI 0.2–1.0).

Conclusion. We found a high incidence of arterial events in this cohort of persons with inflammatory myopathy. Traditional risk factors, particularly hypertension and lipid disorders, were predictors of arterial events, while nonsteroid immunomodulators were inversely associated. Our work suggests a rationale for aggressive risk reduction strategies in persons with inflammatory myopathies. (J Rheumatol First Release Aug 1 2009; doi:10.3899/jrheum.090061)

Key Indexing Terms:
HYPERTENSION POLYMYOSITIS DERMATOMYOSITIS
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Dermatomyositis (DM) and polymyositis (PM) are important autoimmune diseases characterized by muscle inflammation, weakness, and often significant morbidity. In many rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), arterial events are an important adverse outcome. To date, there is little information on arterial events in inflammatory myopathies. We describe the incidence of arterial events in this population, evaluating the role of medications and traditional cardiovascular risk factors.

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MATERIALS AND METHODS

We identified a cohort of individuals with inflammatory myopathies from Quebec provincial physician billing, hospitalization, and pharmacy databases over the period 1994–2003. Essentially all Quebec citizens (about 7.5 million persons) obtaining healthcare are recorded in the physician billing and hospitalization databases. The billing database records information on physician services in the province, including the date and diagnostic code relevant to each physician visit (a single diagnostic code is allowed per visit). The hospitalization database maintains data on admissions, including discharge diagnoses (a primary diagnosis and up to 15 nonprimary diagnoses per hospitalization). These discharge diagnoses are abstracted by medical records clerks using standardized decision tools. For both billing and hospitalization data, diagnoses are provided as *International Classification of Diseases*, 9th ed. (ICD-9) codes.

Our case ascertainment algorithm required ≥ 1 hospital discharge diagnosis of PM or DM (ICD-9 codes 710.3–710.4), or ≥ 2 billing codes at least 8 weeks apart, with at least 1 of the billing diagnoses being contributed by a rheumatologist, neurologist, immunologist, dermatologist, or internist. We required cohort subjects to have ≥ 3 months of billing data prior to study entry (date of hospital discharge diagnosis or second billing code) and to be a beneficiary of the public drug insurance plan (which covers residents aged ≥ 65 years, and younger persons without a private plan). Cohort subjects were followed until the first of outcome event, death, or end of study (December 31, 2003).

Comorbidities included hypertension (ICD-9 codes 401.x, 405.x), nonatherosclerotic heart disease [congestive heart failure (CHF) 428.0 and valve disease, 424.x], lipid disorders (272.x), diabetes mellitus (250.x,

648.8), obesity (278.0), malignancy (140.x-239.x), and interstitial lung disease (515.x, 516.3), defined from hospitalization and billing data (≥ 1 respective discharge diagnosis or ≥ 2 relevant billing codes ≥ 8 weeks apart prior to index date). Exposure to glucocorticoids, nonsteroidal antiinflammatory drugs (NSAID), cyclooxygenase-2 inhibitors (COXIB), and nonsteroid immunomodulators (methotrexate, azathioprine, antimalarial agents, cyclophosphamide) were defined as ≥ 1 prescription for the given drug, any time between cohort entry and index date.

New-onset arterial events included stroke (ICD-9 codes 433-5.x), ischemic heart disease (410-1.x, 413.x), and peripheral arterial disease (444-5.x). Each event was defined by an algorithm requiring ≥ 1 hospital diagnosis or ≥ 2 relevant billing codes ≥ 8 weeks apart; the exception was acute myocardial infarction (AMI), for which we required ≥ 1 hospitalization. For each event, we excluded subjects with the same documented event prior to the diagnosis of inflammatory myopathy.

Using SAS software, we performed nested case-control analyses to determine the association of outcomes with comorbidities and medications. For each case, up to 10 age- and sex-matched controls were randomly selected from those subjects who remained alive and event-free at the index time. Conditional logistic regression was used to estimate the risk ratio (RR) of arterial events associated with each exposure. Multivariate analyses controlled for all covariates, as well as whether the diagnosis of the inflammatory myopathy was initially made in hospital or billing data, and whether or not there was a history of coagulopathy and/or exposure to aspirin or anticoagulants (warfarin and low molecular weight heparin; LMWH).

The public drug plan is estimated to cover about 42% of Quebec residents[1]. The multivariate model examining new-onset arterial events was repeated using all cohort subjects with inflammatory myopathy, not just those who qualified for membership in the pharmacy database. This model left out all drug exposures but kept in all the other variables.

Access to the anonymously-gathered administrative data was granted by the Quebec Commission d'Accès à l'Information. Our study protocol is consistent with the principles of the Declaration of Helsinki, and was approved by the McGill University Institutional Review Board.

RESULTS

There were 607 subjects with inflammatory myopathy who met inclusion criteria; an additional 41 who otherwise met criteria were excluded because of a prior arterial event. The average age at cohort entry was 62.4 [standard deviation (SD) 17.0] years, and 423 (70%) of the cohort subjects were female. Average followup was 4 (SD 3.7) years. Drug exposures included systemic glucocorticoids in 512 (84.4%) cohort members, methotrexate in 159 (26.2%), azathioprine in 130 (21.4%), antimalarial drugs in 86 (14.2%), and cyclophosphamide in 36 (5.9%). A history of aspirin exposure at the time of study entry was present in 170 (28%), and 37 (6.1%) had a history of warfarin or LMWH exposure.

Across the study interval, there were 124 arterial events occurring in 80 subjects (66.3% women), an average of 2.9 (SD 2.9) years after cohort entry. Mean age at incident event was 60 (SD 18) years. There were 34 incident cases of AMI (13.8/1000 person-years) and 13 strokes (5.2/1000 person-years). Figure 1 presents age- and sex-specific rates for our subjects. Applying Canadian age- and sex-specific general population incidence rates for AMI[2] to the years of followup of our subjects, roughly 17 AMI events would be expected (if our subjects had the same rate of events as the general population). Hence the relative risk (standardized incidence ratio) of AMI in our sample, compared to the general population, was 1.95 [95% confidence interval (CI) 1.35, 2.72].

In case-control analyses (Table 1), important determinants of arterial events included non-atherosclerotic heart disease, hypertension, and lipid disorders. Nonsteroid immunomodulators were associated with significantly fewer arterial events. In the multivariate model using all cohort patients regardless of membership in the pharmacy database, similar results were obtained, where the adjusted rate ratio for lipid disorders was 4.9 (95% CI 1.7, 14.2), for hypertension 2.5 (1.6, 4.0), and for CHF or valve disease 3.0 (1.8, 5.2).

DISCUSSION

Until now, although some have raised concerns regarding the risk of arterial disease in persons with inflammatory myopathies[3], there exist almost no relevant epidemiological data. Our figures suggest a high incidence of arterial events in DM and PM. As a general population comparison, the 1996 hospitalization rate for AMI in Canadians < 65 years of age was about 0.9/1000 person-years for women, and 3.2/1000 person-years for men. In those ≥ 65 years, the population rate was 10.6/1000 person-years for women and 13.4/1000 person-years for men[2]. Thus, compared to the general population, we found a trend toward higher incidence of AMI for patients with DM and PM in all demographic groups except men < 65 years. Regarding stroke incidence, available Canadian figures suggest a general population rate of 3.1/1000 person-years[4], close to half the incidence rate in our subjects.

Risk of arterial events is elevated in other inflammatory rheumatic diseases, although comparisons are difficult because of different methodology across studies. However, AMI risk in our cohort appears still greater than the 5.3/1000 person-years reported in 2 Canadian studies of RA[5,6]. Stroke rates in our cohort are very similar to that reported in RA (5.1/1000).

Among the factors we analyzed, lipid disorders and hypertension were strongly associated with arterial events, as is true in the general population. This suggests that attention to these traditional cardiac risk factors is a matter of great importance for physicians caring for patients with DM and PM.

Increasingly, inflammation is recognized as an additional risk factor for arterial disease, even in the general population. In our multivariate analyses, nonsteroid immunomodulators were inversely associated with arterial events in DM and PM. Possibly due to power limitations, when each medication was analyzed individually, this effect was convincing only for azathioprine. Although hydroxychloroquine may improve lipid profiles in SLE[7], we were unable to demonstrate a beneficial effect in terms of arterial events in our sample.

Some postulate that glucocorticoids increase cardiac risk

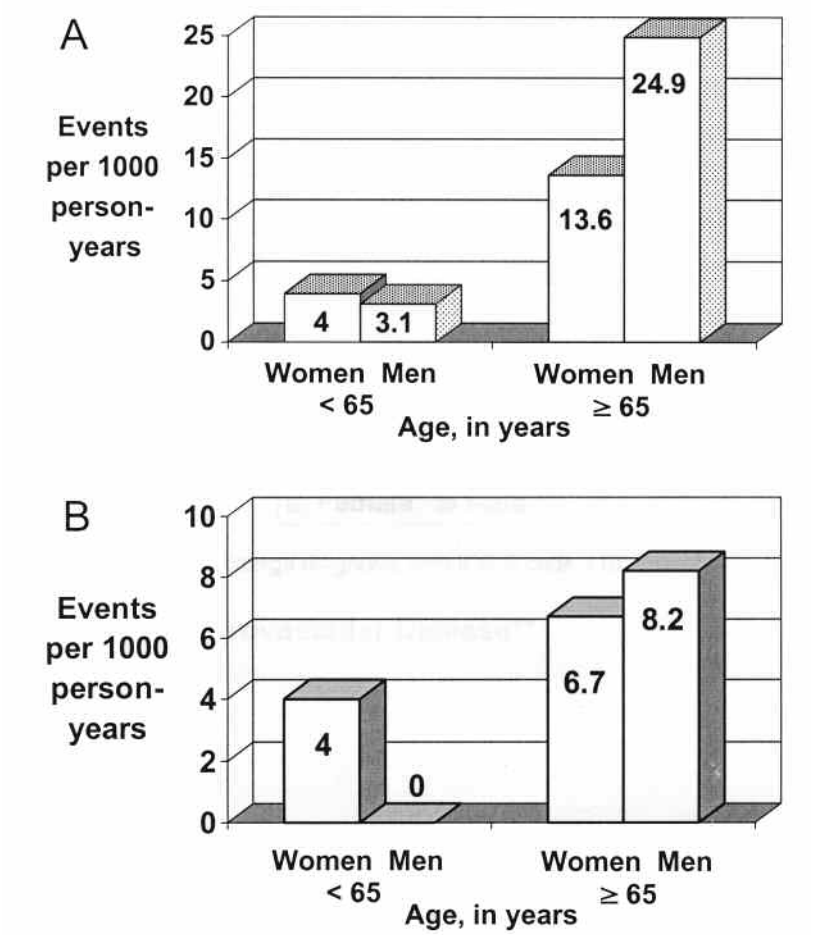

Figure 1. Rates of arterial events in persons with inflammatory myopathy, by age and sex. A. Acute myocardial infarction (based on at least one hospital discharge diagnosis with ICD-9 code 410). B. Atherosclerotic cerebrovascular disease (based on at least one hospital discharge diagnosis, or 2 billing code diagnoses, for atherosclerotic cerebrovascular disease (ICD-9 codes 433-435).

in rheumatic disease[8,9], either through direct vascular damage, or insulin resistance. Alternatively, recent studies in SLE and RA suggest corticosteroids may reduce cardiovascular risk[10,11], possibly by lowering disease activity and inflammation, which itself may drive atherosclerosis[12]. We were unable to demonstrate a precise effect of glucocorticoids; potentially, in some populations, glucocorticoids confer a net neutral effect. The unimpressive influence of NSAID and COXIB might be caused by the same balance, although our study was not powered to detect small effects.

Although our study has considerable strengths, there are potential limitations. With administrative databases, one cannot be completely sure of data accuracy. However, we adopted algorithmic definitions for covariates and outcomes that have been used and validated[5,13]. We do note that the ICD-9 classification system, which has specific codes for PM and DM, does not have a specific code for a related condition, inclusion body myositis (IBM). Although some of the PM cases we identified through our administrative datasets may actually have been IBM, this does not negate the significance of our findings. Additionally, although diagnostic coding in physician billing is not always accurate or complete, the employment of stricter, clinical criteria for case identification may itself miss some cases of autoimmune myopathy, as noted[14].

In our sample the risk of arterial events appeared to be higher in DM and PM, versus general population rates. Traditional risk factors, particularly hypertension and lipid disorders, were associated with an increased risk, while nonsteroid immunomodulators were associated with fewer events. Our work is hypothesis-generating, warranting additional study.

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Table 1. Crude and adjusted risk ratios (RR) for new-onset arterial thromboembolic events in persons with inflammatory myopathies.

	Cases, n = 80	Controls, n = 331	Crude	Adjusted*	
	Percent Exposed		RR	RR	95% CI
Medication exposure					
Glucocorticosteroids	68.8	69.8	1.0	1.5	0.7, 3.4
NSAID	35.0	26.5	1.5	0.9	0.3, 2.4
COX-2 inhibitors	7.5	8.2	0.9	1.0	0.2, 4.6
Immunomodulators	30.0	39.4	0.7	0.5	0.2, 1.0
Methotrexate	15.0	10.5	1.5	0.9	0.3, 2.3
Azathioprine	11.3	22.4	0.4	0.3	0.1, 0.8
Antimalarial agents	5.0	6.5	0.8	0.3	0.0, 1.5
Cyclophosphamide	1.3	5.5	0.2	0.1	0.0, 1.2
Comorbidity					
Hypertension	66.3	46.4	2.5	2.6	1.2, 5.5
Lipid disorders	18.8	16.7	1.3	2.6	1.0, 6.5
Diabetes mellitus	23.8	17.5	1.8	1.2	0.5, 3.0
Non-atherosclerotic heart disease (CHF and valve disease)	47.5	12.5	6.0	7.0	3.2, 15.2
Obesity	6.3	1.9	3.0	0.7	0.1, 4.7
Cancer	42.5	35.1	1.5	1.7	0.8, 3.4
Interstitial lung disease	5.0	10.5	0.4	0.5	0.1, 2.3

* Multivariate analyses controlled for all covariates in the table, as well as whether the diagnosis of inflammatory myopathy was initially made in hospital or billing data, and history of coagulopathy and/or exposure to aspirin, warfarin, or low molecular weight heparin. CI: confidence interval; NSAID: nonsteroidal antiinflammatory drugs; COX-2 inhibitors: cyclooxygenase-2 inhibitors; CHF: congestive heart failure.

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