Sex Differences in Giant Cell Arteritis

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ABSTRACT. ***Objective.*** Although it has been suggested that sex differences underlie the varying presentation of giant cell arteritis (GCA), this has not been proven. We compared medical history, symptoms, and signs in patients with GCA and polymyalgia rheumatica (PMR).

Methods. We performed a retrospective study in the Hadassah University Hospitals in Jerusalem, Israel. We evaluated medical data of 88 patients (59 women, 29 men) admitted with the diagnosis of GCA or PMR between 1980 and 1998.

Results. Comparison of comorbidities among patients showed that non-insulin dependent diabetes mellitus, cerebrovascular accidents, and chronic renal failure are more prevalent in men, while hypertension has a trend to be more prevalent in women. In the clinical presentation of the disease, eye involvement is more prevalent in men, with a tendency towards blindness. Women tend to have higher prevalence of jaw involvement and complaints of polymyalgia. The sexes also seem to differ with respect to laboratory presentation of the disease.

Conclusion. Men and women with GCA and PMR differ in their history, presentation, and laboratory findings. Our results recommend a more aggressive approach to male patients in view of the higher prevalence of severe eye involvement and blindness. (J Rheumatol 2002;29:1219–23)

Key Indexing Terms:
SEX
GIANT CELL ARTERITIS
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Giant cell arteritis (GCA) was first described in 1890[1]. In 1934, Horton, *et al* described 2 cases with similar symptoms, and in the French medical literature the disease is named after him[2]. GCA is considered to be part of a spectrum of vasculitides that also includes polymyalgia rheumatica (PMR), and is prevalent mainly in Caucasians, especially in northern countries. Nevertheless, the disease is well described in other populations. Recently, a large body of data was gathered from different centers and new definitions for the disease were established[3,4]. In contrast, little is known about sex differences in the clinical presentation, course, and laboratory findings of the disease.

In most countries the disease is more prevalent in women[4,5]. However, differences in clinical presentation between men and women have not been reported, but some authors have suggested that the disease might have different presentations in the sexes[6]. Recently, a French group reported a large prospective study on GCA[7,8]. A review of their data suggests that some differences exist in the medical history of the sexes. A similar tendency for the clinical signs of the disease has been reported by Machado, *et al*[9]. We performed a retrospective study on all patients diagnosed with GCA or PMR in the Hadassah University Hospitals in Jerusalem, Israel. Our results show for the first time that differences exist between men and women in the presentation of GCA and PMR. Moreover, these differences are not explained by sex differences in the general population of the same ages.

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MATERIALS AND METHODS

We retrospectively reviewed the computerized database of the Hadassah University Hospitals for all patients with the diagnosis of GCA or PMR, between January 1, 1980, and December 31, 1998. This database includes all the patients admitted to all hospital departments and their diagnoses. Patient data can be pulled out of the database according to diagnosis as determined by the discharging senior physician. A total of 143 patients were diagnosed as having GCA and 101 with PMR. Subsequently, all files were reviewed for patients in whom the diagnoses of either GCA or PMR were made during hospitalization. Then, data referring to history, symptoms, signs, and details of diagnosis were extracted from patient files according to a fixed protocol by 2 authors (RN and AG). All files were reviewed again by only one author (RN). Only patients in whom diagnosis was made during hospital stay, who fulfilled the criteria of the American College of Rheumatology[3] for GCA and Bird's criteria for PMR[10], were included. A total of 88 patients were found eligible for study — 59 women and 29 men, of whom only 15 and 2, respectively, were diagnosed with PMR. Patients were excluded if diagnosis was made out of hospital or did not meet the criteria for GCA or PMR above.

Comorbidities such as hypertension, ischemic heart disease (IHD), non-insulin diabetes mellitus (NIDDM), and neurological problems were considered positive according to self-report of the patient, medical records, patient's medications, and abnormal laboratory tests upon admission. Renal failure was recorded if the patient had elevated creatinine level for more than 2 consecutive tests, or if creatinine clearance was < 60 cc/min. Two potential comorbidities, smoking and hypercholesterolemia, were not included in the analysis. Smoking was underreported in our patients' files, and since the study was retrospective over 20 years, it was impossible to

obtain accurate data. Cholesterol data were not added because the data were not available in patients' files or laboratory data archives.

Patients' laboratory data were collected from the first tests that were ordered for each patient at admission. All data except pathology results were always before the diagnosis was made and before treatment was started. Abnormal laboratory values comprised the following criteria: ESR > 50 mm/h, leukocytosis: > 10×10^3/mm^3, anemia: hemoglobin levels < 11 g/dl, thrombocytosis: > 400×10^3, alkaline phosphatase: > 130 U/l, gamma-glutamyltransferase (GTP): > 80 U/l.

Data analysis was performed with SPSS for Windows release 10 (SPSS Inc., Chicago, IL, USA). The data for men and women were compared using the chi-square, 2 tailed Fisher exact test, or the Mann-Whitney U test when appropriate. A logistic regression with stepwise selection included the variables found to be significant in the univariate analysis. Hypertension and positive temporal artery biopsy were also included in analysis because of their possible influence on disease progression and blindness. Sex was used as the dependent variable, and the other variables were independent.

RESULTS

The data of the whole group are presented in Table 1. The mean age of patients was 71.6 ± 8.9 years, with a male to female ratio of 1:2. Duration of symptoms prior to diagnosis had a median of 6 weeks, with a range from acute onset to 108 weeks. The most prevalent comorbidities in GCA were hypertension (40.9%), ischemic heart disease (15.9%), and diabetes mellitus (15.9%). The most prevalent symptoms in order of frequency were: headache (64%), PMR (55%), fever (51%), weight loss (31%), and eye involvement (27%). Abnormal laboratory results were: elevated ESR (93%), elevated platelet count (42%), high white cell count (38%), anemia (32%), and elevated alkaline phosphatase levels (26%) and gamma-GTP levels (19%).

Table 1. Medical data of all patients.

Factor	Prevalence, %
Age, yrs	71.6 ± 8.9
Male/female ratio	1:2
History	
Hypertension	40.9
Ischemic heart disease	15.9
NIDDM	15.9
CVA	7.9
Renal failure	7.9
Symptoms	
Duration of symptoms, median (range), weeks	6 (0–108)
Headache	63.6
Temporal pain	23.9
Eye involvement	27.3
Jaw involvement	18.2
PMR	54.6
Signs	
Fever (> 37.5˚C)	51.1
Weight loss	30.7
Laboratory data	
Elevated ESR	93.2
Elevated WBC	37.5
Anemia	31.8
Thrombocytosis	42.1
Elevated alkaline phosphatase	26.1
Elevated gamma-GTP	19.3

NIDDM: non-insulin dependent diabetes mellitus, CVA: cerebrovascular accident, PMR: polymyalgia rheumatica, ESR: erythrocyte sedimentation rate, WBC: white blood cell count.

The medical history of male versus female patients is shown in Table 2. NIDDM, cerebrovascular accident (CVA), and chronic renal failure were markedly more prevalent in men than in women and reached statistical significance. These comorbidities also differed significantly between the sexes in the GCA patients alone. Hypertension had a tendency to be more prevalent in women than men. With regard to disease presentation (Table 3), there was no significant difference between the sexes for duration from onset to diagnosis. Eye involvement was more prevalent in men. Men were more prone to blindness than women. This finding was statistically significant and persisted even when the PMR patients were eliminated from both sex groups. When PMR patients were eliminated from both groups, PMR complaints were in almost the same proportion (about 36%) in both groups. The laboratory data (Table 4) showed that higher leukocyte counts were more prevalent in men and lower hemoglobin levels were more prevalent in women. Other laboratory values were not found to be different between the groups. Temporal artery biopsy was done during admission in 43 female and 23 male GCA patients. Eighty-eight percent and 74%, respectively, were found to be positive. That difference did not reach statistical difference ($p = 0.133$). A logistic regression model showed that sex and hemoglobin level were clinically associated with any kind of blindness ($p = 0.005$ and $p = 0.007$, respectively), whereas the interaction between male sex and positive temporal artery biopsy had a protective effect from blindness ($p = 0.008$). All other variables found to be statistically different on univariate analysis (such as NIDDM, chronic renal failure, CVA, leukocyte count) did not reach the 0.05 significance level.

DISCUSSION

Sex differences are known to exist for many vasculitides[4]. However, such differences have not been described in GCA and PMR. We observed that sex determined differences in the associated diseases, signs, symptoms, and severity of GCA.

The most prominent factors distinguishing men and women regarding associated diseases were NIDDM, chronic renal failure, and CVA, which were more prevalent in men, while hypertension had a tendency to be more prevalent in women. Although all these factors are related to atherosclerotic disease, a recent prospective study found smoking and murmurs over arteries were related to GCA only in women[7]. We found that other factors such as hypertension, CVA, and ischemic heart disease were not related to GCA in either sex. It is possible to speculate that such differences might be related to different prevalence of these asso-

Table 2. Medical histories of men and women.

	Patients with GCA and PMR			Patients with GCA Only		
	Men	Women	p	Men	Women	p
Age, mean ± SD, yrs	73.36 ± 9.1	70.71 ± 8.63	0.213	72.7 ± 9	71.6 ± 7.8	0.577
Hypertension, %	27.6	47.5	0.075	29.6	45.5	0.185
IHD, %	24.1	11.9	0.139	22.2	15.9	0.504
NIDDM, %	31.0	8.5	0.011	29.6	6.8	0.016
CVA, %	24.1	0.0	< 0.001	25.9	0.0	0.001
CRF, %	17.2	3.4	0.037	18.5	2.3	0.027

PMR: polymyalgia rheumatica, IHD: ischemic heart disease, NIDDM: non-insulin dependent diabetes mellitus, CVA: cerebrovascular accident, CRF: chronic renal failure.

Table 3. Symptoms and signs for men and women.

	Patients with GCA and PMR			Patients with GCA Only		
	Men	Women	p	Men	Women	p
Duration, median (range), weeks	5.5 (1–54)	6 (0–108)	0.355	5.5 (1–54)	8 (0–108)	0.323
Headache, %	69.0	61.0	0.466	74.1	75.0	0.931
Temporal pain, %	31.0	20.3	0.296	33.3	27.3	0.587
Eye involvement, %	41.4	20.3	0.037	44.4	27.3	0.138
Strabismus, %	3.5	5.1	1.000	3.7	6.8	1.000
Blindness (any), %	37.9	13.6	0.009	40.7	18.2	0.037
Intermittent, %	13.8	6.8	0.431	14.8	9.1	0.459
Complete, %	24.1	6.8	0.036	25.9	9.1	0.090
Jaw involvement, %	13.8	20.3	0.564	14.8	25.0	0.380
Claudication, %	6.9	11.9	0.712	7.4	13.6	0.701
Opening redaction, %	3.5	8.5	0.659	3.7	11.4	0.397
Pain, %	3.5	13.6	0.261	3.7	15.9	0.144
PMR complaints	41.4	61.2	0.082	37.0	50.0	0.287
Fever, mean ˚C	37.5 ± 1.0	37.5 ± 0.8	0.686	37.5 ± 1.0	37.7 ± 0.9	0.584
Fever > 37.5˚C, %	44.8	54.2	0.407	44.4	56.8	0.311
Weight loss, %	37.9	27.1	0.301	33.3	29.5	0.738

PMR: polymyalgia rheumatica.

Table 4. Laboratory data of men and women

	Patients with GCA and PMR			Patients with GCA Only		
	Men	Women	p	Men	Women	p
ESR > 50 mm/h, %	93.1	93.2	1.000	92.6	90.9	1.000
WBC (10^3/mm^3)	11.5 ± 4.6	9.2 ± 2.9	0.021	11.4 ± 4.8	9.3 ± 3.0	0.052
Leukocytosis (> 10 × 10^3/mm^3), %	51.7	30.5	0.053	51.9	31.8	0.096
Hb, g/dl	12.2 ± 1.6	11.3± 1.5	0.012	12.1 ± 1.6	11.2 ± 1.5	0.011
Anemia (Hb < 11g/dl), %	17.2	39.0	0.040	18.5	43.2	0.033
Thrombocytosis (> 400 × 10^3/mm^3), %	44.8	40.7	0.718	48.2	40.9	0.550
Alkaline phosphatase > 130 U/l	27.6	25.4	0.828	29.6	18.2	0.262
Gamma-GTP > 80 U/l	20.7	16.9	0.669	22.2	13.6	0.349

PMR: polymyalgia rheumatica.

ciated diseases between the sexes. Other potential confounding factors related to atherosclerotic disease (smoking and hypercholesterolemia) were not taken into account in our study, since they were thought to be unreliable upon data collection. Hence, it is important to compare the prevalence of the associated diseases with the prevalence of those in the community. Studies concerning disease prevalence and symptoms within the same age groups have been done in our community[11,12]. The studies summarized the prevalence and disease patterns in the population aged 70 years in Jerusalem. In that study the prevalence of NIDDM, CVA, and chronic renal failure in men was 16.1%, 6.9%, and 10%, respectively. When comparing men in that study with our male patients a higher prevalence of NIDDM

and CVA was noted in the men with GCA ($p = 0.0452$ and $p < 0.002$, respectively, chi-square test), while the prevalence of renal failure did not reach statistical difference. Such differences do not exist between the female GCA group and the study in 70-year-old females or when comparing all patients with GCA with the general population. Thus, it is possible that the difference between the men with GCA and men of the same age group represents either a risk factor or a prior indolent involvement of the disease.

The apparently higher prevalence of renal failure in male patients compared to females might be explained by 2 factors: (1) higher prevalence of renal failure in men vs women in the general population (10% vs 6%), and (2) higher prevalence of NIDDM in our male patients, which in this age group might involve diabetic nephropathy.

That our study was a retrospective hospital based cohort might contribute to a bias in the prevalence of difference between the sexes. One might postulate that sicker patients and patients with more complicated course or more background comorbidities will be referred to hospital. Still, these comorbidities (such as NIDDM and CVA) might reflect potential risk factors, since they were reported before the diagnosis of GCA or PMR was made and before treatment was started. Nevertheless, that bias does not necessarily explain the higher prevalence of NIDDM in male patients (31%) compared to the females and the general population. In a recent large prospective study of GCA a trend to similar difference ($p = 0.065$) between the sexes pertaining to NIDDM was apparent[7,13]. But probably the main difference between the groups is related to the prevalence of NIDDM in the general population. In the French male population 5.68% have NIDDM[7,13], while in the male population of Jerusalem NIDDM exists at 16.1%[11]. Consequently, we suggest that this sex difference represents a true factor with regard to background history, especially when the prevalence of NIDDM is high in the general population.

Examination of disease characteristics reveals some important differentiating factors between the sexes. Men tend to have more severe eye involvement, causing an increase of blindness in this group. The higher prevalence of eye involvement and blindness in men could reflect more severe intracranial involvement, as suggested by a more prevalent history of CVA. This is supported by the study of Brack, *et al*[6], which implied that men are more prone to cranial involvement, while women have more involvement of the large vessels. The integration of the data might suggest that men are more prone to internal carotid involvement than women. These observations also indicate the need for more efficient treatment in men due to these devastating complications. Moreover these differences were not affected by the elimination of PMR patients from both groups, and continued to be statistically different in the patients exclusively with GCA.

Some support for that hypothesis can also be made from the logistic regression model. That model showed that male sex is indeed associated with blindness. But in the same sex it was related to negative temporal artery biopsy. Such findings might be explained by different predilection for artery involvement between the sexes. Another explanation for more prominent atherosclerotic disease in men is ruled out by that analysis, since it did not show a relationship to other background diseases involved with arteriosclerosis such as hypertension and NIDDM (as also shown by Duhaut, *et al*[7]).

It can be postulated that the differences between the sexes could be related to delayed diagnoses in men. Nevertheless, our data revealed that men and women did not differ in the time lapse from the onset of symptoms to the diagnosis of the disease. This might reflect that GCA in men has a much more accelerated course. This needs confirmation in larger studies.

In the laboratory results of our patients there were 2 other factors differentiating the sexes: leukocytosis, which is more prevalent in men, and anemia, more prevalent in women. Anemia might reflect a population sex difference in these age groups, as well. Both factors might also be related to a selection bias due to our hospital based population.

The fact that in our study the rate of biopsy proven cases did not differ between the sexes on univariate analysis might reflect a more complicated interaction between the pathology of the artery, the sexes, and disease progression. That was shown by the protective effect of positive pathology in the men. In other studies trying to correlate between positive pathology and blindness, it was shown to be related only in the univariate analysis[8], or not related at all[14]. The difference between the 3 studies might be explained by the different ratio of men to women in the previous studies, 1:3.7[8] and 1:2.7[14], and by the prospective structure of the 2 studies, compared to a male:female ratio of 1:2 and the retrospective approach of our study.

We suggest for the first time that differences do exist between men and women presenting with giant cell arteritis and polymyalgia rheumatica. These differences, and mainly blindness, might reflect a different response to the pathologic process or even different perception of the disease between the sexes. Our results also call for a more aggressive approach to diagnosis and treatment of male patients in view of the higher prevalence of severe eye involvement and blindness.

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