Sex Differences in Temporal Arteritis and Polymyalgia Rheumatica

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ABSTRACT. ***Objective.*** Sex-specific differences in treatment outcomes have been observed in polymyalgia rheumatica (PMR) and temporal arteritis (TA), with a significantly longer course of treatment in women than in men. We analyzed whether these sex differences are related to differences in disease presentation and severity of the inflammatory response.

Methods. The records of 163 cases of PMR and/or TA diagnosed over a 15 year period were reviewed. A comparative study of clinical and laboratory features between men and women was performed.

Results. Of 163 patients, 90 had isolated PMR and 73 had TA. Among patients with TA, 49 women and 24 men were identified, with a ratio of 2. While there were no differences in the frequency of classic disease manifestations, the presence of constitutional syndrome (malaise, anorexia, and weight loss) and fever were significantly more frequent in women than in men. Of note, evaluation of laboratory measures at time of diagnosis also revealed more marked laboratory abnormalities reflecting inflammation in the female group. Among patients with isolated PMR, 58 women and 32 men were identified, a ratio of 1.8. Comparing the clinical features at presentation, significant sex differences were also found, with a higher frequency of constitutional syndrome and lower values of hemoglobin in women. Moreover, women also had higher erythrocyte sedimentation rate values, and higher prevalence of fever and hepatic involvement, although the difference did not reach statistical significance.

Conclusion. Modest differences were found in disease expression between women and men with TA and/or PMR. In both conditions, the inflammatory response seemed to be more severe in women. The strong inflammatory response in women could explain the longer duration of treatment reported in this subgroup of patients. (J Rheumatol 2002;29:321–5)

Key Indexing Terms:
POLYMYALGIA RHEUMATICA TEMPORAL ARTERITIS SEX DIFFERENCES

Polymyalgia rheumatica (PMR) and temporal arteritis (TA) are different but closely related inflammatory conditions that occur in the elderly. PMR is characterized by pain and stiffness involving the neck, shoulder, and pelvic girdle, generally accompanied by constitutional symptoms and findings of a systemic reaction, usually an elevated erythrocyte sedimentation rate (ESR). TA is a vasculitis of large and medium size vessels, with predisposition to the cranial arteries. Both entities have a marked female predominance, with women affected roughly twice more commonly than men. Epidemiologic studies on TA in widely separated countries have noted a declining trend in the annual incidence for men and a marked increase in the incidence rate of TA for women[1,2]. This sex divergence in incidence rates is more marked among the oldest age groups. Why both conditions manifest in old age and show a preference among women is unknown. The increased incidence among women implies a relationship with sex hormones. However, the significance of this observation is not understood, because sex-specific differences in both PMR and TA have not been extensively explored. In a study to identify factors that may influence prognosis and duration of therapy in a series of patients with isolated PMR and TA, we observed that female sex was a significant risk factor associated with long duration of therapy[3]. Of interest and similar to our findings, others have also reported a significantly longer duration of treatment in women than in men in both PMR[4-6] and TA[7], regardless of the treatment regimen. To analyze if these sex differences observed in the clinical course are related to differences in disease presentation and severity of the inflammatory response, we compared the clinical and laboratory features of men and women with PMR and/or TA.

MATERIALS AND METHODS

We analyzed all patients with PMR and/or TA diagnosed from 1985 to 1999 by the Department of Rheumatology of Bellvitge Hospital, a 1000 bed

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teaching institution in Barcelona. The diagnosis of PMR was based on the criteria suggested by Chuang, *et al*[4]: (1) age at disease onset ≥ 50 years, (2) ESR ≥ 40 mm/h, and (3) bilateral aching and stiffness persisting for one month or more, involving at least 2 of the following areas: (a) neck or torso, (b) shoulders or proximal regions of the arms, and (c) hips or proximal aspects of the thighs. Patients were considered to have PMR if they met these criteria and had a rapid and persistent response to corticosteroid treatment. The presence of other diseases that might explain the symptoms, such as chronic infection, connective tissue diseases, or malignancy, excluded the diagnosis of PMR. The diagnosis of TA was made according to the 1990 American College of Rheumatology (ACR) criteria[8]: (1) age at disease onset ≥ 50 years, (2) new headache, (3) temporal artery abnormality on examination (decreased pulses unrelated to arteriosclerosis, nodules, thickening, swelling, or tenderness to palpation), (4) ESR ≥ 50 mm/h, and (5) temporal artery biopsy specimen showing vasculitis mainly characterized by mononuclear cell infiltration of granulomatous inflammation, usually with multinucleated giant cells. Patients were diagnosed as having TA if they had a positive artery biopsy or, in cases with negative biopsy or no biopsy, if they fulfilled the remaining 4 criteria and had a prompt and persistent response to corticosteroid treatment.

After diagnosis, patients with isolated PMR were initially treated with 10–20 mg/day prednisone or equivalent, and patients with evidence of TA were treated with an initial dose of 40 to 60 mg daily. Followup of all patients was by periodic examinations at our outpatient clinic until death or cessation of treatment and permanent disease remission. Inpatient and outpatient charts of all patients were reviewed comprehensively for information on clinical manifestations and laboratory data according to a specifically designed protocol. These data were usually carefully and adequately described in the medical records. Treatment and longterm outcome were not an integral part of this study. Information about the clinical course and duration of therapy of the majority of patients has been reported[3].

Statistical analysis. Continuous data were described as mean ± standard deviation and categorical variables as percentages. To study sex differences in disease presentation, we performed a comparative study between men and women in both TA and PMR. Comparisons were made using Student t test for independent continuous variables or the Mann-Whitney U test when the assumption of normality was not realized. To analyze categorical data, we performed the chi-squared test or Fisher's exact test when the expected values were less than 5. Statistical significance was defined as $p \leq 0.05$.

RESULTS

From 1985 to 1999 inclusive a total of 163 patients (107 women, 56 men, a ratio of 1.9) were diagnosed with TA and/or PMR. Of these, 90 patients had isolated PMR and 73 had TA. In patients with isolated PMR, the possibility of TA was excluded by either a negative temporal artery biopsy or by resolution of the syndrome after low dose prednisone therapy, and absence of TA manifestations during followup.

Mean age at time of diagnosis for all patients was 72 ± 8 years (range 51–89) and the mean duration of symptoms prior to diagnosis was 2.7 ± 2.6 months. The main clinical features and laboratory data of both groups are summarized in Tables 1 and 2. Among patients with TA (Table 3), 49 women and 24 men were identified, with a female:male ratio of 2. Males and females had similar age at onset. For the most part, the clinical features of TA were similar in both sexes, although systemic symptoms (71.4% vs 45.8%; $p < 0.033$) and fever (18.4% vs 0%; $p < 0.026$) were significantly more frequent in women than men. No significant differences in classic features of TA such as headache, jaw claudication, abnormal temporal arteries on examination, transient visual loss, or PMR were observed. Interestingly, evaluation of laboratory measures at time of diagnosis also revealed more marked laboratory abnormalities reflecting

Table 1. Clinical features and laboratory data of patients with TA. Results are presented as mean ± SD or number of cases with prevalence rates.

Number of patients	73
Age at onset of disease, yrs	72 ± 8
Women/men (ratio)	49/24 (2)
Mean diagnostic delay, mo	2.6 ± 2.2
Clinical features (%)	
Headache	73 (100)
Abnormal temporal artery	64 (88)
Jaw claudication	25 (34)
Malaise/anorexia/weight loss	46 (63)
Fever	9 (12)
Transient visual loss	14 (19)
Permanent blindness	0 (0)
Limb claudication	2 (3)
Polymyalgia rheumatica	41 (56)
Peripheral arthritis	8 (11)
Positive biopsy*	49 (67)
Laboratory data (%)	
ESR, mm/h	85 ± 23
Hemoglobin, g/dl	11.4 ± 1.4
Raised ALT/AST**	8 (11)
Raised alkaline phosphatase**	17 (23)

* Not done in 4 cases. ** Increased ALT/AST and alkaline phosphatase was considered if values at diagnosis were ≥ 1.5 times normal value.

Table 2. Clinical features and laboratory data of patients with isolated PMR. Results are presented as mean ± SD or number of cases with prevalence rates.

Number of patients	90
Age, mean yrs ± SD	72 ± 8
Women/men (ratio)	58/32 (1.8)
Mean diagnostic delay, mo, ± SD	2.8 ± 2.8
Clinical features (%)	
Pain and morning stiffness involving the following regions	
Shoulders or proximal regions of the arms	90 (100)
Hips or proximal aspects of the thighs	83 (92)
Neck or torso	65 (72)
Malaise/anorexia/weight loss	49 (54)
Fever	7 (8)
Depression	8 (9)
Peripheral arthritis	18 (20)
Laboratory data (%)	
ESR, mm/h	76 ± 21
Hemoglobin, g/dl	11.8 ± 1.2
Raised AST/ALT*	8 (9)
Raised alkaline phosphatase*	16 (18)

* Increased ALT/AST and alkaline phosphatase was considered if values at diagnosis were ≥ 1.5 times normal value

Table 3. Comparison of clinical and laboratory features between men and women with TA.

	Women (%)	Men (%)	p
Number of patients	49	24	
Age at onset of disease, mean yrs ± SD	73.02 ± 8.05	72.33 ± 9.2	NS
Mean diagnostic delay, mo ± SD	3.11 ± 2.44	1.86 ± 1.8	NS (p = 0.13)
Headache	49 (100)	24 (100)	NS
Abnormal temporal artery	43 (87.7)	21 (87.5)	NS
Jaw claudication	17 (34.7)	8 (33.3)	NS
Transient visual loss	10 (20.4)	4 (16.7)	NS
Malaise/anorexia/weight loss	35 (71.4)	11 (45.8)	0.033
Fever	9 (18.4)	0 (0)	0.026
Polymyalgia rheumatica	28 (57.1)	13 (54.2)	NS
ESR mm/h, mean ± SD	87 ± 23	84 ± 22	NS
Anemia*	22 (44.9)	5 (20.8)	0.045
Raised ALT/AST**	8 (16.3)	0 (0)	0.047
Raised alkaline phosphatase**	14 (28.6)	3 (12.5)	NS

* Anemia defined as hemoglobin < 12 g/dl. ** Increased ALT/AST and alkaline phosphatase was considered if values at diagnosis were ≥ 1.5 times normal value.

inflammation in the female group, which had higher ESR values (87 ± 23 vs 84 ± 22 mm/h; $p > 0.05$, not statistically significant), higher frequency of anemia (44.9% vs 20.8%; $p = 0.045$), and elevated AST/ALT (16.3% vs 0%; $p = 0.047$) and alkaline phosphatase levels (28.6% vs 12.5.1%; $p > 0.05$). These differences could be explained partly by the longer diagnostic delay observed in women.

Among patients with isolated PMR (Table 4), 58 women and 32 men were identified, a ratio of 1.8. Both groups had similar age at onset. While there were no differences in the type of polymyalgia symptoms, in comparing the clinical features at presentation significant sex differences were also found, with a higher frequency of systemic symptoms (67.2% vs 31.2%; $p = 0.001$) and lower hemoglobin values (11.4 ± 1.1 vs 12.2 ± 1.3; $p = 0.017$) in women than men. Moreover, women had also higher ESR values, and higher prevalence of fever and hepatic involvement, but the difference did not reach statistical significance. Altogether, these data suggest a more severe inflammatory response in women.

DISCUSSION

While PMR and TA are roughly twice as common in women as in men, sex-specific differences in the clinical presentation and longterm outcome of both diseases have not been extensively explored. In this study comparing the clinical spectrum of women and men with TA and/or PMR, we found that female patients seem to have a more severe inflammatory response, with greater abnormalities in clinical (constitutional syndrome and fever) and laboratory

Table 4. Comparison of clinical and laboratory features between men and women with isolated PMR.

	Women (%)	Men (%)	p
Number of patients	58	32	
Age at onset of disease, mean yrs ± SD	72.08 ± 8.93	72.3 ± 8.1	NS
Mean diagnostic delay, mo ± SD	3.17 ± 3.07	3.12 ± 2.14	NS
Shoulder girdle involvement	58 (100)	32 (100)	NS
Hip girdle involvement	54 (93.1)	29 (90.6)	NS
Neck involvement	41 (70.6)	24 (75)	NS
Malaise/anorexia/weight loss	39 (67.2)	10 (31.2)	0.001
Fever	6 (10.3)	1 (3.1)	NS
Depression	5 (8.6)	3 (9.4)	NS
Peripheral arthritis	11 (18.9)	7 (21.9)	NS
ESR, mm/h (mean ± SD)	79 ± 23	75 ± 19	NS
Hemoglobin, g/dl	11.4 ± 1.1	12.2 ± 1.3	0.017
Raised alkaline phosphatase*	12 (20.7)	4 (12.5)	NS
Raised ALT/AST*	6 (10.3)	2 (6.2)	NS

*Increased ALT/AST and alkaline phosphatase was considered if values at diagnosis were ≥ 1.5 times normal value.

markers of inflammation. Although this has never been clearly elucidated before, there is scattered information in the literature supporting our results. Similar to our findings, a report on TA in southwestern Spain has also observed a strong inflammatory response in women, characterized by higher frequency of anemia, thrombocytosis, and hepatic involvement[9]. Moreover, in another multicenter collaborative study in 3 hospitals in northern Spain, female patients had a more complex syndrome with higher frequency of anemia[10]. The more severe inflammatory response observed in women could explain the more protracted course reported in this subgroup. In a study to identify factors that may influence prognosis and duration of therapy in a series of patients with isolated PMR and TA, we observed that female sex was a significant risk factor associated with long duration of therapy[3]. Of interest, similar to our findings, some authors have reported a significantly longer course of treatment and disease in women than in men in both PMR[4-6] and TA (5.5 vs 2.3 years)[7], regardless of the treatment regimen. Together, these observations indicate that female patients with these conditions are expected to be at particularly high risk for steroid toxicity. Supporting this approach, Gabriel, *et al*[11], in a recent study from the Mayo Clinic to evaluate the incidence and risks of adverse events associated with corticosteroid therapy among patients with PMR, also found that female sex was a significant risk factor for the development of an adverse event. Consequently, preventive strategies to decrease the incidence of iatrogenic complications, such as the ACR recommendations for the prevention of glucocorticoid induced osteoporosis[12] or the addition of a steroid sparing agent, should be systematically considered in this subgroup of patients. In addition, the more severe inflammatory response observed in women with TA provides a rationale for testing less aggressive treatment schedules in these patients, since there is an increasing number of reports supporting the association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in TA[13-15].

The question arises why these sex differences exist. A possible explanation is sex based hormonal differences. A number of studies indicate that sex hormones play an important role in immunology. Animal studies have shown androgens inhibit and estrogens enhance autoimmunity[16,17]. It might thus be speculated that a lower androgen level in women compared to men may account for more active disease in female patients with the 2 conditions. The importance of androgens in autoimmunity is supported by the findings of significant reductions in disease activity after the administration of oral androgens in male patients with rheumatoid arthritis (RA)[18] and female patients with systemic lupus erythematosus (SLE)[19]. One study has shown reduced blood levels of dehydroepiandrosterone sulfate (DHEAS) in patients with PMR, with and without associated TA, although sex-specific differences in blood levels of DHEAS have not been explored[20]. The low levels of this steroid found in patients with PMR and/or TA are in agreement with data from patients with SLE and with RA[21-24]. Estrogen is a less likely explanation of the more active disease found in women with TA and/or PMR, since both conditions primarily affect postmenopausal women. This represents a period of declining estrogen levels. However, a recent epidemiologic study indicates that former pregnancies may be a protective factor against TA[25], which supports the contention that estrogen could be pathogenetically involved.

In summary, in our area there appear to be modest differences in disease expression between women and men with TA and/or PMR. Based on our own and other large studies[9,10], we conclude that the clinical picture of TA and PMR in Spain seems to be more severe in female patients. The strong inflammatory response observed in women could explain the longer duration of treatment observed in this subgroup of patients[3]. Further studies in other populations are needed to provide information for comparison with our results.

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