Gender differences in giant cell arteritis: a case-control study

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Received on September 19, 2015; accepted in revised form on November 23, 2015.

Clin Exp Rheumatol 2016; 34 (Suppl. 97): S70-S72.

Key words: giant cell arteritis, colour duplex sonography, gender, age, disease pattern.

Competing interests: none declared.

ABSTRACT

Objective. *To determine sex differences in the clinical spectrum and disease pattern of cranial and extracranial giant cell arteritis (GCA).*

Methods. *Data on 153 consecutive patients with a confirmed diagnosis of GCA between 2002 and 2013 were retrospectively obtained from our database. For every male patient, two age-matched female patients were identified. Clinical symptoms, vascular physical examination findings, laboratory values, and the disease patterns as assessed by colour duplex sonography of the temporal and axillary arteries were compared between women and men. Subgroup analyses were performed for patients aged 50-69 years and ≥70 years at disease onset.*

Results. *No significant differences between sexes were noted with regard to cranial GCA. Female patients significantly more frequently had axillary artery involvement (48.9 vs. 27.5%, p=0.03), a difference mainly driven by a higher rate of axillary artery involvement in women ≥70 years of age (38.6 vs. 4.5%, p<0.01). Women aged 70 years or older significantly more frequently had axillary artery stenosis (27.3 vs. 0%, p<0.01), symptoms of upper extremity ischaemia (20.5 vs. 0%, p<0.01), and polymyalgia rheumatica (36.4 vs. 9.1%, p=0.02) compared to men. Significant sex differences were observed with regard to the frequency of anaemia and the mean platelet count.*

Conclusion. *In GCA involvement of the cranial arteries does not differ between sexes. Female patients with GCA significantly more frequently exhibit extracranial (i.e. axillary) arterial involvement than men.*

Introduction

Giant cell arteritis (GCA) is the most common form of the primary systemic vasculitides, almost exclusively occurring in people above the age of 50 (1). Women are affected at least twice as much as men (2). A decade ago sex differences in the clinical spectrum of GCA were discussed controversially (3-7). This discussion was exclusively focused on patients with cranial GCA, not reflecting current knowledge on frequent involvement of extracranial arteries. Of note, several cohort studies suggest that involvement of the extracranial arteries could be more common in females than in males suffering from GCA (8-11). Moreover, the pattern of vascular involvement and disease presentation seems to be highly dependent on the age at onset of the disease (12). Applying a case-control study design comparing male and female patients matched by age, we sought to determine meaningful sex differences in the clinical spectrum and disease pattern in a contemporary cohort of patients with cranial and/or extracranial GCA.

Patients and methods

All consecutive patients with a diagnosis of GCA made at our institution between 2002 and 2013 were retrospectively identified from a prospectively maintained database. All patients were required to be at least 50 years of age at disease onset, and all patients underwent colour duplex sonography of the temporal and axillary arteries during the initial diagnostic workup. A circumferential, hypoechogenic, homogenous wall thickening of the temporal arteries (Halo) and/or the axillary arteries was considered a distinct imaging feature of GCA (9, 13).

The diagnosis of GCA was based on a positive temporal artery biopsy, and fulfillment of at least three of the 1990 American College of Rheumatology classification criteria for GCA (14), and/or in the presence of typical sonographic findings of the temporal and/or axillary arteries, together with a typical clinical and laboratory constellation rapidly responsive to corticosteroid treatment (12).

Data regarding clinical symptoms, vas-

Table I. Gender differences in clinical presentation and disease pattern in the overall cohort and different age groups.

Variables	Men			Women			*p*-values		
	Overall cohort (n=40)	Age >70 years (n=22)	Age 50-69 years (n=18)	Overall cohort (n=80)	Age >70 years (n=44)	Age 50-69 years (n=36)	Overall cohort	Age >70 years	Age 50-69 years
Age (years)	70.9 ± 8.8	77.3 ± 5.0	62.9 ± 5.3	70.9 ± 8.7	77.2 ± 5.1	63.2 ± 5.1	0.98	0.93	0.88
Time to diagnosis (weeks)	17.4 ± 26.5	7.2 ± 9.6	29.7 ± 34.7	16.3 ± 20.3	14.8 ± 21.9	18.2 ± 18.1	0.83	0.06	0.20
Polymyalgia rheumatica	10 (25)	2 (9.1)	8 (44.4)	33 (41.3)	16 (36.4)	17 (47.2)	0.11	**0.02**	1.00
Constitutional symptoms	21 (52.5)	8 (36.4)	13 (72.2)	46 (47.5)	20 (45.5)	26 (72.2)	0.70	0.60	1.00
Upper extremity claudication	4 (10)	0 (0)	4 (22.2)	14 (17.5)	9 (20.5)	5 (13.9)	0.42	**0.02**	0.46
Cranial symptoms	30 (75)	21 (95.5)	9 (50)	60 (75)	37 (84.1)	23 (63.9)	1.00	0.25	0.39
Headache	22 (55)	15 (68.2)	7 (38.9)	44 (55)	24 (54.5)	20 (55.6)	1.00	0.43	0.39
Jaw claudication	14 (35)	9 (40.9)	5 (27.8)	34 (42.5)	20 (45.5)	14 (38.9)	0.55	0.80	0.55
Temporal artery Tenderness	7 (17.5)	5 (22.7)	2 (11.1)	22 (27.5)	13 (29.5)	9 (25)	0.27	0.77	0.30
Permanent visual Loss	12 (30)	9 (40.9)	3 (16.7)	27 (33.8)	25 (56.8)	2 (5.6)	0.84	0.30	1.00
Acute ischaemic stroke	2 (5)	1 (4.5)	1 (5.6)	0	0	0	0.11	0.33	0.33
Abnormal temporal artery	18 (45)	14 (63.6)	4 (22.2)	34 (42.5)	23 (52.3)	11 (30.6)	0.85	0.44	0.75
Abnormal upper extremity arterial status	9 (22.5)	1 (4.5)	8 (44.4)	23 (28.8)	13 (29.5)	10 (27.8)	0.52	**0.02**	0.24
Temporal artery Halo	24 (60)	18 (81.8)	6 (33.3)	47 (58.8)	32 (72.7)	15 (41.7)	0.84	0.35	0.77
Temporal artery biopsy	26 (65)	16 (72.7)	10 (55.6)	40 (50)	28 (63.6)	12 (33.3)	0.17	0.58	0.15
Positive temporal artery biopsy	19 (47.5)	14 (63.6)	5 (27.8)	30 (37.5)	24 (54.5)	6 (16,7)	0.33	0.60	0.48
≥3 ACR criteria	29 (72.5)	19 (86.4)	10 (55.6)	58 (72.5)	35 (79.5)	23 (63.9)	1.00	0.74	0.57
Axillary artery involvement	11 (27.5)	1 (4.5)	10 (55.6)	39 (48.9)	17 (38.6)	22 (61.1)	**0.03**	**< 0.01**	0.77
Axillary artery stenosis	7 (17.5)	0 (0)	7 (38.9)	21 (26.3)	12 (27.3)	9 (25)	0.36	**< 0.01**	0.35
Anaemia*	29 (76.3)	15 (75)	14 (77,8)	43 (54.4)	24 (54.5)	19 (54,3)	**0.03**	0.17	0.14
Platelet count*	357 ± 110	350 ± 118	365 ± 103	412 ± 134	391 ± 148	438 ± 111	**0.03**	0.28	**0.02**
White blood cell count*	9.7 ± 2.6	9.7 ± 3.0	10 ± 9	9.8 ± 2.3	9.9 ± 2.1	10 ± 3	0.77	0.83	0.86
C-reactive protein (mg/dl)*	6.2 ± 5.3	5.2 ± 4.2	7.4 ± 6.3	7.5 ± 6.0	6.8 ± 6.4	8.2 ± 5.5	0.27	0.30	0.64
ESR (mm / 1 hour)*	63 ± 37	53 ± 34	73 ± 38	74 ± 34	68 ± 36	82 ± 31	0.13	0.15	0.39

Values given as mean ± SD or n (%).
*Laboratory values obtained before treatment initiation were available for 117 out of 120 patients.

cular physical examination findings (temporal artery inspection and palpation, axillary artery bruit, upper extremity pulse loss, blood pressure difference between both arms of at least 15 mmHg), laboratory values (C-reactive protein, erythrocyte sedimentation rate, blood count) and colour duplex sonography findings of the temporal and axillary arteries were obtained from the database.

For every male patient, two age-matched female patients were identified. Clinical, sonographic and laboratory findings in male and female patients were compared, with specified subgroup-analyses for patients aged between 50-69 years and ≥70 years at disease onset. For statistical analysis, SPSS version 21.0 (SPSS Inc, Chicago, Il, USA) was applied. Fisher's exact test was used for comparison of categorical variables, and the unpaired *t*-test was used for comparison of continuous variables. Two-sided *p*-values <0.05 were considered significant. Retrospective data analysis was approved by the local ethics committee.

Results

Out of 153 patients identified, 40 patients (26.1%) were men, corresponding to a male to female ratio of 1:3. According to the study design, the control group consisted of 80 women. The two groups were well matched for age (men, 70.9±8.8 years *vs*. women, 70.9±8.7 years; *p*=0.98). Sixty-six patients were aged 70 years or older, and 54 patients were between 50 and 69 years of age. Comparisons between male and female patients in the overall cohort and in age-related subgroups are listed in Table I.

In the overall cohort, there were no meaningful differences between male and female patients regarding classical cranial symptoms or the frequency of positive sonographic or histological findings of the temporal arteries. A difference in the prevalence of PMR (women 41% *vs*. men 25%) did not reach statistical significance. The most important difference between both sexes was that axillary artery involvement, as documented by colour duplex sonography, was significantly more common in women. In addition, female patients had a higher rate of anaemia compared to men and significantly higher mean platelet counts. Mean CRP- and ESR-values also were higher in women, but these differences were not statistically significant.

When looking at the group of patients aged 70 years and older, a strikingly higher rate of symptomatic upper extremity ischaemia was observed in women, corresponding to a markedly higher frequency of axillary artery involvement, vasculitic axillary artery stenosis, and abnormal upper extremity vascular physical examination. Moreover, symptoms of PMR were significantly more common in women compared to men in this age group.

Except a significantly higher mean platelet count in women, no further apparent sex differences with regard to clinical, sonographic and laboratory variables were noticed in younger patients between 50 and 69 years of age.

Discussion

To evaluate sex differences in the clinical

presentation and disease pattern in GCA, we used a case control study design with male and female patients matched by age. This study design has the advantage of eliminating the substantial influence of age on the disease pattern and clinical spectrum in GCA (12).

The male to female ratio in our hospital-based cohort of consecutive patients with GCA from Munich, Germany was 1:3. In a population based study from Northwestern Spain, Gonzalez-Gay *et al*. documented that the sex ratio in GCA is dependent on the place of residence. In their study, the male to female ratio was almost 1:1 in rural areas, whereas in urban areas it was about 1:3 (7).

Our study shows that extracranial arterial (i.e. axillary artery) involvement is more common in women than in men. These findings underscore the results of previous cohort studies which revealed a higher percentage of female patients in extracranial GCA compared to isolated cranial GCA (8-11). A striking difference regarding the frequency and severity of axillary artery involvement was found in patients above the age of 70. While axillary artery involvement seems to be very uncommon in men of this age group, it is still highly prevalent in women aged 70 years or older. Moreover, in women ≥70 years of age vasculitic lesions of the axillary arteries frequently lead to arterial stenosis or occlusion, together with clinical symptoms of upper extremity ischaemia and/or an abnormal upper extremity vascular status. Our results implicate that the awareness for GCA should be high in elderly women presenting with symptoms or signs of upper extremity ischaemia. In addition, imaging of the extracranial arteries, *i.e*. colour duplex sonography of the axillary arteries, appears to be of particular importance in women.

Corroborating the results of previous studies from Israel, Spain, and France, we did not observe any sex-related differences in the frequency of cranial symptoms of GCA (3, 4, 6, 7). Only one report on the population-based cohort of GCA patients in Olmstedt County, Minnesota, U.S., documented a lower rate of cranial symptoms in men compared to women (56 *vs*. 81%). The significance of this study`s findings, published back in 1988, might be limited by the small number of male patients analysed (n=16) (15). When specifically looking on permanent visual loss, we and others also found no significant differences between both sexes (6, 7, 15). In contrast, Nir-Paz *et al*. from Israel observed a non-significantly higher rate of permanent loss in men than in women (9 *vs*. 25%) (3). Surprisingly, permanent visual loss was not observed in a study from Catalonia, Spain (4).

In our cohort, symptoms of polymyalgia rheumatica were more common in women than in men (40 *vs*. 25%). However, this difference reached statistical significance only in individuals above the age of 70. In line with our findings, most of the previous studies documented a higher frequency of polymyalgia rheumatica in women *versus* men with GCA (3, 6, 7, 15). There is only one study with contradictory results, reporting a very similar prevalence of PMR-symptoms in male and female patients with GCA (4).

Three out of four women in our cohort were anaemic at the time of diagnosis, compared to only every second man. However, this comparison may be hampered by the different haemoglobin reference ranges in male and female patients. We also found significantly higher platelet counts in women than in men. This may reflect the more systemic nature of the vasculitis in women, as documented by the more frequent involvement of the axillary arteries.

In conclusion, our study indicates that extracranial arterial (*i.e*. axillary artery) involvement) is more common in women than in men. This difference between both sexes is most pronounced in the age group 70+, together with a significantly higher rate of signs and symptoms of upper extremity ischaemia and polymyalgia rheumatica in women above the age of 70. We found no sex differences with regard to the classical cranial disease pattern of GCA.

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