Implication of the age in the clinical spectrum of giant cell arteritis

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Received on July 16, 2007; accepted in revised form on October 2, 2007.

Clin Exp Rheumatol 2008; 26 (Suppl. 49): S16-S22.

Key words: Giant cell (temporal) arteritis, temporal artery biopsy, age, epidemiology, clinical manifestations.

Competing interests: none declared.

ABSTRACT

Objective. *To assess the potential influence of the age in the clinical spectrum of giant cell arteritis (GCA).*

Methods. *The case records of all patients diagnosed with biopsy-proven GCA at the Department of Medicine of the Hospital Xeral-Calde (Lugo, Northwest Spain) between 1981 and 2006 were reviewed.*

Results. *During the period of study, 273 Lugo residents were diagnosed with biopsy-proven GCA. The mean age ± standard deviation at the time of disease diagnosis was 75.1±6.8 years (median: 75 years; interquartile range 71-80 years). A longer delay to the diagnosis was observed in patients younger than 70 years of age (13.2±12.8 weeks) compared to those 70 years and older (9.4±10.2 weeks) (p=0.03). Patients younger than 70 years presented more frequently polymyalgia rheumatica (p=0.02), cerebrovascular accidents (p=0.004), peripheral arteriopathy of recent onset due to large artery stenosis (p=0.03) and high alkaline phosphatase values (p=0.001) than those 70 years and older. Individuals 70-79 years of age at the time of disease diagnosis had ESR values (90.2±22.8 mm/1st hour) lower than those observed in patients younger than 70 years (98.3±22.2 mm/1st hour) or 80 years and older (99.5±20.6 mm/1st hour) (p=0.005). However, no significant differences in the frequency of visual ischemic complications according to the age at the time of disease diagnosis were observed.*

Conclusion. *The results from this study display differences in the clinical spectrum of the disease according to the age of disease onset.*

Introduction

Giant cell, temporal, arteritis (GCA), also called Horton's or granulomatous arteritis, is a large and medium-sized blood vessel systemic vasculitis characterized by the granulomatous involvement of the aorta and its major branches, with predilection for the extracranial arteries of the carotid artery (1-3). Despite having an increased risk of severe ischemic complications, in particular permanent visual loss, mortality rates of GCA patients are comparable to those of the general population (4).

GCA is the most common vasculitis in elderly individuals from Western countries (1, 3, 5, 6). It mainly affects white population (5, 7), and almost exclusively occurs in individuals older than 50 years (2, 7-16). In this regard, the mean age of onset in different studies ranged between 72 and 74 years (3, 17, 18) and its incidence increases with aging (16, 19, 20). The highest rates of incidence are observed in age groups over 70 years of age (16, 19).

In a former study carried out by our group that included 210 biopsy-proven GCA patients we observed a trend for a longer delay to diagnosis and a marginal increase in the frequency of polymyalgia rheumatica (PMR) in GCA patients with disease onset at under 70 years old compared to 70 years old and over (21). Also, in a recent study on the epidemiology of GCA in Lugo over the period 1981-2005, we observed that incidence of biopsy-proven GCA in Lugo increased dramatically with advancing age up to a maximum of 23.16/100,000 people in the 70-79 age group (22). Then, annual incidence rates decreased slightly in the 80 years old and over age group (20.57/100,000 people). Moreover, incidence was very low in individuals under 70 years old (0.55/100,000 people in the 50-59 age group and 4.83 in individuals 60-69 years old) (22). Due to this, in the present study we have extended our analysis on the influence of the age in

the clinical spectrum of GCA in this well-defined region of Northwestern Spain. We have focused on the influence of the age at the time of disease diagnosis on clinically relevant outcome parameters of GCA.

Patients and methods

A retrospective review of the case records of all patients diagnosed with biopsy-proven GCA at the Department of Medicine of the Hospital Xeral-Calde (Lugo, Northwest Spain) between January 1, 1981 and December 31, 2006 was performed. This hospital is the single reference center for a mixed rural and urban population of almost a quarter of a million people. Information about the characteristics of this white population has been reported elsewhere (11, 23-25). Patients were sent to the hospital by general practitioners or they self-referred to the emergency unit.

Patients included in this study were diagnosed as having biopsy-proven GCA when the temporal artery biopsy (TAB) showed a compatible pathology report, describing the characteristic mononuclear cell infiltration of the arterial wall, with or without the presence of granulomas and/or multinucleated giant cells (26).

TAB procedure in our patients has previously been reported (19, 27). Briefly, TAB was routinely performed to all patients with clinical manifestations of GCA (28, 29). The side with predominant local temporal, neck or shoulder symptoms and signs was selected for TAB (30). Segments longer than 2.5 cm were generally obtained. In those individuals with clinically isolated PMR, without any vascular manifestation of GCA, biopsies were also considered if they had constitutional syndrome (asthenia anorexia and weight loss of at least 4 kg) and/or the erythrocyte sedimentation rate (ESR by Westergren method) was greater than 80 mm/1st hour (27, 29, 31). Following this procedure we have observed 9% positive TABs in patients with isolated PMR (19, 30). As previously reported (19, 32), the positive/negative TAB ratio did not change significantly over the period of study.

Data collection

Demographic and clinical data at the time of diagnosis or within the 4 weeks after the onset of treatment of all the patients with biopsy-proven GCA were analyzed. Due the special characteristics of our center, the vast majority of patients included in this and former studies on GCA were admitted to hospital for diagnosis (31, 33, 34).

Since the purpose of this study was to assess the influence of the age in the clinical spectrum of presenting manifestations of GCA, as previously reported (24, 35), clinical manifestations were considered within the category of presenting features of the disease if they occurred within a period of time between the onset of GCA symptoms and 4 weeks after the start of steroid therapy (initial dose 40 to 60 mg/prednisone/day for 3-4 weeks or intravenous methylprednisolone pulse therapy [1g daily for 3 consecutive days] followed by 60 mg/prednisone/day for 3-4 weeks in most patients who had visual manifestations) (24, 35).

Full blood cell count and ESR were determined when the patient presented at the hospital. Other routine biochemistry parameters assessed in the present study were analyzed if they were determined prior to the onset or within the first 24 hours after the onset of the steroid therapy. However, when available, for the purpose of this study and to minimize the effect of treatment, C-reactive protein (CRP) levels were only analyzed if they were determined prior to steroid therapy or within the first 12 hours after the onset of this medication (31).

In the present study we assessed the following laboratory parameters: white blood cell count (WBC), hemoglobin, platelet count, ESR, CRP, alkaline phosphatase (ALP), and serum albumin.

Clinical definitions

Patients were classified as having biopsy-proven GCA associated with PMR when, besides the pathologic abnormalities in the TAB described above, they met the following criteria: 1) aged 50 years or older at the onset of symptoms, 2) severe and bilateral pain associated with morning stiffness (lasting at least 30 minutes) in at least 2 out of 3 areas: neck, shoulder and/or pelvic girdles, 3) ESR at the time of diagnosis of at least 40 mm/1st hour, and 4) exclusion of other diseases that may present with polymyalgia manifestations or mimic PMR except GCA (27-29, 36, 37).

As previously described, biopsy-proven GCA patients were considered to have visual manifestations if they suffered transient visual loss including amaurosis fugax, permanent visual loss, or diplopia (24,38). Also, patients were considered to have severe ischemic manifestations if they suffered visual manifestations, cerebrovascular accidents (stroke and/or transient ischemic attacks), jaw claudication or peripheral arteriopathy (large-artery stenosis of the extremities that caused signs of occlusive manifestations- limb claudication-of recent onset) (24, 34, 35).

Laboratory definitions

ESR was considered elevated if it was greater than 20 mm/1st hour. Leukocytosis if WBC was greater than 11,000/mm^3. Thrombocytosis if platelet count was greater than 400,000/mm^3. Anemia if hemoglobin value was less than 12 g/dl. Since the normal cut-off limit of ALP changed over the 26-year period of study according to the different methods used at Hospital Xeral-Calde to determine this parameter, as previously reported (31, 35) and for the purpose of this analysis, ALP was considered abnormal if values at diagnosis were >2 times above the upper normal range. Hypoalbuminemia if serum albumin level fell below 3.0 g/dl. CRP levels (measured until 2002 by nephelometry and since then by a latex immunoturbidity method) were considered abnormal if CRP values were greater than 5 mg/l (31).

Statistical analysis

Continuous data were described as mean and standard deviation (mean ± SD), and categorical variables as percentages. Categorical variables were compared using chi-squared test (or Fisher exact test when needed). When more than two ordered categories were compared, we used the Goodman-Kruskal gamma test for obtaining the *p*-value for

trend. Equality of means for continuous variables was tested by Student's *t*-test or ANOVA (when comparing more than two groups). The trend of age at GCA diagnosis was represented as 5-year moving average.Statistical significance was defined as $p \leq 0.05$. Calculations were performed with the statistical package Stata 8/SE (Stata Corporation, College Station, TX, USA).

Results

From 1981 to 2006 273 Lugo residents were diagnosed with biopsy-proven GCA. All of them met the 1990 American College of Rheumatology criteria for the classification of GCA (39).

Clinical and laboratory features

The mean age at the time of disease diagnosis was 75.1±6.8 years (median: 75 years; interquartile range: 71-80 years, range: 55-94 years). Women outnumbered men (146 [53.5%] *vs*. 127 [46.5%]).

Headache was the most common complaint observed in 229 (83.9%) patients. Sixty-one (22.3%) patients experienced visual ischemic complications. In 6 of them these manifestations occurred during admission (after the onset of corticosteroid therapy) while patients were receiving at least 40mg/prednisone/day. Thirty-five (12.8%) suffered irreversible (permanent) visual loss (unilateral or bilateral) that did not improve despite receiving corticosteroid therapy. No visual improvement was observed in patients who had visual loss prior to the onset of corticosteroid therapy when this treatment was delayed more than 48 hours. However, ocular complications were not found in patients treated with a dose of 40 mg/prednisone or greater for at least 72 hours. One hundred and five (38.5%) presented PMR manifestations. Anemia was observed in 151 (55.3%) and thrombocytosis in 135 (49.5%) of the patients. All patients had an ESR greater than 20 mm/1st hour at the time of disease diagnosis (mean ± SD: 94.0±22.5 mm/1st hour; median: 96 mm/1st hour; interquartile range: 78-110 mm/1st hour).

Evolution of the age at disease diagnosis according to sex for calendar-time

To establish whether there was a change in the age at disease diagnosis of biopsy-proven GCA patients over the 26-year period of study, 5-year moving averages for age at diagnosis of the disease were assessed (Fig. 1). Between 1981 and 1993 a trend for a gradual increase in the age at the time of disease diagnosis of GCA was found. However, from 1993 through 2006 this trend was no longer evident. In this regard, no statistically significant trend in the evolution of the mean age at the time of disease diagnosis over the whole period of study was found (*p*-value for men = 0.38, and *p*-value for women = 0.15).

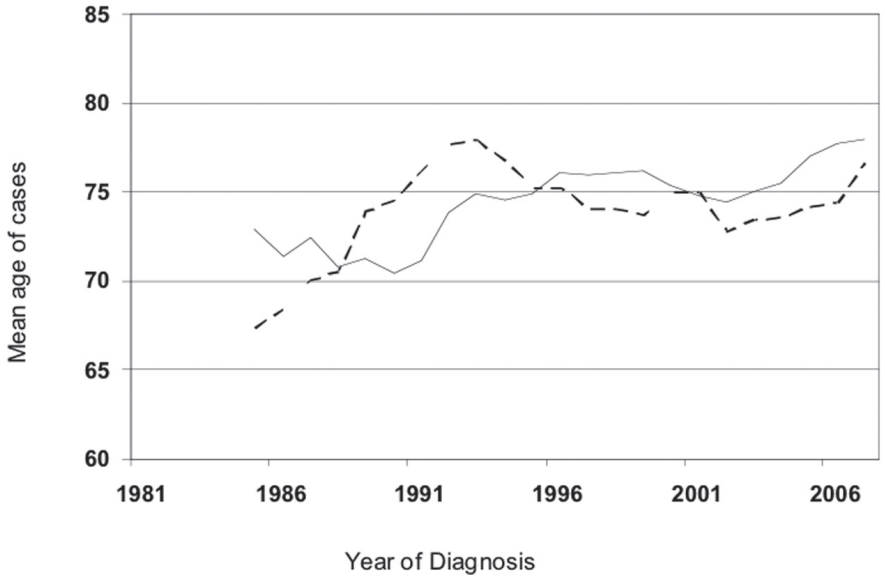

Fig. 1. Five-year moving averages for age at diagnosis of GCA. Solid line: women; dashed line: men.
ALP: Alkaline phosphatase; CI: Confidence intervals; CRP: C-reactive protein;
ESR: Erythrocyte sedimentation rate; GCA: Giant cell arteritis; PMR: Polymyalgia rheumatica; SD: Standard deviation; TAB: Temporal artery biopsy; WBC: White blood cell count.

Differences according to the mean age at the time of disease diagnosis

To start the analysis on the potential influence of the age in the clinical spectrum of the disease in this series of 273 patients with biopsy-proven GCA, we established two different groups according to the mean age at the time of disease diagnosis (75.1 years). However, apart from ALP, which was found to be more commonly found increased in patients 75.1 years of age or younger (29.5% *vs*. 18.1% in those older than 75.1 years; *p*=0.03), no other differences regarding clinical or laboratory findings were observed (data not shown).

Differences between patients under 70 years of age and those 70 or older

Since GCA is more common in individuals 70 years and older, in a further step we sought to determine whether differences might exist when patients younger than 70 years of age and those 70 years and older at the time of disease diagnosis were compared (Table I). Following this procedure, a statistically significant longer delay to the diagnosis was observed in patients younger than 70 years of age (13.2±12.8 weeks *vs*. 9.4±10.2 weeks in the group of GCA 70 years and older; *p*=0.03). Patients younger than 70 years presented more frequently PMR (54.4% *vs*. 35.2%; *p*=0.02). Although no significant differences in the incidence of visual ischemic manifestations or irreversible visual loss were seen between both age groups (Table I), cerebrovascular accidents and peripheral arteriopathy leading to limb claudication of recent onset were more commonly observed in patients younger than 70 years of age ($p \leq 0.03$ for both comparisons) (Table I). Again, as reported when patients were distributed according to the mean age at the time of disease diagnosis, a high ALP was more commonly found in patients younger than 70 years of age (43.5% *vs*. 20.3%; *p*=0.001).

Table I. Differences according to age less than 70 years or 70 years and older at the time of disease diagnosis in 273 patients with biopsy-proven GCA from Lugo (Northwestern Spain).

Age (years)	≤ 69 years (%) n=46 (16.8%)	≥ 70 years (%) n=227 (83.2%)	*p*
Delay to diagnosis (mean ± SD) weeks	13.2 ± 12.8	9.4 ± 10.2	0.03
Women	24 (52.2)	122 (53.7)	0.85
Constitutional syndrome	32 (69.6)	131 (57.7)	0.14
Fever (temperature ≥ 38ºC)	5 (10.9)	27 (11.9)	0.84
Headache	40 (87.0)	189 (83.3)	0.53
Abnormal temporal artery on physical examination	30 (66.2)	165 (72.7)	0.31
Scalp tenderness	13 (28.3)	78 (34.4)	0.42
Dysphagia	0 (0.0)	13 (5.7)	0.10
Jaw claudication	13 (28.3)	78 (34.4)	0.42
Polymyalgia rheumatica	25 (54.4)	80 (35.2)	0.02
Visual ischemic manifestations	9 (19.6)	52 (22.9)	0.62
Transient visual loss (including amaurosis fugax)	3 (6.5)	29 (12.8)	0.23
Irreversible visual loss	5 (10.9)	30 (13.2)	0.66
Cerebrovascular accidents	4 (8.7)	3 (1.3)	0.004
Peripheral arteriopathy of recent onset*	3 (6.5)	3 (1.3)	0.03
Severe ischemic manifestations	23 (50.0)	120 (52.9)	0.72
ESR (mean± SD) mm/1st hour	98.3 ± 22.2	93.1 ± 22.5	0.15
Hemoglobin (mean ± SD) g/dL	11.4 ± 1.6	11.8 ± 1.6	0.18
Anemia (Hemoglobin < 12 g/dL)	28 (60.9)	123 (59.2)	0.41
Platelet count (x10^{3}cells mm^3) (mean ± SD)	424 ± 151	401 ± 179	0.27
Thrombocytosis (>400,000/ mm^3)	26 (56.5)	109 (48.0)	0.29
WBC count (mm^3)	10076 ± 3308	9481 ± 2863	0.21
Leukocytosis /WBC > 11000/mm^3)	17 (37.0)	60 (26.4)	0.15
Albumin (g/dl)	3.3 ± 0.5	3.3 ± 0.6	0.87
Hypoalbuminemia (< 3g/dl)	8 (22.9)	55 (28.1)	0.52
Raised ALP	20 (43.5)	46 (20.3)	0.001
CRP** mg/L	86.1 ± 65.2	97.1 ± 62.9	0.49

*Limb claudication due to large artery stenosis.
**Tested in 18 patients with age < or equal to 69 years and 103 equal or greater than 70 years of age.

Differences according to the different age groups stratified by decades at the time of disease diagnosis

To determine if the clinical spectrum of the disease was different in the oldest patients (80 years and older), patients were stratified in three different groups; younger than 70 years, 70 to 79 years and 80 years and older (Table II). As described before, patients younger than 70 years of age had a longer delay to the diagnosis (13.2±12.8 weeks) than those 70-79 years (8.7±7.6 weeks) or 80 years and older (11.2±14.2 weeks) (p=0.03). Similarly, 4 of the 8 patients who experienced cerebrovascular accidents were younger than 70. In this regard, the frequency of cerebrovascular accidents was significantly increased in the younger age group (8.7%) compared to that found in patients 70-79 years (1.3%) or 80 years and older (1.4%) (p=0.03). Although a high ESR was found in the different age groups, individuals 70-79 years of age at the time of disease diagnosis had lower ESR values (90.2±22.8 mm/1st hour) than patients younger than 70 years of age (98.3±22.2 mm/1st hour) or older than 79 years (99.5±20.6 mm/1st hour) (p=0.005). It was also the case for hemoglobin levels that were higher in patients 70-79 years of age (mean 11.9 g/dl) than in the other two age groups (mean 11.4 g/dl in both age groups) (p=0.03). Also, the higher frequency of raised ALP observed in patients under 70 years of age remained statistically significant when patients 70 years and older were categorized in two different age groups (70-79 years of age and 80 years and older) (p=0.001). Other non-significant differences according to the age at the time of diagnosis are shown in Table II.

Discussion

GCA is the prototype of systemic vasculitis affecting elderly people (1-3, 5, 6). Due to this, an issue of major importance in the study of the epidemiology of GCA may be to determine if the age at the time of diagnosis of this vasculitis may influence the clinical spectrum of the disease. To assess this question we reviewed the clinical records of a large series of consecutive patients diagnosed with biopsy-proven GCA over a 26-year period. In this regard, the period of study included in the present study is one of the longest in a well-defined population that has been examined for biopsy-proven GCA.

In keeping with previous reports (3, 17, 18), the mean age at the time of disease diagnosis in biopsy-proven GCA patients from the Lugo region of Northwestern Spain was 75 years. Also, as reported in patients from Catalonia in Northeastern Spain (40), unlike initial reports from our group (28), this new study also supports the claim of a higher frequency of biopsy-proven GCA in women from Northwestern Spain.

We have recently reported a progressive decline in the number of patients with visual ischemic manifestations that was also linked to a significant trend for a decline in the frequency of permanent visual loss over the period 1981-2005 in Lugo (22). This fact was not due to an earlier diagnosis and different therapy (22). According to the results shown in the present study, the decline in the frequency of visual ischemic events is not due to a change in the age at disease diagnosis over the whole period of study.

The analysis of the age at disease diagnosis in the present series of 273 consecutive patients showed a statistically longer delay to the diagnosis of GCA in individuals younger than 70 years of age. This observation may indicate the need for higher physician awareness of this vasculitis among individuals under 70 years of age. Of particular interest, differences in the frequency of PMR between the different age groups were also evident. In this regard, more than 50% of patients diagnosed with GCA at an age under 70 years presented with PMR. However, a progressive decline in the frequency of PMR was observed

Table II. Differences according to the different age groups stratified by decades at the time of disease diagnosis in 273 patients with biopsy-proven GCA from Lugo (Northwestern Spain).

Age (years)	≤ 69 n=46 (16.8%)	70-79 n=156 (57.1%)	≥ 80 n=71 (26.0%)	*p*
Delay to diagnosis (mean ± SD) weeks	13.2 ± 12.8	8.7 ± 7.6	11.2 ± 14.2	0.03
Women	24 (52.2)	82 (52.6)	40 (56.3)	0.85
Constitutional syndrome	32 (69.6)	86 (55.1)	45 (63.4)	0.16
Fever (temperature ≥ 38ºC)	5 (10.9)	18 (11.5)	9 (12.7)	0.95
Headache	40 (87.0)	131 (84.0)	58 (81.7)	0.75
Abnormal temporal artery on physical examination	30 (65.2)	111 (71.2)	54 (76.1)	0.45
Scalp tenderness	13 (28.3)	61 (39.1)	17 (23.9)	0.06
Dysphagia	0 (0.0)	9 (5.8)	4 (5.6)	0.25
Jaw claudication	13 (28.3)	63 (40.4)	30 (42.3)	0.26
Polymyalgia rheumatica	25 (54.4)	61 (39.1)	19 (26.8)	0.01
Visual ischemic manifestations	9 (19.6)	35 (22.4)	17 (23.9)	0.86
Transient visual loss (including amaurosis fugax)	3 (6.5)	20 (12.8)	9 (12.7)	0.49
Irreversible visual loss	5 (10.9)	17 (10.9)	13 (18.3)	0.27
Cerebrovascular accidents	4 (8.7)	2 (1.3)	1 (1.4)	0.03
Peripheral arteriopathy of recent onset*	3 (6.5)	2(1.3)	1 (1.4)	0.12
Severe ischemic manifestations	23 (50.0)	82 (52.6)	38 (53.5)	0.93
ESR (mean± SD) mm/1st hour	98.3 ± 22.2	90.2 ± 22.8	99.5 ± 20.6	0.005
Hemoglobin (mean ± SD) g/dL	11.4 ± 1.6	11.9 ± 1.6	11.4 ± 1.7	0.03
Anemia (Hemoglobin < 12 g/dL)	28 (60.9)	78 (50.0)	45 (63.4)	0.12
Platelet count (x10^{3}cells mm^3) (mean ± SD)	424 ± 151	396 ± 131	411 ± 125	0.40
Thrombocytosis (>400,000/ mm^3)	26 (56.5)	70 (44.9)	39 (54.9)	0.21
WBC count (mm^3)	10076 ± 3308	9386 ± 2723	9693 ± 3159	0.35
Leukocytosis /WBC > 11000/mm^3)	17 (37.0)	38 (24.4)	22 (31.0)	0.21
Albumin (g/dl)	3.3 ± 0.5	3.3 ± 0.6	3.2 ± 0.6	0.54
Hypoalbuminemia (< 3g/dl)	8 (22.9)	33 (25.0)	22 (34.4)	0.31
Raised ALP	20 (43.5)	36 (23.1)	10 (14.1)	0.001
CRP** mg/L	86.1 ± 65.2	94.8 ± 66.3	103.5 ± 53.3	0.65

*Limb claudication due to large artery stenosis.
**Tested in 18 patients with age < or equal to 69 years, 75 aged 70-79 and 28 over 80 years old.

in individuals 70-79 years or older. Likewise, although no significant differences in the frequency of visual ischemic complications were found according to the age of disease diagnosis, severe and frequently irreversible vascular events such as cerebrovascular accidents or peripheral arteriopathy were more commonly observed in individuals under 70 years of age. In this regard, while the number of cases with visual loss tended to increase with aging the number of patients with cerebrovascular accidents decreased. It is possible that the longer diagnostic delay in the group of patients under 70 might explain in part these differences. However, the relatively small number of patients with cerebrovascular accidents observed in this series may reduce the clinical implication of the age in the occurrence of this finding.

GCA is clearly an age-restricted disease. Cases in individuals younger than 50 years are exceptional (3). Since genetic susceptibility to GCA has been observed (41-43), it is possible that changes in the immune system due to aging in some genetically predisposed individuals might explain the higher incidence of this vasculitis in people 70 years and older (44). However, the way aging of the immune system affects immune reactivity in a patient with GCA needs to be elucidated. It is known that decreased antibody production and shortened duration of protective immunity following immunization occurs in the elderly (45). These events may predispose to increased risk of infections in the elderly.

Hormonal influence plays a role in a wide variety of human autoimmune diseases. In this regard, it is known that dehydroepiandrosterone is able to influence the differentiation of T helper lymphocytes and thus the direction of immune response between T helper 1 and T helper 2 lymphocytes (46). Interestingly, a decrease in the production of dehydroepiandrosterone and other adrenal, such as dehydroepiandrosterone sulphate and adrostenedione, and gonadal steroids, leading to less inhibitory effects on the production of proinflammatory cytokines has been found in the elderly. With respect to this, Straub *et al*. reported that serum dehydroepiandrosterone, dehydroepiandrosterone sulphate, and adrostenedione decrease significantly whereas serum interleukin-6 levels increase significantly with age (47). Moreover, changes in the activity and reactivity of the hypothalamus-pituitary-adrenal axis have also been found in the elderly (48). Interestingly, in a recent study, Narvaez e*t al*. found that GCA patients with new-onset active disease before steroid therapy had normal serum values of ACTH and inappropriately normal cortisol levels in relation with the ongoing inflammation (49). These authors also reported significantly lower levels of dehydroepiandrosterone sulphate compared to age- and sex-matched controls (49). These results confirm the presence of relative adrenal hypofunction in GCA patients.

In line with the above, in assessing the polymorphisms of the promoter region of the corticotropin releasing hormone gene in biopsy-proven GCA patients, we observed that patients carrying the corticotropin releasing hormone -A2 allele had a higher frequency of visual ischemic complications (50).

In conclusion, the results from this study display clinical differences in the clinical spectrum of GCA according to the age of disease onset.

Acknowledgements

The authors thank Drs. Teresa Armada and Jaime Capellá from the Medical Record Department of the Hospital Xeral-Calde for their excellent collaboration in carrying out this study.

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