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Giant cell arteritis and polymyalgia rheumatica in northwestern Turkey: Clinical features and epidemiological data

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ABSTRACT

Objective. *In this study, we evaluated clinical and epidemiologic features of our giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) patients.*

Methods. *We retrospectively recorded down the general features of patients with GCA and PMR diagnosed at our center within the last 6 years. The incidence rates per 100000 aged ≥50 were calculated. In addition, we reported the frequencies of GCA/PMR in our previous epidemiologic study.*

Results. *Nineteen patients were diagnosed with GCA (10F, 9M) and 53 with isolated PMR (39F, 14M). The annual incidence for GCA in subjects ≥50 years old was 1.13/100000, and for PMR it was 3.15/100000. The incidence of GCA and PMR in females were, respectively, 1.14/100000 and 4.48/100000. In males, the incidences of GCA and PMR were, respectively, calculated as 1.1/100000 and 1.72/100000. In our population-based study, the prevalences of GCA and PMR (≥50 ages) were estimated as 20/100000. Fourteen (73.7%) GCA patients had symptoms of PMR. Two patients had developed unilateral and one patient bilateral permanent visual loss. Initial ESR was lower than 40 mm/hr in one GCA patient (5.3%) and in 6 PMR patients (11.3%). The median duration of follow-up was 16 months in GCA; and 8 months in PMR patients. One patient with PMR and another patient with GCA had lung cancer. One PMR patient had myelodysplastic syndrome. During follow-up, 4 patients with GCA died.*

Conclusions. *We detected a lower frequency of GCA/PMR in our center in northwestern Turkey than in Scandinavian and southern European countries.*

Introduction

Giant cell arteritis (GCA) is a vasculitis of unknown etiology and it involves medium and large-sized vessels in old people (1-3). Cranial ischemic complications are a source of major chronic disability in GCA patients (1, 3, 4). They are secondary to inflammation of the arterial wall, yielding to a series of structural changes, such as intimal hyperplasia and fragmentation of internal elastic laminae, resulting in luminal occlusion (5). Polymyalgia rheumatica (PMR) is encountered in the same population as GCA; typically, the patients present with severe pain and stiffness over the shoulders and pelvic girdle (6). GCA and PMR and often overlapping conditions in the elderly (7). Approximately 40% of patients with biopsy-proven GCA have PMR manifestations at the time of disease diagnosis (8). PMR may also be the initial manifestation in GCA patients without overt ischemic manifestations of this vasculitis (9). In this regard, a temporal artery biopsy may disclose histopathologic features of GCA in approximately 10% of patients who present with isolated PMR (7).

GCA is the most frequent type of vasculitis in western countries and it is more frequent in Scandinavian countries than in Mediterranean and southern European countries (10-14). A lower incidence of GCA was reported in Afro-American individuals (15). Also, GCA is very uncommon in Asian population. With respect to this, the prevalence of GCA in Japanese people patients 50 years of age and older in 1997 was only 1.47/100000 population (16). Epidemiological studies of GCA in different regions showed that the incidence of the disease has been progressively increasing (17-19). Nevertheless, there has been no study from Turkey evaluating the epidemiology of GCA and PMR.

As reported for GCA, the incidence of PMR is also higher in individuals of Scandinavian background than in populations from southern Europe (12, 20-22). In our study, we aimed to evaluate the epidemiology of GCA and PMR by taking into account patients being followed up at our center which is in Thrace region, located in southeastern Europe and northwestern Turkey. In addition, we evaluated the epidemiology of GCA and PMR detected in our previous field survey in the same region.

Patients and methods

We included 72 patients diagnosed with GCA and/or PMR between April 2002 to April 2008 at Trakya University Medical Faculty. The diagnosis of GCA in all cases was based upon the ACR criteria (17). Patients who had malignancy or another autoimmune disease

at diagnosis were not included. Other conditions mimicking PMR or presenting with polymyalgic features different from PMR associated to GCA were excluded in our study (23). The diagnosis of PMR was based upon previously defined criteria (24). Our hospital is the single tertiary referral center for rheumatic diseases for a mixed rural and urban population of almost of 1300000 people.

The clinical and demographic medical data about the patients were obtained from hospital files. All patients with GCA and PMR were initially treated with prednisone. Patients with PMR were started with prednisone 10 mg daily, treatment for GCA began with prednisone 40 to 60 mg daily. After the initial control of the disease, the dose of corticosteroids was progressively reduced according to clinical disease activity. After diagnosis, all selected patients underwent periodic examinations at the outpatient clinic until death or cessation of treatment and permanent disease remission. Relapse of GCA and PMR was defined as the return of signs and/or symptoms, along with regression of these signs or symptoms when the dosage of medication was increased or therapy was resumed. All patients were examined by a rheumatologist (ÖNP). The study design was approved by our local ethical committee. All subjects gave written informed consent.

There were one million, three hundred thousand people were living in the interland of our hospital. Of these, 280000 (135000 males, 145000 females) were 50 years of age or older. Age- and sex-specific incidence rates per 100000 population (the ratio of new cases diagnosed each year after January 2002 to population at risk) and prevalence (the ratio of all cases to population at risk) were calculated, based on the mid-year population. Data on the region population throughout the study period was collected from the State Statistical Institute. The population at risk was deemed to include people of 50 years of age or older.

In addition, we had previously investigated the prevalences of various rheumatic diseases including GCA and PMR in the Havsa district and its villages, in the Edirne Province which is in northwestern Turkey (25). The number of all participants was 17835 (mean age: 39.1, male/female: 0.99, rural/suburban: 2/1). Medical faculty students and physicians had visited the inhabitants' houses and face-to-face filled in a questionnaire with 20 questions about rheumatic diseases including past and current history of GCA and PMR. For new cases with suspect clinical findings, blood samples were obtained for antinuclear antibody and rheumatoid factor. Above-mentioned criteria had been used to diagnose GCA and PMR. Patients were considered to have PMR if they met these criteria and had a rapid and persistent response to corticosteroid treatment.

Analysis was performed by descriptive statistics, and further by chi-square analysis of contingency tables for the categorical variables. Continuous variables were compared by means of unpaired *t*-test.

Results

Nineteen patients were diagnosed with GCA (10 F, 9 M) and 53 with isolated PMR (39 F, 14 M). The mean age of GCA patients (70±6.8) was significantly higher than that of PMR patients (63.9±9.4) (p=0.005). The median time from the onset of complaints until diagnosis was 2 months in GCA patients and 5 months in PMR patients (p>0.05).

Fourteen (73.7%) GCA patients had symptoms of PMR. Constitutional symptoms like fever, weight loss were present in 15 (78.9%) of GCA and 26 (49.1%) of PMR patients (p=0.024). Eighteen (94.7%) GCA patients had headache; 9 (47.4%), jaw claudication; 11 (57.9%) tenderness of scalp, 12 (63.2%) tenderness of temporal area; and 7 (36.8%) had visual symptoms.

Two patients had developed unilateral and one patient bilateral permanent visual loss before initiation of steroid therapy. Their visual acuities did not improve after steroids. Biopsy of temporal artery was undertaken in 19 GCA patients; and in 13 cases (68.4%) the findings were compatible with GCA. Biopsy revealed giant cells in only 5 cases. Large vessel involvement (abdominal aortic aneurysm) was detected in one patient with GCA.

At the time of initial diagnosis, GCA patients had higher ESR (90.8±33.7 *vs*. 71.9±32 mm/hr, p=0.04), required higher steroid doses (36.5±22.1 vs. 14.6±7.7 mg/day, p=0.001) than PMR patients; and their duration of hospitalization (15.9±13.6 *vs*. 7±9 days, p=0.002) was also longer. In addition, the time for the normalization of ESR (11.5±15.6 *vs*. 7.8±16.2) and CRP (11.9±17 *vs*. 9.4±19.7) after steroid therapy was similar in GCA and in PMR patients (p-values >0.05).

Initial ESR was lower than 40 mm/hr in one GCA patient (5.3%) and in 6 PMR patients (11.3%). Initial CRP values of one GCA patient (5.3%) and 8 PMR patients (15.1%) were within normal ranges.

Median duration of follow-up was 16 months (3-80 months) in GCA patients; and 8 months (2-72 months) in PMR patients. Steroid-related osteonecrosis of the shoulder developed in one patient. Steroid-related symptomatic multiple vertebral compression fractures developed in one patient. During follow-up, one patient with PMR (one year after diagnosis) and another patient with GCA (8 years after diagnosis) developed lung cancer. One patient with PMR was diagnosed with myelodysplastic syndrome (9 months after diagnosis). During follow-up, cerebrovascular accident occurred in 2 GCA patients and acute myocardial infarction in 3 GCA patients. Until now, 4 patients with GCA died. One GCA patient died of pulmonary infection, another 2 GCA/PMR patients died of lung cancer. The PMR patient with myelodysplastic syndrome died of disease-related neutropenia plus pulmonary infection.

During follow-up, 15 patients relapsed. Relapses were characterized by recurrence of symptoms of PMR and elevation of ESR. Eight of all the recurrences (8/15) occurred within the first 6 months. The cause of 7 of these early recurrences (7/8) was steroid withdrawal. All relapses were treated by increasing the dose of steroids.

During the study period, the annual incidence for GCA for subjects 50 years of age or older was calculated as 1.13/100000, and the incidence for PMR was calculated as 3.15/100000.

The incidences of GCA and PMR for females older than 50 years of age or older were, respectively, 1.14/100000 and 4.48/100000. The incidences of GCA and PMR for males of similar ages were, respectively, 1.1/100000 and 1.72/100000.

In our population-based study in the same area, there was only one patient with GCA and another patient with PMR. The prevalences of GCA and PMR (≥50 years old) was estimated as 20/100000 (95% CI.: 0.016-0.024).

Discussion

In our study, we observed that the annual incidences of GCA and PMR were, respectively, 1.13 and 3.15 per 100000 population. Our previous study found a crude prevalence of 20/100000. Both of our values are quite lower than the frequencies in western studies. In Scandinavian countries, an annual incidence of more than 20/100000 has been reported among the population aged 50 years of age or older (1, 12-14, 20, 26, 27). The prevalences of PMR in subjects aged ≥50 years of age in Denmark and Sweden were reported to be quite frequent, respectively, 68.3/100000 (12) and 50/100000 (20). Contrarily, in southern Europe, however, the annual incidence in subjects older than 50 years old and older is lower than 12/100000 (11). The incidences in southern Europe vary; and GCA was detected to be 2 times more frequent in northwest Spain than in northern Italy (11, 21). One study from Reggio Emilia in Italy reported the prevalence of PMR as 12.7/100000 (21); similarly, another study from Spain found that the prevalence of total PMR was 18.7/100000 and isolated PMR was 13.5/100000 in people aged 50 years and older (22). A hospital-based study from Israel which included data for 25 years reported an annual incidence of 11.3/100000, similar to that in southern Europe (28). A recent epidemiologic study disclosed a very low prevalence (1.47 per 100000 population) of GCA in patients aged 50 years of age and older in 1997 in Japan (19). The prevalence in our study was lower than that in the western population, including southern Europe. However, it was slightly higher than the Japanese population. The results of our study are important because there are no epidemiological data on GCA/PMR in our region.

The regional differences in the prevalences of GCA and PMR are affected by not only genetic factors, but, also possibly by environmental factors. Various studies demonstrated that the onset of GCA was more frequent in late summer and in early spring (28, 29); and that there were different distinctive peaks in the annual incidence of GCA (28, 30, 31). Although no agent could be isolated until now, this condition points to infectious or other environmental etiologies. The follow-up period in our study was relatively short; therefore, we did not observe significant seasonal differences or peak incidence periods.

Countries like Israel and Spain report an increasing incidence in GCA (18, 19). The period of follow-up in our study was not long enough to reflect the increase in incidence. We observed that PMR in our GCA patients (73.7%) was quite frequent. When we compared subjects with isolated GCA to those with PMR, we observed that the mean age and ESR level and frequency of constitutional symptoms in isolated GCA patients were higher. These results were in accordance with a former population-based study that disclosed the same data when they compared patients with PMR associated to biopsy-proven GCA with those presenting with isolated PMR (32). Although an elevated ESR is an important finding in GCA/PMR, ESR lower than 40 mm/hr have been reported in GCA (4, 6) and also in isolated PMR (33). Similar to data reported in literature, at the time of initial diagnosis, one of our GCA patients (5.3%) and 6 of PMR patients (11.3%) had low ESR.

Important treatment complications were osteonecrosis, serious infection and multiple compression fractures. It was an interesting finding that these patients were without follow-up and they regulated the dose of their steroids by themselves.

Three of our patients with GCA/PMR developed malignancies. Classical necropsy-based studies suggested an association between active GCA and concurrent malignancy (34, 35). Recently, Liozon *et al*. (36) stated that the risk for the development of hematological and solid malignancy within the first year after the diagnosis of GCA was not low. However, there are also studies which did not find any increase in malignancies in GCA (12, 37, 38). Our main objective in that sudy was not to search for the incidence of malignancy. Nevertheless, although our follow-up was not long, it was noteworthy that most of the mortalities (3/4) were associated with malignancy.

We saw that relapses were relatively more frequent in our patients with GCA/PMR. Most of these relapses were early relapses. Detailed interrogation revealed that the majority of these relapses were related to steroid withdrawal. These patients were more likely to be of rural origin and have low sociocultural status. The dramatic influence of therapy might have made the patients assume that the disease has been cured. Another important result was that relapses were likely to be with findings of PMR even if the patient had GCA.

Our study had some limitations. First of all, it was a retrospective study with no prospective data. The second limitation was that although our center is the only referral center for rheumatology in our region, some patients might have gone to other centers. This might have prevented us from making a true generalization about our region.

As a result, we noted a lower frequency of GCA/PMR in our center in northwestern Turkey and southeastern Europe when compared to the southern European data. We cannot generalize our data as to the whole of Turkey because the frequencies of Behçet's disease versus FMF are lower in our region than in other regions reported from Turkey. We think that the reasons for this difference could be attributable to genetic factors.

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