Increased Mortality Due to Cardiovascular Disease in Patients with Giant Cell Arteritis in Northern Sweden

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ABSTRACT. ***Objective***. To study the cause of death pattern in patients with giant cell arteritis (GCA) or polymyalgia rheumatica (PMR), and to analyze the effect of the disease, or its therapy, on the risk of a cardiovascular event (CVE).

Methods. Patients with biopsy proven GCA or with PMR, whose condition was diagnosed between 1973 and 1979, were followed until December 31, 1995. The standardized mortality ratio (SMR) was estimated using data for the population of Västerbotten, Northern Sweden, as reference value. Information for sex, age at diagnosis, erythrocyte sedimentation rate (ESR) at diagnosis, corticosteroid therapy, comorbidity from diagnosis, and date and cause of death was collected.

Results. A total of 136 patients with GCA and 35 with PMR were identified. At the time of followup 114 patients with GCA and 25 with PMR were deceased. The overall mortality was significantly increased in the female patients, SMR = 133 (95% CI 110–162). Death due to cardiovascular disease (CVD) was significantly increased in both women and men, SMR = 149 (95% CI 118–189) and 158 (95% CI 112–224), respectively, and mainly due to ischemic heart disease. An excess mortality was found in women with the highest ESR, the highest prescribed dose of prednisolone at diagnosis, or a daily prednisolone dose of 10 mg or more one year after diagnosis. In multiple Cox regression analysis, male sex and hypertension significantly increased the risk of a CVE.

Conclusion. Death due to CVD was increased in patients with GCA. Increased mortality was related to either the corticosteroid therapy itself or insufficient control of inflammation. (J Rheumatol 2002;29:737–42)

Key Indexing Terms:
GIANT CELL ARTERITIS POLYMYALGIA RHEUMATICA MORTALITY
CARDIOVASCULAR DISEASE ISCHEMIC HEART DISEASE

Giant cell arteritis (GCA) is an inflammatory disease of the arteries that may result in fatal occlusion of cerebral or coronary arteries, or aneurysm of the aorta[1,2]. Corticosteroid therapy rapidly relieves the disease symptoms and is considered to prevent blindness due to ischemic optical neuropathy[3]. Reports of a low incidence of stroke or myocardial infarction in followup studies of GCA have led to the conclusion that these complications are prevented by the therapy[4-6]. However, autopsy studies have shown that vascular inflammation may continue for several years after initiation of corticosteroid therapy[1,7].

Most studies have shown that survival of patients with GCA is similar to that of control populations[4,8] and that the standard mortality ratio (SMR) is not increased[9,10]. However, in 1989, Nordborg and Bengtsson[11] reported an increased death rate compared with a control group only during the first months after diagnosis. Nesher, *et al*[12] found increased mortality during the first year, while Bisgård, *et al*[13] observed increased mortality over a 10 year period. Graham, *et al*[14] also found an increased death rate, but only in women.

The disease course in polymyalgia rheumatica (PMR) is considered benign and, compared with GCA, lower corticosteroid doses are required to control disease symptoms[15]. The distinction from biopsy negative GCA is sometimes difficult and fatal arteritis has been described in PMR based on autopsy studies[1]. Studies of PMR have been contradictory, with reports of an increased survival rate compared with a reference population[16], but also of increased mortality due to vascular disease during the first 2 years only in men[17].

We investigated the causes of death in patients with biopsy proven GCA or PMR. The effect of erythrocyte sedimentation rate (ESR) at diagnosis and corticosteroid therapy on the risk of death was analyzed. These variables, together with the presence of eye complications and the traditional risk factors for cardiovascular disease (CVD) (hypertension and diabetes mellitus), which are also associated with corticosteroid therapy, were used to test for the risk of a cardiovascular event (CVE).

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MATERIALS AND METHODS

Patients. All patients with GCA diagnosed by analysis of the temporal artery biopsy at the Department of Pathology, Umeå University Hospital, and all patients with PMR diagnosed at the Department of Rheumatology, Umeå University Hospital, between 1973 and 1979 were included in the study. The Department of Rheumatology, Umeå, in the county of Västerbotten, was the reference center for patients with PMR. Temporal artery biopsies were collected from the 4 northern-most counties of Sweden, of which Västerbotten is one. Medical records of all patients with GCA were reviewed. These patients also fulfilled ≥ 3 of the five 1990 American College of Rheumatology (ACR) classification criteria for GCA (traditional format)[18]. Medical records of all patients with PMR were reviewed and patients were included if they had proximal myalgia and fulfilled another 2 or more criteria suggested by Bird, *et al*[19]. The patients were followed through their medical records from diagnosis until December 1995 or death.

Information on the date and underlying cause of death was obtained from the records held by Statistics Sweden. The cause of death pattern for women and men in the county of Västerbotten for a single year in the middle of the study period (i.e., 1987) was obtained from Statistics Sweden and used as the reference population for statistical analysis.

Data collection. Data collected from medical records included age, sex, ESR, and prednisolone dose at diagnosis and at 12 months (± 2 mo) and the duration of prednisolone therapy. When other glucocorticosteroids were prescribed the equivalent doses of prednisolone were calculated and used in the analyses.

Data were also collected regarding treatment for hypertension and diabetes mellitus before and after diagnosis of GCA or PMR, and skeletal fractures after diagnosis, including symptomatic fractures of the vertebrae confirmed by radiography. Eye complications diagnosed by an ophthalmologist and that were due to arteritis were recorded.

Myocardial infarction was diagnosed according to WHO criteria[20]. Any cerebrovascular lesion was diagnosed by computerized tomography, or when a typical clinical picture with neurological deficits persisted for more than 24 hours. Transient ischemic attack was defined as a focal neurological deficit of presumed ischemic origin that persisted < 24 hours. Classification of a cardiovascular event also included dissecting aortic aneurysm, coronary angioplasty, amputation due to arterial insufficiency, pulmonary embolism diagnosed by pulmonary angiography or at autopsy, and deep vein thrombosis verified by phlebography. Information for fatal CVE was obtained from the medical record and/or autopsy for 32 patients and the registered cause of death of 6 patients.

Medical records of 6 patients after diagnosis were missing and incomplete for 2 other patients with GCA. Insufficient data on corticosteroid therapy included the initial dose in 4 patients with GCA, length of therapy in 5, and dose at 12 months in 8 patients with GCA and one with PMR. Two patients with GCA were receiving corticosteroid therapy due to bronchial asthma and rheumatoid arthritis (RA).

Statistical methods. SMR and 95% confidence intervals (CI) were calculated separately for female and male patients for overall and cause-specific mortality. Survival was calculated with Kaplan-Meier and comparison of survival within the patient groups was tested by log-rank test statistics. The Mann-Whitney U test was used for comparison of clinical data between patient groups. Results were expressed as medians with the interquartile range (IQR; 25th to 75th percentiles).

The time between diagnosis and CVE was analyzed by Cox regression incorporating the proportional hazard assumption. The relative risk (RR) was calculated with 95% CI. The variables sex, age at diagnosis, eye complications due to arteritis, GCA or PMR diagnosis, initial ESR, initial and 12 month prednisolone doses, and hypertension or diabetes mellitus after diagnosis were included as covariates, first individually in a simple Cox regression model and then simultaneously in a multiple Cox regression model. Additionally a separate analysis was performed for women only. The proportional hazard assumption was checked graphically by examining the log-log survival curves. In the above regression models, the dose of prednisolone was categorized into intervals: initial dose into 5–19, 20–39, and ≥ 40 mg, respectively; and the dose after 12 months into 0, 0.5–5.0, 5.5–9.5, and ≥ 10 mg intervals. Age was categorized into 10 year intervals.

RESULTS

There were 136 patients with biopsy proven GCA and 38 with the diagnosis of PMR. Of those patients registered as PMR it was not possible to confirm diagnosis from the medical records of 3 patients. Median time for followup in the remaining 171 patients from diagnosis until December 1995 or death was 10 years (range 0–22 yrs).

Mortality. At followup (i.e., December 1995) 139 patients had died, of whom 114 were patients with GCA (76 women, 38 men) and 25 patients with PMR (23 women, 2 men). Autopsy had been performed on 43 of the patients.

The overall mortality was significantly increased in the women with GCA or PMR, SMR = 133 (95% CI 110–162) (Table 1). Death due to CVD was significantly increased in both women and men, SMR = 149 (95% CI 118–189) and SMR = 158 (95% CI 112–224), respectively (Table 2). The increase was mainly due to ischemic heart disease (IHD), SMR = 151 (95% CI 107–213) and SMR = 189 (95% CI 123–287), respectively. The results were similar when analyzed for GCA patients only.

Female patients with ESR ≥ 110 mm/h at diagnosis, initial prednisolone dose ≤ 40 mg/day, or prednisolone dose 10 mg/day at 12 months had a significantly increased mortality (Table 3). Mortality due to CVD was higher in patients with GCA compared with PMR (p = 0.05). Overall survival rate did not differ between male and female patients (p = 0.26).

Morbidity after diagnosis. One or more CVE occurred in 101 of 167 (61%) patients after GCA or PMR was diagnosed. The most prevalent first events were

Table 1. Total mortality in 114 patients with GCA and 25 patients with PMR diagnosed 1973–79. Reference population: *County of Västerbotten*, Sweden, 1987.

Age at Entry, yrs	Number of Person–yrs	Number of Deaths Observed	Expected	SMR	95% CI
Women					
50–69	302	6	2.6	231	106–504
70–79	642	36	21.2	170	123–235
80–89	390	47	38.1	123	93–164
90–99	54	10	12.4	81	44–150
50–99	1388	99	74.3	133	110–162
Men					
50–69	133	6	3.1	192	87–420
70–79	225	15	12.2	123	74–203
80–89	112	17	15.5	110	69–177
90–99	3	2	1.0	205	53–798
50–99	473	40	31.8	126	92–171

SMR: standardized mortality ratio;
CI: confidence interval.

Table 2. Cause-specific mortality in 114 patients with GCA and 25 patients with PMR diagnosed 1973–79, according to the International Classification of Diseases (ICD), 9th revision. Reference population: *County of Västerbotten,* Sweden, 1987.

Cause of Death	ICD–9	Number of Deaths		SMR	95% CI
		Observed	Expected		
GCA and PMR					
Women					
Malignancy	140–239	7	11.4	61	30–128
Cardiovascular disease	390–459	68	45.5	149	118–189
Ischemic heart disease	410–414	32	21.2	151	107–213
Cerebrovascular disease	430–439	15	10.7	140	85–231
Aneurysm	441–442	3	1.3	224	74–673
Total	000–999	99	74.3	133	110–162
Men					
Malignancy	140–239	2	5.2	39	10–147
Cardiovascular disease	390–459	31	19.6	158	112–224
Ischemic heart disease	410–414	21	11.1	189	123–287
Cerebrovascular disease	430–439	2	3.6	55	14–217
Aneurysm	441–442	1	0.9	114	16–808
Total	000–999	40	31.8	126	92–171
GCA					
Women					
Malignancy	140–239	5	8.2	61	26–145
Cardiovascular disease	390–459	53	32.9	161	123–210
Ischemic heart disease	410–414	24	15.3	157	105–233
Cerebrovascular disease	430–439	11	7.8	142	79–255
Aneurysm	441–442	2	1.0	208	54–805
Total	000–999	76	53.6	142	113–177
Men					
Malignancy	140–239	2	4.9	41	11–157
Cardiovascular disease	390–459	29	18.9	154	107–220
Ischemic heart disease	410–414	19	10.6	180	115–279
Cerebrovascular disease	430–439	2	3.4	58	15–228
Aneurysm	441–442	1	0.8	120	17–849
Total	000–999	38	30.6	124	90–170

SMR: standardized mortality ratio; CI: confidence interval.

cerebrovascular accident/transient ischemic attack in 40 patients and acute myocardial infarction in 38 patients. Aortic aneurysm was diagnosed in 4 patients. The first event was fatal in 38 patients.

The prevalence of hypertension and diabetes mellitus at diagnosis and at followup and fractures after diagnosis is presented in Table 4. After diagnosis the prevalence of diabetes mellitus and hypertension was similar in patients with GCA and with PMR. Patients with hypertension were not prescribed higher corticosteroid doses initially or 12 months after diagnosis (data not shown). Fractures after diagnosis were significantly more common in female patients with GCA or PMR, 43/121 (36%) compared with the male patients: 6/42 (14%); $p < 0.01$. Vertebral fractures were diagnosed after GCA/PMR diagnosis in 23 patients, and limb fractures in 30 patients, of whom 4 had had both vertebral and limb fractures.

Cox regression of time to CVE. In a simple Cox regression analysis, men had significantly higher risk of CVE than women, with a relative risk (RR) of 1.75 (95% CI 1.15–2.68). In multiple Cox regression analysis using the first CVE as the dependent variable, hypertension after diagnosis of GCA or PMR was associated with a significantly increased RR, 1.78 (95% CI 1.11–2.83). This finding was confirmed in a separate analysis of women, for whom age was also a significant risk factor, RR 1.45 (95% CI 1.00–2.11).

Clinical data and corticosteroid therapy. Data on age of patients, ESR, corticosteroid dose at diagnosis, and duration of therapy by diagnosis are shown in Table 5. Prednisolone dose and ESR at diagnosis were significantly higher in patients with GCA compared with those with PMR. The median duration of prednisolone therapy in the 111 patients whose corticosteroid therapy had been discontinued before death was 2.8 years for GCA and 2.7 years for PMR. Forty-two patients were taking prednisolone at time of death, and 6 (19%) of the 32 patients surviving at December 1995 continued corticosteroid therapy. Two patients with GCA and 4 with PMR never received corticosteroids.

Twenty-nine (17%) of 170 patients had eye complications due to arteritis. Eye symptoms preceded corticosteroid therapy in 26 patients and appeared during therapy in

Table 3. Mortality in all patients by ESR at diagnosis, initial prednisolone dose, and 12 months later.

	Number of Deaths			
	Observed	Expected	SMR	95% CI
ESR at diagnosis, mm/h				
Women				
0–69	21	14.9	141	92–215
70–109	43	38.1	113	84–152
110-	28	15.7	178	124–256
Men				
0–69	5	4.4	113	47–271
70–109	17	11.2	152	95–243
110–	17	15.7	108	67–174
Initial prednisolone dose, mg/day				
Women				
5–19	21	17.0	124	81–189
20–39	32	29.7	108	76–152
40–	37	21.2	175	127–240
Men				
5–19	6	4.8	124	56–275
20–39	17	10.9	156	97–250
40–	15	14.7	102	62–169
Prednisolone dose at 12 mo, mg/day				
Women				
0	10	8.1	123	66–228
0.5–5	32	26.0	123	87–173
5.5–9.5	16	17.5	92	56–149
10–	22	14.0	157	104–238
Men				
0	5	5.1	98	41–234
0.5–5	17	14.5	117	73–188
5.5–9.5	7	5.8	120	57–250
10–	7	5.6	124	59–260

SMR: standardized mortality ratio; CI: confidence interval.

Table 4. Prevalence of diabetes mellitus and hypertension at diagnosis and at followup and fractures after diagnosis in patients with GCA and with PMR.

	GCA n (%)	PMR n (%)	Total n (%)
Diabetes mellitus			
At diagnosis	8/135 (5.9)	2/35 (5.7)	10/170 (5.9)
After diagnosis	25/128 (20)	5/35 (14)	30/163 (18)
Hypertension			
At diagnosis	39/134 (29)	15/35 (43)	54/169 (32)
After diagnosis	56/130 (43)	20/35 (57)	76/165 (46)
Fracture			
After diagnosis	39/128 (31)	10/35 (29)	49/163 (30)

Table 5. Clinical data and prednisolone therapy in 136 patients with giant cell arteritis (GCA) and 35 patients with polymyalgia rheumatica (PMR). Medians (interquartile range).

	GCA	PMR	p
At diagnosis			
Age, yrs	71 (66–76)	68 (64–74)	NS
ESR, mm/h	99 (71–115)	90 (73–100)	< 0.05
Prednisolone dose, mg/day	30 (20–49)	10 (5–20)	< 0.001
Prednisolone dose at 12 mo, mg/day	5.0 (2.5–10.0)	5.0 (0.2–7.4)	NS
Duration of therapy, mo	35 (17–58)	28 (12–62)	NS

NS: not significant.

3 patients after 6, 5, and 3 months, respectively. Two of them were clearly taking inadequate corticosteroid doses previous to eye complications. The third patient seemed to require unusually high doses of corticosteroids. Eye complications were amaurosis fugax (n = 9), permanent visual loss in one eye (n = 12) or both eyes (n = 1), blurred vision (n = 4), and diplopia (n = 3). Two patients with PMR had clinical symptoms of GCA with eye complications but a negative temporal artery biopsy. Another patient, without clinical GCA at known onset of disease, had a positive temporal artery biopsy after 7 years. Two patients with biopsy proven GCA also had RA according to the 1987 ACR criteria, with disease duration of 19 and 20 years, respectively.

DISCUSSION

Giant cell arteritis was associated with an increased overall mortality in women. Our finding confirms 2 earlier studies that reported an increased overall mortality in patients with GCA[12,13]. Previous contradictory results[4,5,8-10] might be due to the relatively short followup time, which means that possible effects of late complications of the disease, or therapy, were not detected. Also, genetic and environmental differences between populations might influence the severity of the disease and the late complications. The excess mortality in women with high ESR at diagnosis and high prednisolone doses either initially or after a year indicate that the severity of the inflammation, or its treatment, increased the risk for death. This contrasts with 2 recent reports from Spain that show negative correlation between a strong inflammatory response and cranial ischemic complications in early disease[21,22]. In a study of patients with biopsy proven GCA Graham, *et al* found that a maintenance dose of more than 10 mg prednisolone daily predicted lower survival in the patients. The authors concluded that the increased mortality rate was associated with the therapy itself[14].

When causes of death were considered, increased mortality due to CVD and IHD was found in both men and women. In Northern Sweden mortality due to CVD is high, according to the WHO MONICA study[23], thus the reference population from Västerbotten was used instead of the population from all of Sweden. Malignancy as cause of death was not found to be increased, in accord with an earlier report[24].

The etiology and pathogenesis of CVD in GCA is probably multifactorial. The local inflammation of arteries in GCA is distinguished morphologically from atheromatosis.

In GCA, the inflammatory process extends throughout the arterial wall from the neovessels in the adventitia into the intimal layer, providing alternative sites for endothelial injury. Histopathologically, local vasculitic changes are found in the arterial wall in GCA patients with fatal vascular complications[1,7]. Increased mortality due to vascular disease early after diagnosis of GCA has been verified by autopsy and interpreted as lack of control of inflammation[11]. Several months or years after diagnosis, CVD may be seen as a complication due to atherosclerosis, and an association to the vasculitis goes unrecognized.

There is increasing evidence that inflammation continues in patients with GCA or PMR despite therapy. Longstanding elevation of von Willebrand factor in GCA[25] and PMR[26] during corticosteroid therapy suggests a continued endothelial dysfunction. Proinflammatory cytokines, such as interleukin 6 (IL-6), are produced in areas of vasculitis and from circulating monocytes in untreated GCA[27]. Continued elevated plasma IL-6 levels during corticosteroid treatment have been found in a subset of patients with GCA[28] and in patients with PMR even during clinical remission[29]. Intercellular adhesion molecule-1 (ICAM-1) is upregulated by proinflammatory cytokines and is expressed in the vascular lesions seen in patients with GCA[30]. Elevated serum levels of soluble (s) ICAM-1 have been found in active PMR and GCA[31,32].

Increased levels of markers of inflammation such as C-reactive protein[33] and sICAM-1[34] are independent risk factors for future coronary events in otherwise healthy individuals. Consequently, the continued systemic inflammation in GCA might accelerate, or trigger, a preexisting atherosclerosis and/or a procoagulant state. Previous arterial disease and smoking are independent risk factors for GCA in women[35], suggesting that the patients are predisposed for CVD.

Studies in patients with PMR have included either temporal artery biopsy positive patients or biopsy negative GCA patients[16,17], and report an expected survival rate equivalent to that of controls[16]. However, cardiovascular death was overrepresented in male patients with PMR[17]. The subgroup of PMR patients in our study was too small to permit conclusive results on mortality. Within the patient group there was a better survival in PMR patients compared to GCA patients; this supports the opinion of PMR as a more benign disease than GCA. The main difference in therapy was lower initial prednisolone doses in the PMR versus GCA patients, in agreement with the recommendations at the time[15].

Our study does not allow us to distinguish the contribution of corticosteroid therapy per se to mortality rates. Corticosteroid treatment is associated with a considerable number of possible side effects[36], and in GCA and PMR is related to increased comorbidity[12,37]. In a study of 43 patients in Israel, corticosteroid therapy was reported to increase mortality in early disease due to infection[12]. Infection as a cause of death was uncommon in our patients, probably as the corticosteroid doses were relatively low or because of epidemiological differences.

Corticosteroid therapy has been associated with premature cardiovascular complications in systemic lupus erythematosus and related to steroid induced hypercholesterolemia and hypertension[38]. In patients with PMR, serum cholesterol levels are normal and those of lipoprotein(a), a strong atherogenic factor, normalize during corticosteroid therapy[39]. Although hypertension, but not diabetes mellitus, predicted a cardiovascular event in our study, there was no relationship between the corticosteroid doses and hypertension. However, as there is impaired endothelial function in hypertension[40], the presence of hypertension might add to the damage caused by the endothelial inflammation in GCA.

Plasminogen activator inhibitor-1 (PAI-1) is a risk factor for recurrent infarction in patients with recent myocardial infarction[41]. Glucocorticoids induce PAI-1 synthesis in a variety of cells and tissues[42]. We have shown[26] that serum levels of PAI-1 increase rapidly with corticosteroid therapy in patients with PMR. Thus, the therapy itself might induce and/or maintain a decrease in fibrinolytic activity in the patients.

To conclude, increased mortality in patients with GCA was due to CVD, particularly IHD. An association with corticosteroid therapy is difficult to identify. Is there a direct effect of corticosteriods, or an indirect effect caused by reduced fibrinolysis, or is the association due to an extensive and continued inflammation that is not treated adequately?

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REFERENCES

1. Save-Sopderberg J, Malmwall B-E, Andersson R, Bengtsson B-Å. Giant cell arteritis as a cause of death. JAMA 1986;255:493-6.
2. Evans JM, Batts KP, Hunder GG. Persistent giant cell arteritis despite corticosteroid treatment. Mayo Clin Proc 1994;69:1060-1.
3. Myles AB, Perera T, Ridley MG. Prevention of blindness in giant cell arteritis by corticosteroid treatment. Br J Rheumatol 1992;31:103-5.
4. Huston KA, Hunder GG, Lie JT, Kennedy RH, Elveback LR. Temporal arteritis. A 25-year epidemiologic, clinical and pathologic study. Ann Intern Med 1978;88:162-7.
5. Bengtsson B-A, Malmvall B-E. Prognosis of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. Acta Med Scand 1981;209:337-45.
6. Von Knorring J. Treatment and prognosis in polymyalgia rheumatica and temporal arteritis. A ten-year survey of 53 patients. Acta Med Scand 1979;205:429-35.
7. Lie JT. Aortic and extracranial large vessel giant cell arteritis: A review of 72 cases with histopathologic documentation. Semin Arthritis Rheum 1995;24:422-31.
8. Andersson R, Malmvall BE, Bengtsson B-Å. Long-term survival in giant cell arteritis including temporal arteritis and polymyalgia rheumatica: a follow-up study of 90 patients treated with

corticosteroids. Acta Med Scand 1986;220:361-4.
9. Matteson EL, Gold KN, Bloch DA, Hunder GG. Long-term survival of patients with giant cell arteritis in the American College of Rheumatology giant cell arteritis classification criteria cohort. Am J Med 1996;100:193-6.
10. Gonzalez-Gay MA, Blanco R, Abraira V, et al. Giant cell arteritis in Lugo, Spain, is associated with low longterm mortality. J Rheumatol 1997;24:2171-6.
11. Nordborg E, Bengtsson B-A. Death rates and causes of death in 284 consecutive patients with giant cell arteritis confirmed by biopsy. BMJ 1989;299:549-50.
12. Nesher G, Sonnenblick M, Friedlander Y. Analysis of steroid related complications and mortality in temporal arteritis: A 15-year survey of 43 patients. J Rheumatol 1994;21:1283-6.
13. Bisgard C, Sloth H, Keiding N, Juel K. Excess mortality in giant cell arteritis. J Intern Med 1991;230:119-23.
14. Graham E, Holland A, Avery A, Russell RW. Prognosis in giant-cell arteritis. BMJ 1981;282:269-71.
15. Mowat AG, Hazleman BL. Polymyalgia rheumatica — a clinical study with particular reference to arterial disease. J Rheumatol 1974;1:190-202.
16. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. Epidemiology of polymyalgia rheumatica in Olmsted County, Minnesota, 1970-1991. Arthritis Rheum 1995;38:369-73.
17. Schaufelberger C, Bengtsson B-A, Andersson R. Epidemiology and mortality in 220 patients with polymyalgia rheumatica. Br J Rheumatol 1995;34:261-4.
18. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-8.
19. Bird HA, Esselinckx W, Dixon ASTJ, Mowat AG, Wood PHN. An evaluation of criteria for polymyalgia rheumatica. Ann Rheum Dis 1979;38:434-9.
20. Nomenclature and criteria for diagnosis of ischemic heart disease; Report of the Joint International Society and Federation of Cardiology/World Health Organisation Task Force on Standardization of Clinical Nomenclature. Circulation 1979;59:607-9.
21. Cid MC, Font C, Oristrell J, et al. Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. Arthritis Rheum 1998;41:26-32.
22. Gonzalez-Gay MA, García-Porrua C, Llorca J, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine (Baltimore) 2000;79:283-92.
23. Tuomilehto J, Kuulasma K, Torppa J. WHO-MONICA Project: Geographic variation in mortality from cardiovascular diseases — baseline data on the population demographics and cardiovascular mortality in the WHO-MONICA Project. World Health Stat Q 1987;40:171-84.
24. Haga H-J, Eide GE, Brun J, Johansen A, Langmark F. Cancer in association with polymyalgia rheumatica and temporal arteritis. J Rheumatol 1993;20:1335-9.
25. Cid MC, Monteagudo J, Oristrell J, et al. Von Willebrand factor in the outcome of temporal arteritis. Ann Rheum Dis 1996;55:927-30.
26. Uddhammar A, Nilsson TK, Rantapää-Dahlqvist S. A long term follow-up study of von Willebrand factor and plasminogen activator inhibitor-1 in patients with polymyalgia rheumatica. Ann Rheum Dis 1997;56:698-9.
27. Wagner AD, Goronzy JJ, Weyand CM. Functional profile of tissue-infiltrating and circulating CD68+ cells in giant cell arteritis — evidence for two components of the disease. J Clin Invest 1994;94:1134-40.
28. Weyand CM, Fulbright JW, Hunder GG, Evans JM, Goronzy JJ. Treatment of giant cell arteritis. Interleukin-6 as a biological marker of disease activity. Arthritis Rheum 2000;43:1041-8.
29. Weyand CM, Fulbright JW, Evans JM, Hunder GG, Goronzy JJ. Corticosteroid requirements in polymyalgia rheumatica. Arch Intern Med 1999;159:577-84.
30. Wawryk SO, Ayberk H, Boyd AW, Rode J. Analysis of adhesion molecules in the immunopathogenesis of giant cell arteritis. J Clin Pathol 1991;44:497-501.
31. Macchioni P, Boiardi L, Meliconi R, et al. Elevated soluble intercellular adhesion molecule-1 in the serum of patients with polymyalgia rheumatica: influence of steroid treatment. J Rheumatol 1994;21:1860-4.
32. Uddhammar A, Sundqvist K-G, Ellis B, Rantapää-Dahlqvist S. Cytokines and adhesion molecules in patients with polymyalgia rheumatica. Br J Rheumatol 1998;37:766-9.
33. Koenig W, Sund M, Frolich M, et al. C-reactive protein, a sensitive marker for inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men. Results from the MONICA-Augsberg Cohort Study 1984-1992. Circulation 1999;99:237-42.
34. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampger MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risk of future myocardial infarction in apparently healthy men. Lancet 1998;351:88-92.
35. Duhaut P, Pinede L, Demolombe-Rague S, et al. Giant cell arteritis and cardiovascular risk factors. Arthritis Rheum 1998;41:1960-5.
36. Maxwell SRJ, Moots RJ, Kendall MJ. Corticosteroids: do they damage the cardiovascular system? [review]. Postgrad Med J 1994;70:863-70.
37. Gabriel SE, Sunuku J, Salvarani C, O'Fallon WM, Hunder GG. Adverse outcome of antiinflammatory therapy among patients with polymyalgia rheumatica. Arthritis Rheum 1997;40:1873-8.
38. Petri M, Perez-Gutthann S, Spence P, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992;93:513-9.
39. Wallberg-Jonsson S, Uddhammar A, Dahlén G, Rantapää-Dahlqvist S. Lipoprotein(a) in relation to acute phase reaction in patients with rheumatoid arthritits and polymyalgia rheumatica. Scand J Clin Lab Invest 1995;55:309-15.
40. Puddu P, Puddu GM, Zaca F, Muscari A. Endothelial dysfunction in hypertension. Acta Cardiol 2000;55:221-32.
41. Hamsten A, de Faire U, Waldius G, et al. Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. Lancet 1987;2:3-9.
42. Morange PE, Aubert J, Peiretti F, et al. Glucocorticoids and insulin promote plasminogen activator inhibitor 1 production by human adipose tissue. Diabetes 1999;48:890-5.