EXTENDED REPORTS

Biopsy proven and biopsy negative temporal arteritis: differences in clinical spectrum at the onset of the disease

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Abstract

***Objectives*—To assess the clinical features of biopsy proven and negative biopsy temporal arteritis at the time of diagnosis and during a three year follow up.**

***Methods*—Newly diagnosed cases of giant cell arteritis were included in a prospective, multicentre study. Initial clinical and biological features, season of diagnosis, and cardiovascular events occurring during the follow up were recorded. Biopsy proven and negative biopsy cases were compared.**

***Results*—Two hundred and seven biopsy proven, and 85 negative biopsy cases were included from 1991 to 1997. Fifty eight per cent of the biopsy proven cases, compared with 39.29% of the negative biopsy cases, were diagnosed during the autumn or winter (p = 0.003). Visual problems (31.5%, *v* 19.1%, p = 0.031), blindness (9.7% *v* 2.38%, p = 0.033), jaw claudication (40.8%, *v* 28.243%, p = 0.044), and temporal artery palpation abnormalities (61.3% *v* 29.5%, p = 7.10^{-7}) were more frequent in the biopsy proven than in the negative biopsy group. Less specific symptoms, such as headache (82.5% *v* 92.9%, p = 0.021), or associated polymyalgia rheumatica (40.1% *v* 65.9%, p = 9×10^{-5}) were more prevalent in the negative biopsy cases. Biological markers of inflammation were significantly more increased in the biopsy proven group. All cases of blindness occurring after treatment belonged to the biopsy proven group.**

***Conclusion*—Biopsy proven cases seem to be more severe than biopsy negative cases at the time of diagnosis and during follow up. Seasonal difference at diagnosis may suggest a different aetiological pattern.**

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Giant cell arteritis (GCA) is an inflammatory disease of the medium sized arteries, mainly affecting patients over 50. It is associated with polymyalgia rheumatica (PMR) in 40% of the cases.[1–4] In typical cases, it is characterised by multinucleated giant cells and an infiltrate of plasmocytes, lymphocytes and neutrophils in the artery wall.[5] However, the temporal artery biopsy may be normal in 42% to 61% of the patients[6–8] and the diagnosis in that case is made on the clinical features and the presence of a biological inflammatory syndrome. It is usually believed that the biopsy may be negative because the pathological lesion is segmental and localised to some fragments of the artery wall, whereas other fragments are free of the lesion.[5] As the diagnosis of negative biopsy temporal arteritis (TA) relies on the signs and symptoms that have been recognised in positive biopsy temporal arteritis, it is also usually accepted in the large epidemiological studies that both positive and negative biopsy temporal arteritis share the same clinical features and represent the same disease.[2 3 9–12] In the American College of Rheumatology classification, a positive temporal artery biopsy represents one diagnostic criteria among others, such as jaw claudication, increased sedimentation rate, age over 50 or headache.[13] However, no study has included enough cases to ascertain the similarities or the differences between biopsy proven and negative biopsy temporal arteritis.

We designed a multicentre, prospective study on incident cases of GCA, and we determined at the time of diagnosis, based on pre-established clinical, biological and pathological criteria, the initial features of patients with positive biopsy and of patients with negative temporal artery biopsy.

Some studies have suggested that cardiovascular events were more frequent in GCA patients than in the general population, even if these events did not always increase the mortality rate.[14–16] We followed up the patients for up to 36 months, and the incidence of ocular complications and of cardiovascular events was recorded in each group.

Methods

Every department of internal medicine, rheumatology, geriatrics, neurology and ophthalmology of university hospitals in France, and each of

Table 1 Predefined inclusion criteria

1	Age over 50.
2	Erythrocyte sedimentation rate above 40 mm 1st h by the Westergren method.
3	Clinical response within 72 hours to corticosteroid treatment (disappearance of fever or pain).
4	Positive temporal artery biopsy.
	Temporal arteritis signs
5	Clinically abnormal temporal artery (tenderness, swelling, redness, nodular artery).
	Temporal arteritis symptoms
6	Visual disturbances (blindness, diplopia, blurred vision) including those occurring during the first week of treatment.
7	Jaw claudication.
8	Temporal headache, headache, facial pain or sensation of facial swelling.
	General symptoms
9	Systemic symptoms, such as fever, weight loss >10% of total weight, anorexia, malaise, asthenia.
	Polymyalgia rheumatica symptoms
10	Persistent proximal muscle pain, tenderness or morning stiffness lasting more than one hour, involving neck, shoulders and/or pelvic girdle (duration more than two weeks).

these departments in the general hospitals of the Rhône-Alpes Region, was contacted in January 1991.

For each new patient, a questionnaire reporting the medical history and clinical examination data had to be filled, and a blood sample had to be taken before corticosteroid treatment or at the latest 48 hours after its onset. The questionnaire was to be completed directly with the patient, and not from the data recorded in the medical chart. Only incident cases on pre-established diagnostic criteria were included, to avoid at best misclassification and recall bias. A copy of the temporal artery biopsy interpretation was requested, and the slides on which the diagnosis of positive or negative biopsy was made were reviewed by one expert pathologist in Louis Pradel Hospital, Lyons, according to MacDonnel's criteria.[5] When the biopsy specimen itself could not be obtained, the initial biopsy interpretation was reviewed (8% of the cases). The biopsy was unilateral in all but two cases.

Table 1 lists the pre-established diagnostic criteria. All patients had to fulfil criteria 1, 2 and 3.

In addition to these three criteria: (1) patients included in the positive biopsy TA group needed to have criterion 4. (2) Patients included in the negative biopsy TA group had to fulfil two criteria among criteria 5, 6, 7, 8, and 9. Criterion 10 could be present, or not.

Exclusion criteria consisted in current malignant diseases, current infectious diseases, history of rheumatoid arthritis, systemic lupus erythematosus, and periarteritis nodosa. Patients with PMR alone, without any sign of TA as defined by criteria 5 to 8, were excluded from the study.

The patients were included on the basis of the pre-defined criteria by the participating physicians. They were classified into subgroups once the inclusion criteria were reviewed by the coordinating centre, and the biopsy reviewed by the referent pathologist. A positive response to corticosteroids was required for all patients, and this was assessed by the participating physicians before the inclusion questionnaire was sent to the coordinating centre. The temporal artery biopsy was performed before corticosteroid treatment, or at the latest 72 hours after its beginning.

VARIABLES AT THE TIME OF DIAGNOSIS

The data collected were of three types:

Initial clinical signs and symptoms: characteristics of the palpation of the temporal artery, such as rigidity, visible inflammation, nodules; visual problems, such as blindness, diplopia, or blurred vision; jaw claudication; recent headache, whether temporal, diffuse, or facial; systemic symptoms, such as fever, anorexia, malaise, weight loss, asthenia; symptoms of PMR, as long as they were associated with symptoms of TA.

Biological data: erythrocyte sedimentation rate (ESR) (Westergren method), C reactive protein (CRP), haptoglobin, orosomucoid, α2 macroglobulin, fibrinogen, haemoglobin level, mean globular volume, platelet count. Free thyroxine and thyroid stimulating hormone were measured by standard radioimmunoassays (Immunotech, CIS Bio International, France and Dynotest anti-TPO, Germany, respectively).

The time of diagnosis, and the delay between the onset of the symptoms and the diagnosis.

Cardiovascular risk factors, such as total cholesterol, glycaemia and history of diabetes, smoking and history of smoking, blood pressure and history of hypertension. The presence of symptomatic lower limb arteritis was assessed by the patient's interview (including history of vascular surgery, angioplasty or sympathectomy). Data about the palpation of the carotid, radial, femoral, dorsalis pedis and posterior tibial pulses, and about the auscultation of the carotic, abdominal aorta, femoral and popliteal arteries, were recorded.

VARIABLES COLLECTED DURING FOLLOW UP

Patients were followed up for up to 36 months. The specialist who included the patient, or the general practitioner who followed up the patient after the hospitalisation, filled up a questionnaire every six months with the following data:

(1) Occurrence of blindness, blurred vision, of cardiovascular events such as myocardial infarction, transient ischaemic attack, stroke, lower limbs arteritis, hypertension, death, causes of death, occurrence of cancers, of new cases of diabetes.

(2) Dose of corticosteroid.

ANALYSIS

Data analysis was performed on SAS (Statistical Analysis System, SAS Institute Inc, Cary, North Carolina). The χ^2 test or Fisher's exact test were applied to dichotomous variables. Odds ratio with 95% confidence intervals were computed. For continuous variables, a *t* test was performed for the comparison of the means when the variable distribution was normal, and a Wilcoxon rank sum test was performed when the latter condition was not fulfilled.

A logistic regression with stepwise selection included the variables found to be significant in the univariate analysis.

Survival of patients was analysed using the log rank test (SAS lifetest procedure), and the incidence densities of the occurring events in

Table 2 Biopsy confirmed and negative biopsy temporal arteritis: clinical features

Clinical features	*Positive biopsy (n=207)*	*Negative biopsy (n=85)*	*p*	*Odds ratio (95% CI)*
F/M ratio	3.14	1.93	0.082	
Temporal artery:				
palpation abnormalities	61.35	29.41	7×10^{-7}	3.81 (2.21, 6.56)
a rigidity	51.21	29.41	0.0007	2.52 (1.47, 4.32)
b inflammation	14.01	3.53	0.007	4.45 (1.32, 15.04)
c palpable nodules	8.70	2.35	0.05	3.95 (0.99, 15.77)
Visual problems	31.55	19.05	0.031	1.96 (1.06, 3.64)
a blindness	9.71	2.38	0.033	4.41 (1.29, 17.22)
b diplopia	5.34	1.19	0.19	4.68 (0.59, 36.85)
c troubled vision	21.84	16.67	0.32	1.40 (0.72, 2.71)
Jaw claudication	40.78	28.24	0.044	1.75 (1.01, 3.03)
Headache	82.52	92.94	0.021	0.36 (0.15, 0.88)
a temporal headache	41.67	38.55	0.627	1.14 (0.68, 1.92)
b diffuse headache	47.06	55.42	0.199	0.715 (0.43, 1.19)
c facial headache	10.29	8.43	0.630	1.25 (0.51, 3.05)
d facial oedema	4.41	2.41	0.520	1.87 (0.40, 8.84)
Systemic symptoms	90.82	89.41	0.710	1.17 (0.51, 2.70)
a fever	47.09	51.76	0.468	0.83 (0.50, 1.37)
b weight loss >10%	26.21	27.06	0.88	0.96 (0.54, 1.70)
c anorexia	50.49	47.06	0.595	1.14 (0.69, 1.90)
d malaise	11.17	14.12	0.481	0.76 (0.36, 1.61)
e asthenia	82.52	80.00	0.612	1.18 (0.62, 2.24)
Polymyalgia symptoms	40.10	65.88	9×10^{-5}	0.35 (0.20, 0.59)

A χ^2 test or Fisher's exact test has been performed. Data shown as percentages.

each group were compared using the Mantel-Haenszel test. The Mantel-Haenszel weighted relative risk has been computed across the six, six month strata of the follow up. Cumulative incidences were computed for the cancers occurring during follow up.

Results

Two hundred and ninety two cases were included during the 1991–1997 period. Among them, 207 had biopsy proven TA (157 women, mean (SD) age: 75.6 (8.0) years, and 50 men, mean age: 74.1 (7.4) years), and 85 had negative biopsy TA (56 women, mean age: 75.1 (7.8) years, and 29 men, mean age: 74 (8.6) years).

SENSITIVITY AND SPECIFICITY OF THE SET OF DIAGNOSTIC CRITERIA USED FOR THE NEGATIVE BIOPSY GROUP

Eighty five per cent of the biopsy proven cases (considered as the gold standard) would have been recognised as GCA with the diagnostic criteria set used for the negative biopsy group—that is, the sensitivity of this set is equal to 85%. During the follow up, five patients previously included in the negative biopsy group have been excluded, for another diagnosis was made (Wegener's disease, infectious endocarditis with septic cerebral embolism diagnosed two weeks after the inclusion, sinusitis regressive within six weeks, two cases of rheumatoid arthritis). These five patients have been excluded from the present series. They all fulfilled the ACR criteria, with an ESR greater than 50 mm 1st h and localised headache of recent onset. Therefore the specificity of our criteria may be estimated at 95%.

Table 3 Biopsy confirmed and negative biopsy temporal arteritis: biological characteristics

Variable	*Negative biopsy (n=85)*	*Positive biopsy (n=207)*	*p*	*Test used*
Sedimentation rate (mm 1st h)	81.8 (26.8)	88 (27.5)	0.05	*t* test
C reactive protein (mg/l)	64 (2–200)	84 (2–431)	0.048	Wilcoxon
Fibrinogen (g/l)	6.19 (1.65)	6.46 (1.70)	0.22	*t* test
Haemoglobin (g/l)	118.23 (16.88)	111 (15.61)	0.001	*t* test
Mean globular volume (fl)	90 (78–111)	87 (68–104)	0.0004	Wilcoxon
Serum iron (µmol/l)	8 (0.7–26)	7 (0.7–32)	0.05	Wilcoxon
Platelet count (10^9/l)	353 (167–700)	424 (177–1051)	0.0041	Wilcoxon

A *t* test has been computed for all the normally distributed variables, and a Wilcoxon rank sum test has been computed when the distribution was not normal. The mean (SD) are given for the normally distributed variables, and the median and the extremes are given for the other variables.

MAIN CLINICAL VARIABLES (TABLE 2)

Palpation abnormalities of the temporal artery were twice as frequent in the biopsy proven group than in the negative biopsy group ($p = 7 \times 10^{-7}$). Among the different types of visual dysfunction, sudden blindness was significantly more frequent in the biopsy proven group with a fivefold increase in risk, whereas the prevalence of "troubled vision" was similar in both groups. Although jaw claudication was more frequent in the biopsy proven group, headache was more frequent in the negative biopsy group.

PMR symptoms were significantly more frequent in the negative biopsy group (65.9% versus 40.1%, $p = 9 \times 10^{-5}$). The prevalence of systemic symptoms (fever, weight loss > 10%, anorexia, malaise, asthenia) was similar in the two groups.

The female/male ratio was slightly higher in the biopsy proven group (3 versus 2, p = 0.082).

There was a strong association between the clinical perception of an abnormal temporal artery and blindness or jaw claudication (prevalence of blindness in clinically abnormal temporal artery/clinically normal: 11.84% versus 2.90, p = 0.004, OR = 4.50, 95% CI: 1.48, 13.65; prevalence of jaw claudication in clinically abnormal temporal artery/clinically normal: 45.03% versus 28.57%, p = 0.004, OR = 2.05, 95% CI: 1.26, 3.33)

BIOLOGICAL VARIABLES (TABLE 3)

Except for fibrinogen, all markers of the inflammatory syndrome are significantly different between the two groups, and inflammation is always more severe in the positive biopsy group: the ESR, the CRP and the platelets count are significantly higher in the biopsy proven group, serum iron, haemoglobin and mean globular volume, as markers of inflammatory anaemia, are lower. Although all the patients presented with an ESR above 40 mm 1st h, the value of the CRP was below 6 mg/l in 5% of the cases in both group.

CIRCUMSTANCES OF DIAGNOSIS AND EPIDEMIOLOGICAL DATA

The time interval between the onset of the symptoms and diagnosis was similar in the two groups (negative biopsy: median = 33 days, extremes: 4–1096 days; positive biopsy: median = 48 days, extremes: 5–2113 days; Wilcoxon rank sum test: p = 0.18).

The onset of most cases of positive biopsy TA (58.33%) occurred during the autumn-winter time, whereas the onset of most cases of negative biopsy TA (60.71%) occurred during the spring-summer time (p = 0.003).

MULTIVARIATE ANALYSIS

When included in the logistic regression model, a clinically abnormal temporal artery

Table 4 Major causes of death

	Positive biopsy group (n=38)	*Negative biopsy group (n=14)*
Myocardial infarction	1	2
Cardiac insufficiency	6	1
Stroke	9	2*
Infection	total: 9	total: 3
Pulmonary	7	1
Urinary tract	2	1
Tuberculosis	0	1
Other infections		
Colic perforation	3	1
Cachexia	1	1
Cancer	2	1
Sudden death at home (unexplained)	4	2
Miscellaneous	1: sudden post-surgical death (surgery for hip fracture) 1: dementia 1: intestinal infarction*	1: severe nephrotic syndrome with mutivisceral failure

*Only one patient in the positive biopsy group, and one patient in the negative biopsy group, underwent a postmortem examination.

Table 5 Biopsy confirmed and negative biopsy temporal arteritis. Rates of patients under treatment during follow up

	Months					
	6	*12*	*18*	*24*	*30*	*36*
Biopsy +	90.57	88.89	86.11	75.59	63.06	64.29
(n=207)	(n=159)	(n=162)	(n=144)	(n=127)	(n=111)	(n=98)
Biopsy −	90.91	81.82	76.92	73.33	66.67	54.55
(n=85)	(n=66)	(n=66)	(n=52)	(n=45)	(n=36)	(n=33)

p=0.14; RR=1.21, 95% CI: 0.95, 1.54. A Mantel-Haenszel test has been used. A Mantel-Haenszel weighted relative risk for all strata, with a Greenland-Robins test 95% confidence limits, has been computed. Data shown as percentages.

and the seasonal factor remained positively associated with biopsy proven TA (p = 0.0001 and p = 0.011, respectively), whereas headache and symptoms of polymyalgia rheumatica remained positively associated with negative biopsy TA (p = 0.002 and p = 0.0005, respectively). Blindness and jaw claudication, being strongly associated with a clinically abnormal temporal artery, did not reach the 0.05 significance level. When the ESR and the CRP were added to the model, only the increase in the CRP remained positively associated with the biopsy proven cases (p = 0.008).

FOLLOW UP

At the time of diagnosis, there was no difference between the groups of biopsy proven and negative biopsy TA, as regards the prevalence of cardiovascular risk factors (hypercholesterolaemia: 5.18% versus 3.95%, p = 1.00; history of diabetes: 6.80% versus 11.90%, p = 0.15; smoking history: 28.16% versus 31.76%, p = 0.54; history of hypertension: 38.05% versus 42.86%, p = 0.45). The prevalence of symptomatic lower limb arteritis was similar in both groups (3.18% versus 3.57% in women, 10.00% versus 13.79% in men), as well as the prevalence of at least one arterial murmur (14.65% versus 12.50% in women, 14.00% versus 17.24% in men). However, the prevalence of one non-palpable artery at clinical examination was greater in the biopsy proven group, in women only (23.57% versus 7.14% in women, p =0.007, and 30.00% versus 24.14% in men p = 0.57).

None of the patients presented with aortic aneurysm at the onset of the disease, and none of them during the follow up. However, we did not request a systematic cardiac echography in asymptomatic patients for the study purpose.

The mean duration of follow up was 22 months for the patients of the negative biopsy group, and 23 months for those of the biopsy proven group. Thirty eight of the 207 patients died in the biopsy proven group, and 14 of 85 in the biopsy negative group (p value of the log rank test: 0.133). Table 4 shows the major causes of death. Only one patient in the positive biopsy group, and one patient in the negative biopsy group, underwent a postmortem examination. For the patient with intestinal infarction, it showed very severe signs of GCA generalised to the whole mesenteric sphere. The patient died one week after the onset of the corticosteroid treatment.

For one of the two patients who died from stroke in the negative biopsy group, it showed classic, atheromatous lesions of the left carotid, which explained the stroke. There was no involvement of GCA in the central nervous system.

Among the 12 patients who died from infection, seven were still receiving corticosteroid treatment. Also, the three patients who died from colonic perforation were under corticosteroid treatment at the time of the perforation.

There is a non-significant trend for the patients with biopsy proven TA to be treated longer than those with biopsy negative TA (table 5).

Table 6 gives the incidence densities of the occurring events: all cases of blindness during follow up occurred in patients with biopsy proven TA, whereas the incidence density of blurred vision is similar in both groups. Relapses occurred at the same rate in both groups, also (one third of the patients every year). There was no significant difference in the occurrence of myocardial infarction (1%/year), transient ischaemic attack (2.5%/year), or lower limb arteritis (about 1%/year). Strokes occurred more frequently in the negative biopsy group, as well as diabetic patients receiving corticosteroid treatment, although the mean and the median of the corticosteroid dose in each six month stratum were quite similar in both groups (Wilcoxon rank test: 0.08 < p value < 0.68, depending on the strata).

Table 6 Biopsy confirmed and negative biopsy temporal arteritis. Evolution over a three year period (mean duration of follow up: 23 months)

	Incidence density (number/year/100)			
	Biopsy confirmed (n=207)	*Negative biopsy (n=85)*	*RR (95% CI)*	*p*
Relapses	38.2	36.93	1.01 (0.95, 1.08)	0.72
Blindness	2.97	0	1.01 (1.01, 1.02)	0.09
Visual problems	10.70	13.88	0.98 (0.95, 1.02)	0.31
Myocardial infarction	0.84	1.68	0.99 (0.97, 1.01)	0.43
Stroke	1.74	6.74	0.97 (0.95, 01.00	0.008
Transient ischaemic episode	2.23	3.41	0.99 (0.98, 1.01)	0.50
Lower limb arteritis	1.54	0.34	1.01 (0.99, 1.02)	0.76
Hypertension	12.47	14.41	0.98 (0.95, 1.02)	0.39
Diabetes	8.00	17.66	0.95 (0.92, 0.99)	0.005

Occurring events have been recorded at each six month assessment. Incidence densities have been computed for each six month period of follow up, and compared with a Mantel-Haenzsel test. A Mantel-Haenzsel weighted relative risk (RR) has been computed across the six month strata, with a Greenland-Robins test with 95% confidence intervals.

ASSOCIATED DISEASES

Thyroid stimulating hormone (TSH) and free T4 were determined in the first 203 patients at the time of diagnosis. The prevalence of hyperthyroidism, as assessed by TSH lower than 0.2 mUI/l, was equal to 5.59% (n =8) in the positive biopsy group, versus 3.33% (n = 2) in the negative biopsy group (p = 0.726), and the prevalence of hypothyroidism, as assessed by TSH greater than 4 mUI/l, was equal to 4.20% (n = 6) in the positive biopsy group, versus 1.67% (n = 1) in the negative biopsy group (p = 0.676).

The cumulative incidence of cancer during follow up was equal to 8/149 patient years in the negative biopsy group, and to 9/351.5 patients years in the positive biopsy group (RR = 0.49, 95% CI: 0.19, 1.25, p = 0.128). In the negative biopsy group, the site of the cancer was gastric and prostatic in two cases, vesical and colonic in one case. There was one melanoma, and one chronic myelogenous leukaemia. In the positive biopsy group, there was one chronic lymphocytic leukaemia, one adrenal tumour, one ORL cancer, one prostatic cancer, one tumour of the ampulla of Vater, one breast cancer, two colonic cancers, and one breast cancer.

Discussion

Predictors of the positivity of temporal artery biopsy before diagnosis, or predictors of the positivity of the biopsy among patients presenting symptoms of PMR, have been previously studied.[17–21] We did not assess the positive predictive value of various symptoms in patients undergoing temporal artery biopsy, but rather focused on diagnosed cases of GCA. Patients with pure PMR were excluded from this work.

Biopsy proven and negative biopsy TA do not seem to share the same epidemiological features. A few studies have suggested seasonal peaks of incidence (December in Scotland, February-March in France, May-June in Israel,[2 22 23] while a more recent study suggested that the peaks of incidence of the disease are concomitant with the peaks of incidence of respiratory infectious diseases.[24] Our study shows that biopsy proven cases are more frequent during the winter time, whereas biopsy negative cases are more frequent during the summer time. If, as it has been suggested by some studies,[24 25] an epidemic pattern exists, or if TA is triggered by an infectious agent,[26] our data would suggest that biopsy proven and negative biopsy TA may have a different aetiological spectrum.

Most cases of blindness, at the time of diagnosis, occur in the biopsy proven cases, and blindness is rather rare in biopsy negative cases. Although the difference is not significant, diplopia and blurred vision are also more frequent in the biopsy proven cases. These late symptoms, however, may be difficult to interpret in the elderly, who may present many other causes of visual problems. The palpation abnormalities of the temporal artery, more frequent in the biopsy proven group, may be seen only as predictors of the positivity of the biopsy.

Headache (especially in its diffuse form) and symptoms of PMR are more frequent in the negative biopsy group. The data were collected in the same way, with the same inclusion questionnaires, by the same investigators. This difference may be attributable to the fact that, when the biopsy is negative, more criteria are necessary to diagnose the disease: inflammatory syndromes without specific clinical criteria may be diagnosed as TA when the biopsy is positive, but not when the biopsy is negative. The sensitivity of our clinical criteria for negative GCA is estimated at 85%. Therefore, we probably missed 15% of cases, who did not present headache or the required clinical criteria, and this increases the proportion of headache in the diagnosed cases. However, the different prevalence of certain symptoms at diagnosis may also reflect different mechanisms of disease: we recorded the presence of PMR symptoms, but they were not part of the diagnostic criteria set. They also were more frequent in the negative biopsy group. One explanation may be that, when the biopsy was negative, some participating physicians spontaneously asked for more criteria than required to be surer of the diagnosis. Another interpretation could be that the unknown nature of the association between TA and PMR may be different in the two types of GCA.

Although the frequency of the clinical signs of severity (systemic signs) is similar in both groups, all biological markers of inflammation are higher in the biopsy proven group. The differences are statistically significant, but may not be seen as clinically significant. However, inflammation always seems more severe in the biopsy proven group, and the concordance of the results of all the markers are unlikely to be attributable to chance alone. Although an ESR greater than 40 mm 1st h was requested to include a case, the CRP was normal in 5% of the patients. We cannot exclude that in some rare cases, the CRP was not determined on the same blood sample than the ESR, and that the onset of the corticosteroid treatment induced a rapid decrease of the CRP value in less than 48 hours. However, the rate of biopsy proven GCA, or of PMR, with a normal ESR at the onset of the disease has been estimated at 5%, and our results are consistent with those of previously published series.[27 28] The prevalence of biological thyroid dysfunction was similar in both groups, and does not seem to be different from the prevalence observed in the general population.[29]

Thirteen per cent of the deceased patients died from infectious diseases while taking corticosteroid treatment, one patient died after surgery for hip fracture, and the question of the role of corticosteroid treatment in the pathogenesis of colonic perforation may be raised. Therefore, potentially iatrogenic complications may explain up to 20% of the deaths.

Interestingly, the incidence of blindness during follow up is also higher in the positive biopsy group, and no case of blindness occurred in the negative biopsy group after the treatment was started. There does not seem to be more relapses in the biopsy proven cases.

No aortic aneurysm was diagnosed, either at the onset of the disease, or during the follow up: several explanations may be given: (1) we did not request for a systematic cardiac echography at the time of diagnosis, and we may have missed some asymptomatic cases, not visible on the chest radiograph. However, these potential cases did not get symptomatic during follow up. (2) The length of follow up may be too short for an aortic aneurysm to develop (the mean follow up in the study of Evans *et al* was 10 years, and the cumulative incidence of aortic aneurysm over this period has been estimated at 10%).[15] (3) All our patients have been included during the 1991–1997 period, and the disease is now well known by the general practitioners. It may be that the referral delay is shorter nowadays than in the 1950–1985 period, when the patients described by Evans *et al* had been included, and that our series included less "historical" cases.

The higher incidence of stroke in the negative biopsy group is not explained by a difference in the prevalence of cardiovascular risk factors at diagnosis, and remains unclear. In some cases, the disease may have been localised to branches of the internal carotid rather than to the external one, and this could explain the negativity of the temporal artery biopsy. However, this would not account for the higher rate of blindness in the biopsy proven group, or for the more severe biological signs of inflammation. The higher incidence of stroke could also be related to the higher incidence of diabetes in this group, which is another unexplained feature: it may be fortuitous and because of chance alone, as the median and the extreme doses of corticosteroid did not differ between groups at each six month assessment. It may also be speculated that biopsy proven and negative biopsy TA have different aetiological patterns, that GCA and diabetes share a common genetic predisposition (HLA-DR4),[30–32] and that the same agent, more related to one form of GCA than to the other, may, in some cases, also trigger the occurrence of diabetes. The higher prevalence of one non-palpable artery in positive biopsy cases may be related to the disease itself, or to a previous, asymptomatic atheromatous disease. The latter is more plausible, as a more detailed analysis showed no difference for the carotid or the upper limb artery.

The artery lesion being segmental and focal, positive biopsies could represent cases with a larger extension of the disease, compared with negative biopsy cases. This could account for the higher incidence of blindness in the former group, and for the increased markers of inflammation, but not for the different seasonal pattern or for the different incidence of diabetes and stroke during the follow up. We suggest that the different seasonal pattern may reflect different aetiological patterns, which could explain the different features of the two types of the disease. This needs to be confirmed by other epidemiological or biological studies, and further work on the pathogenesis of the disease and on the potential risk factors is necessary to clarify the nosology of the GCA syndrome.

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