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Research Letter

Frequency and Significance of Hepatic Involvement in New-Onset Giant Cell Arteritis: A Study of 514 Patients

To the Editor:

Abnormalities of liver function in giant cell arteritis (GCA) have long been described[1] and are present at the acute phase of the disease in 30% to 60% of cases.[2-4] Hepatic involvement is mostly anicteric cholestasis (eg, elevated alkaline phosphatase [ALP] and gamma-glutamyl transferase [GGT]), and, more rarely, cytolytic hepatitis (eg, elevated aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]). Pathologic documentation of hepatic involvement is seldom required in patients with GCA and is mostly normal, or shows various specific or nonspecific changes.[5,6] Although a positive association between hepatic cholestasis (HC) and higher acute-phase response at GCA onset is plausible, so far, only 1 study has specifically addressed this issue.[7] In this study,[7] raised ALP (> 2 times above the upper limit of normal [ULN]) was associated with age, more frequent constitutional syndrome and fever; higher mean erythrocyte sedimentation rate (ESR), hemoglobin, and platelet count; and lower mean albumin. Patients in both groups (raised/normal ALP) had similar rates of ischemic complications. However, C-reactive protein (CRP) was measured in only 40% of cases, and no other hepatic enzymes were studied, nor was any information on the prognostic value of HC available.[7]

We therefore conducted a study aimed at determining the frequency of occurrence, patterns, and disease associations of hepatic involvement in untreated, new-onset GCA. We also looked at the prognostic effect of HC. All data concerning these elderly patients with GCA were retrospectively collected. This study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. In accordance with French law, approval from an ethics committee and written informed consent were not required for this type of retrospective study, provided the patient has not exercised the right to refuse participation in the study.

We selected from a large, single-center inception cohort of patients with GCA[8] all those who had complete liver enzyme tests (including ALP, GGT, AST, and ALT) performed before glucocorticoid (GC) treatment. Using univariate analyses, we determined which baseline and outcome variables were associated with the presence of HC at GCA onset. Among 655 patients, 514 (78.5%, 347 biopsy-proven) met the entry criteria and were included. GCA was diagnosed based on the 1990 American College of Rheumatology (ACR) criteria. Of 59 patients diagnosed before 1990, 52 had a positive temporal artery biopsy, and the 7 remaining patients retrospectively met 3 or 4 of the 1990 ACR criteria. At least 1 liver enzyme abnormality was present in 219 (42.6%) patients, 3 (1.4%) of whom had elevated aminotransferase levels only, 18 (8.2%) had elevated ALP level only, 161 (73.5%) had raised ALP and GGT levels, and 37 (16.9%) had mixed hepatitis (eg, both cholestasis and elevated AST and ALT levels). Most enzyme elevations were mild, at < 3 times above the ULN. The highest ALP, GGT, AST, and ALT values were 879 IU/L, 1028 IU/L, 251 IU/L, and 641 IU/L, respectively. No patients with liver involvement developed jaundice or liver pain or enlargement, and all assessed patients quickly cleared their hepatic enzyme abnormalities upon GC treatment, making it unnecessary to investigate other causes of liver dysfunction or perform a liver biopsy. During follow-up, only 2 patients had a subsequent diagnosis of autoimmune hepatitis made. Among the studied variables (Table), mean levels of blood acute-phase reactants and serum albumin level, as well as blood cell counts, were the strongest predictors of liver abnormalities; HC was associated with higher mean ESR, CRP, fibrinogen, leukocyte and platelet values, and lower hemoglobin and albumin levels. The strongest correlations, as assessed by Spearman ρ test, were between ALP, ESR, and CRP. In addition, patients with HC had fewer ischemic complications overall, but they had similar rates of permanent visual loss compared to the other patients. The presence of aortitis was negatively associated with HC, which might point to a distinct immuno-inflammatory pattern in large-vessel vasculitis. Finally, patients of either group shared similar late GCA outcome issues and prognosis, although those with HC had higher prednisone burden in the first 6 months. The higher death rate observed in the HC group may rely on longer median duration of follow-up (76 vs 64 months); rates of death occurring during GC treatment were similar in both groups.

The present study confirms and expands on previous data on liver enzyme abnormalities in new-onset GCA. Silent HC is a frequent finding, whereas cytolytic hepatitis is rare. HC is associated with a strong systemic inflammatory response but not with a reduced ischemic visual risk, and is mostly fully reversible with adequate GC treatment. Our finding of similar ischemic visual risk in patients with or without HC at disease onset highlights the unclear boundaries existing between the vascular component and the inflammatory component of GCA. Indeed, vascular and systemic inflammation may be discordant in GCA, so much so that 2 opposing subgroups of patients may be identified. The first subgroup is characterized by severe systemic inflammation and a low frequency of ischemic complications, whereas in the second subgroup, there is less systemic inflammation but prominent neuro-ophthalmic ischemic complications.[9,10] The finding of HC being associated with higher GC doses in the first 6 months could reflect more prudent prednisone tapering related to a low-level, persistent acute-phase reaction. Raised ALP levels have been reported to mirror a higher state of inflammation in patients with clinically isolated polymyalgia rheumatica (PMR) as well.[11] Whether liver involvement in patients with PMR can represent a risk factor for overlapping GCA deserves further investigation.[12]

Table. Characteristics of the cohort with comparison between patients with and without hepatic cholestasis.

	No Hepatic Cholestasis, n = 298	Hepatic Cholestasis, n = 216	Total, N = 514	*P**
Demographic and clinical characteristics				
Male sex, n (%)	106 (35.6)	74 (34.3)	180 (35.0)	0.83
Age, yrs	74.5 (7.5)	74.8 (8.1)	74.6 (7.8)	0.46
Body weight, kg	62.8 (12.1)	64.4 (13.2)	63.5 (12.6)	0.29
Hypertension, n/N (%)	129/295 (43.7)	97/215 (45.1)	226/510 (44.3)	0.82
Diabetes, n/N (%)	37/296 (12.5)	28 (13.0)	65/512 (12.7)	0.98
Dyslipidemia, n/N (%)	35/295 (11.9)	22 (10.2)	57/511 (11.2)	0.66
Delay to diagnosis, d	87.4 (92.1)	76.2 (80.3)	82.7 (87.5)	0.12
No. of ACR criteria met	4.0 (1.0)	4.1 (0.9)	4.0 (0.9)	0.14
Acute disease onset, n/N (%)	123/294 (41.8)	93/211 (44.1)	216/505 (42.8)	0.68
Fever, n/N (%)	115/294 (39.1)	91/214 (42.3)	206/508 (40.6)	0.52
Weight loss > 5%, n/N (%)	110/291 (37.8)	101/210 (48.1)	211/501 (42.1)	0.03
Polymyalgia symptoms, n (%)	88 (29.5)	69 (31.9)	157 (30.5)	0.62
Systemic (masked) GCA, n (%)	34 (11.4)	25 (11.6)	59 (11.5)	> 0.99
Headache, n (%)	239 (80.2)	174 (80.6)	413 (80.4)	> 0.99
Scalp tenderness, n/N (%)	137/286 (47.9)	110/212 (51.9)	247/498 (49.6)	0.43
Facial/orbital edema, n/N (%)	41 (13.8)	29/214 (13.6)	70/512 (13.7)	> 0.99
Jaw claudication, n/N (%)	86 (29.1)	81 (37.5)	167/512 (32.6)	0.06
Permanent visual loss, n (%)	40 (13.4)	29 (13.4)	69 (13.4)	> 0.99
Ischemic stroke, n (%)	15 (5.0)	5 (2.3)	20 (3.9)	0.18
Limb artery involvement, n (%)	31 (10.4)	17 (7.9)	48 (9.4)	0.42
Mean ENT symptoms[a], n	1.7 (1.7)	2.0 (2.0)	1.8 (1.8)	0.08
Imaging and pathological findings				
Imaging of the aorta, n/N (%)	113/283 (39.9)	74/200 (37.0)	187/483 (38.7)	0.58
Presence of aortitis, n (%)	55 (18.5)	19 (8.8)	74 (14.4)	< 0.01
Positive TAB result, n/N (%)	190/281 (67.6)	157/212 (74.1)	347/493 (70.4)	0.15
Laboratory results				
Mean ESR, mm/h	78.5 (28.8)	94.9 (25.9)	85.2 (28.8)	< 0.001
Mean CRP, mg/L	79.2 (57.2)	119.6 (72.1)	96.1 (66.8)	< 0.001
Mean fibrinogen level, g/L	6.6 (1.5)	7.3 (1.8)	6.9 (1.7)	< 0.001
Mean hemoglobin, g/L	116.5 (16.4)	112.1 (17.7)	114.6 (17.1)	0.01
Mean leukocyte count, G/L	8.7 (2.5)	9.8 (3.7)	9.1 (3.1)	< 0.001
Mean platelet count, G/L	398 (133)	479 (176)	432 (157)	< 0.001
Mean serum albumin, g/L	34.9 (5.3)	32.6 (5.9)	33.9 (5.7)	< 0.001
Positive IgG aCL, n/N (%)	47/234 (20.1)	33/158 (20.9)	80/392 (20.4)	0.95
Treatment and outcomes				
Pulse methylprednisolone, n (%)	78 (26.2)	59 (27.3)	137 (26.7)	0.85
Initial prednisone dose, mg/kg/d	0.79 (0.17)	0.78 (0.16)	0.78 (0.16)	0.22
Dose at 3 mos, mg/d	17.2 (5.9)	18.6 (5.8)	17.8 (5.9)	< 0.01
Dose at 6 mos, mg/d	11.1 (4.1)	12.5 (4.8)	11.7 (4.4)	< 0.01
Dose at 12 mos, mg/d	6.7 (4.1)	7.4 (4.4)	6.94 (4.2)	0.08
Use of GC-sparing treatment, n (%)	64 (21.5)	43 (19.9)	107 (20.8)	0.75
Treatment stopped, n/N (%)	181/297 (60.9)	134/215 (62.3)	315/512 (61.5)	0.82
Treatment duration, mos	27.2 (25.2)	27.8 (23.9)	27.5 (24.6)	0.97
Treatment duration in recovered patients, mos	27.9 (15.3)	31.7 (20.4)	29.5 (17.7)	0.41
No. of relapses/patient[b]	1.0 (1.2)	1.1 (1.3)	1.0 (1.3)	0.58
Recovered patients[c], n (%)	165 (55.4)	120 (55.6)	285 (55.4)	1.00
Death, n (%)	93 (31.2)	95 (44.0)	188 (36.6)	< 0.01
Death during GC treatment, n (%)	29 (9.7)	26 (12.0)	55 (10.7)	0.64

Values are expressed as mean (SD) unless indicated otherwise. * Proportions were analyzed using Pearson chi-square tests; comparisons of continuous variables were performed with *t* tests. [a] ENT includes jaw claudication, difficulty opening mouth, toothache, earache, tongue pain, sore throat, dry cough, and carotidodynia. [b] Before 2003, relapse was defined as the recurrence of clinical symptoms or inflammatory variables that were attributable to GCA and required increased medication. Thereafter, only events involving clinical symptoms, or persistently raised acute-phase reactants with demonstration of new large-vessel involvement, were labeled as relapses. [c] Patients free of relapse for at least 12 months following the cessation of GC treatment. aCL: anticardiolipin antibody; ACR: American College of Rheumatology; CRP: C-reactive protein; ENT: ear, nose, and throat; ESR: erythrocyte sedimentation rate; GC: glucocorticoid; GCA: giant cell arteritis; TAB: temporal artery biopsy.

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