Hepatic function in ankylosing spondylitis

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SUMMARY Values for alkaline phosphatase and gamma glutamyl transpeptidase (GGTP) and the prevalence of their elevation was significantly higher in 35 patients with ankylosing spondylitis (AS) than in 35 age and sex matched controls. The abnormal enzyme levels appeared to reflect a non-specific reaction to inflammation and could thus aid in assessment of disease status.

Raised alkaline phosphatase activity has previously been reported in patients with AS, the incidence ranging from 14 to 47.5%.^{1,2} But which enzyme fraction is increased is unclear; it has been variously reported as of hepatic origin and of bony origin. In addition many of the patients were receiving non-steroidal anti-inflammatory drugs at the time of investigation, which could have contributed to the abnormal biochemistry observed.³

The present study was designed to investigate hepatic function in patients with AS who had received no therapy in the preceding 3 months and to assess possible relationships between hepatic function and disease activity.

Materials and methods

Seventy subjects were studied. Thirty-five had AS, the New York criteria⁴ being satisfied for diagnosis, and 33 were HLA B27 positive (94%). Patients with inflammatory bowel disease were excluded. The remaining 35 corresponded in age and sex distribution to the AS patients and were healthy volunteers with no history of arthritis or backache.

No subject had coexisting disease which might of itself produce changes in the biochemical parameters measured, and none had hepatosplenomegaly or other stigmata of chronic liver disease. Patients initially included who were found to have Paget's disease of bone were excluded. A detailed history of alcohol consumption was taken in all cases.

The study was conducted in 2 phases.

STUDY A

Venous blood was obtained from the 70 subjects for estimation of erythrocyte sedimentation rate (ESR) and serum immunoglobulins. In addition, serum was

screened for the presence of markers of liver disease, namely mitochondrial antibody and smooth muscle antibody, and the following estimates of 'liver function' were recorded: bilirubin, alkaline phosphatase, albumin, globulin, gamma glutamyl transpeptidase (GGTP), and serum aspartate aminotransferase (SGOT).

STUDY B

Patients with initial evidence of disease activity were reassessed after 3 months' treatment, which included use of nonsteroidal anti-inflammatory drugs. Parameters measured were identical to those in study A.

Results

STUDY A

The mean values for ESR and serum immunoglobulins are shown in Table 1; there is a marked difference for the variables IgA and ESR between the 2 groups. Eleven patients with AS (31%) and one control (3%) had a raised ESR, while 8 AS subjects (23%) had increased IgA activity. No control had abnormal immunoglobulin levels, while in the AS subjects a significant correlation was demonstrated between ESR and IgA values ($p < 0.05$). No subject had smooth muscle or mitochondrial antibodies.

Table 1 Mean ESR and serum immunoglobulin levels in healthy control subjects and AS patients

Cases	Age (years)	ESR (mm/h)	IgA (IU/ml)	IgM (IU/ml)	IgG (IU/ml)
AS (n=35)	37.9	33	210	120	156
Controls (n=35)	37.9	16	140	114	143
Statistical significance		$p < 0.005$	$p < 0.01$	NS	NS

NS = not significant.

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The prevalence of abnormal liver function tests is shown in Table 2. A raised level of GGTP was found in 9 of the patients, (26%) and of alkaline phosphatase in 6 (17%), GGTP being abnormal in all subjects with elevated alkaline phosphatase values. In the control group one (3%) had a high alkaline phosphatase, no abnormal GGTP being detected. No subject had raised bilirubin or transaminase activity, while all values for albumin fell within the normal range. Eight (23%) AS subjects had hyperglobulinaemia, reflecting the increased IgA activity observed.

Table 2 Prevalence of abnormal liver function tests in healthy control subjects and AS patients

	Normal range	Number abnormal in controls	Number abnormal in AS
GGTP (IU/l)			
Females	5-40	0	9 (26%)
Males	10-55		
Alkaline phosphatase (IU/l)	30-100	1 (3%)	6 (17%)
Bilirubin (mmol/l)	3-15	0	0
SGOT (IU/l)	8-22	0	0
Albumin (g/l)	37-49	0	0
Globulin (g/l)	24-37	0	8 (23%)

Fig. 1 Mean GGTP levels in AS patients with elevated ESR (≥ 25 mm/h) and elevated IgA levels (≥ 250 IU/l) compared with values from patients having normal ESR (< 25 mm/h) and normal IgA activity (< 250 IU/l).

No correlation was found between levels of alkaline phosphatase, GGTP, and alcohol consumption in any subject.

To assess the relationship of the hepatic enzymes GGTP and alkaline phosphatase to disease activity AS patients were divided into 2 groups according to their ESR, one group consisting of patients with an ESR below 25 mm/h ('normal') and the other an ESR of 25 mm/h or more ('raised'). The mean serum GGTP in patients having a raised ESR was 77 IU/l (Fig. 1), while in those with a 'normal' ESR it was 53 IU/l, this difference being statistically significant ($p < 0.001$). In addition, the mean serum GGTP in patients with a raised ESR was 54% higher than the mean GGTP in control subjects, ($p < 0.001$), but there was no significant difference between mean GGTP in patients with a normal ESR and mean GGTP in controls. (By using GGTP all patients with raised alkaline phosphatase were automatically included.)

Similarly, patients were divided into 2 groups according to their IgA levels, one having IgA activity of 250 IU/l or more and the other normal IgA values, namely below 250 IU/l. The mean serum GGTP in patients with abnormal IgA levels was 88 IU/l and in those with normal immunoglobulin estimations it was 53 IU/l (Fig. 1), this difference being statistically

Fig. 2 Mean GGTP in patients with active disease before (TO) and after (T3/12) therapy.

Table 3 Indices of disease activity, GGTP, and alkaline phosphatase before and after 3 months' therapy in 11 AS patients

Variable	Baseline	3 months	p
ESR (mm/h)	46	25	<0.005
IgA (IU/ml)	305	200	<0.005
GGTP (IU/l)	77	59	<0.05
Alkaline phos. (IU/l)	98	62	<0.05

significant ($p < 0.001$). The mean GGTP in patients with elevated IgA levels was 76% higher than in controls ($p < 0.001$), and, as with the ESR, the other index of disease activity, no statistically significant difference occurred between mean GGTP of the 'normal' IgA group and the controls.

STUDY B

All 11 patients with a raised ESR and/or IgA had these indices of disease activity reassessed 3 months after the introduction on nonsteroidal anti-inflammatory therapy. Hepatic function was also re-evaluated and related to disease status (Fig. 2). All variables (IgA, ESR, GGTP, and alkaline phosphatase) showed significant differences after treatment (Table 3). Furthermore the significant drop in abnormal hepatic values correlated with the reduction in the objective indices of disease activity.

Discussion

An abnormality in one or more of the parameters of hepatic function measured was detected in 26% of the patients in the study. GGTP proved to be the most sensitive and was elevated in all subjects with a raised alkaline phosphatase, implying a hepatic origin for the latter biochemical abnormality.

This hepatic dysfunction could conceivably have occurred as a result of coincidental liver pathology. However, no patient had clinical stigmata or serological markers (mitochondrial or smooth muscle antibodies) of chronic disease. But clearly without histological evidence it is impossible to confirm or refute this.

Alternatively the abnormal hepatic function could have resulted from ingestion of alcohol and/or non-steroidal anti-inflammatory drugs. However, no correlation was found between elevated alkaline phosphatase, GGTP, and alcohol consumption. In addition, as no patient had received any therapy in the 3 months prior to evaluation, drugs cannot be implicated in this study. Finally, in a number of subjects the elevated laboratory parameters returned to normal despite treatment with these agents.

Theoretically amyloidosis, an unusual complication of AS,⁵ might have affected the results, as it was not specifically excluded except on clinical grounds. We feel it more probable, however, that the abnormal biochemical findings represent a nonspecific reaction to inflammation and could perhaps be regarded as acute-phase reactants. This is based on the observation that the raised hepatic enzyme values were found to occur in patients with laboratory evidence of active disease^{6,7}—namely raised IgA and ESR—and supported by return of liver function towards normal when adequate control of the disease was achieved. Thus, our findings would suggest that elevation of GGTP and/or alkaline phosphatase may be used to assess disease status in patients with AS, the greater frequency of abnormal baseline GGTP making it more useful than alkaline phosphatase.

References

- 1 Kendall M, Lawrence D, Shuttleworth G, Whitfield A. Haematology and biochemistry of ankylosing spondylitis. *Br Med J* 1973; **ii**: 235–7.
- 2 Smith D, Spencer D, Allam B, Farish E, Borland W. Serum alkaline phosphatase in ankylosing spondylitis. *J Clin Pathol* 1979; **32**: 853–4.
- 3 Cooney A. Pharmacological complications of microsomal enzyme induction. *Pharmacol Rev* 1967; **19**: 317–66.
- 4 Bennet P, Wood P. In: Bennet P, Wood P H N, eds. *Population studies of the rheumatic diseases*. Amsterdam: Excerpta Medica, 1968: 476.
- 5 Titu M L. Amyloidosis complicating ankylosing spondylitis. *J Assoc Physicians India* 1975; **22**: 393–6.
- 6 Dowling P, Ebringer R, Ebringer A. Association of inflammation with raised serum IgA in ankylosing spondylitis. *Ann Rheum Dis* 1980; **39**: 545–9.
- 7 Cowling P, Ebringer R, Cawdell D, Islie M, Ebringer A. C-reactive protein, ESR and klebsiella in ankylosing spondylitis. *Ann Rheum Dis* 1980; **39**: 45–9.