CLINICAL RESEARCH

Objective monitoring of disease activity in polyarteritis by measurement of serum C reactive protein concentration

C R K HIND, C O SAVAGE, C G WINEARLS, M B PEPYS

Abstract

Serial measurements of the serum concentration of C reactive protein were made in 27 patients with polyarteritis over six years. The concentration was invariably raised when the disease was active, even in patients receiving immunosuppressive treatment, and fell rapidly in association with clinical remission induced by immunosuppression. During periods of complete remission, in the absence of any intercurrent condition, the value remained within the normal range. The correlation between C reactive protein concentration and disease activity was much closer than that between erythrocyte sedimentation rate and disease activity.

These results indicate that serial measurement of the serum C reactive protein concentration fills the urgent need for an objective index of the activity of polyarteritis and its response to treatment.

Introduction

The term polyarteritis is used to describe a range of systemic disorders characterised pathologically by necrotising vasculitis.¹ These disorders are occasionally seen in patients presenting to district general hospitals² and the prognosis has been greatly improved by aggressive anti-inflammatory and immunosuppressive treatment with corticosteroids and cytotoxic drugs.^{3,4} These agents may cause serious complications, however, and the

objective assessment of disease activity and response to treatment is therefore a vital aspect of patient management, particularly as deterioration in renal function may result from progressive glomerular scarring in the absence of continuing inflammation. No single clinical or laboratory abnormality is specific for polyarteritis, and hitherto the best available non-specific index of inflammation and tissue damage has been the erythrocyte sedimentation rate.³

The sedimentation rate is largely determined by the plasma concentration of proteins such as fibrinogen, acute phase α globulins, and immunoglobulins, all of which have half lives of the order of days to weeks, so that the rate of change of the reading falls within this range.⁵ Furthermore, the sedimentation rate is greatly affected by size and number of the red cells and unless its measurement is conducted under strictly standardised conditions it is not highly reproducible.⁶ By contrast, C reactive protein is a sensitive acute phase reactant, the concentration of which varies over an exceptionally wide incremental range with a half time of hours rather than days.⁷ Various techniques are now available for its precise and rapid estimation and we have therefore investigated its possible role in monitoring patients with polyarteritis.

Patients and methods

We studied 27 patients with polyarteritis. They were referred between April 1977 and September 1983 to the renal unit at this hospital, which is a tertiary referral centre for the treatment of systemic vasculitis. In all cases the diagnosis was based on clinical evidence of injury to two or more organ systems in the presence of histological confirmation of vasculitis or focal necrotising glomerulonephritis. A diagnosis of microscopic polyarteritis was made in 23 patients (18 male, five female; mean age 47 years, range 14-73) based predominantly on disease of small vessels and in the absence of evidence of granulomas in the upper or lower respiratory tract.⁸ The other four patients (three men, one woman; mean age 50 years, range 46-57) were diagnosed as polyarteritis nodosa, based on angiographic or necropsy evidence of disease of medium sized arteries in the renal, hepatic, and visceral vasculature.⁸ The table shows the anatomical distribution of disease in the patients.

Investigations—Frequent clinical, haematological, biochemical, microbiological, and radiological tests were performed, including

Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS

C R K HIND, BSC, MRCP, honorary senior registrar, immunological medicine unit

C O SAVAGE, BSC, MRCP, honorary registrar, MRC Clinical Immunology Research Group

C G WINEARLS, DPHIL, MRCP, senior registrar, renal unit

M B PEPYS, MD, FRCP, reader in immunological medicine, head of MRC Acute Phase Protein Research Group

Correspondence to: Dr C R K Hind.

Organs and systems affected in 27 patients with polyarteritis. Figures are numbers of patients

	Kidney	Skin	Joints	Eye	Gastrointestinal tract	Lung	Nervous system	Ear, nose, or throat	Hypertension
Microscopic polyarteritis (n = 23)	23	15	15	9	9	7	5	5	4
Polyarteritis nodosa (n = 4)	4	3	2	2	1		2		4

measurements of diffusion capacity to detect pulmonary haemorrhage.⁹ Blood was taken for estimation of the serum C reactive protein concentration at least twice a week during induction of immunosuppressive treatment and at each subsequent clinic visit, when the erythrocyte sedimentation rate was also measured. Serum C reactive protein was assayed by electroimmunoassay, as described.¹⁰ Intra-assay and interassay replicates gave results with a coefficient of variation of less than 10%. Ninety nine per cent of normal healthy people have C reactive protein concentrations of less than 10 mg/l.¹¹ Sedimentation rate was measured by the method of Westergren.⁶

Clinical assessment of disease activity—Disease activity was assessed according to the following standard subjective and semiobjective clinical criteria,³ which correspond precisely with the extensive experience of these disorders in our department. Criteria for *active*

4 l plasma protein fraction, were undertaken in some patients. Subsequently patients were maintained with prednisolone 5-15 mg/day and sometimes also azathioprine 2-3 mg/kg/day for at least 12 months.

Statistical analysis—Differences in results of the various objective measurements between groups of patients were sought using the Wilcoxon rank sum test.

Results

SERUM CONCENTRATION OF C REACTIVE PROTEIN IN ACTIVE DISEASE

During the study 22 of the 27 patients had active disease at the time of referral, and all had a raised serum C reactive protein concentration. Of these, three had overt pulmonary haemorrhage (as detected by a raised diffusion capacity), which in its own right results in an acute phase response. In the other 19 patients (figure 1 a) the median C reactive protein concentration was 141 mg/l (range 28-348). There was no significant difference in concentrations between the 15 patients with microscopic polyarteritis (median 167 mg/l, range 28-348) and the four with polyarteritis nodosa (median 108 mg/l, range 50-150). Seven patients had already been prescribed some form of immunosuppressive treatment by their referring physicians and had a significantly lower serum C reactive protein concentration (median 68 mg/l, range 28-141) when compared with those not already receiving treatment at the time of referral (median 204 mg/l, range 102-348) ($p < 0.01$). The erythrocyte sedimentation rate was also increased in all 19 patients at the time of referral (mean 126 (SD 22) mm in first hour, range 86-158), but there was no significant difference in values between the seven patients already receiving immunosuppressive treatment (mean 140 (SD 17) mm in first hour, range 128-152) and the 12 who were not (mean 124 (SD 22) mm in first hour, range 86-158).

During the study there were eight relapses of disease activity in six patients with microscopic polyarteritis, and on each occasion the serum C reactive protein concentration was raised. In the five patients in whom relapse occurred while they were not taking any immunosuppressive treatment (fig 1 b) the median serum C reactive protein concentration was 46 mg/l (range 42-115). In the three relapses that occurred during immunosuppressive treatment (fig 1 c) the median serum C reactive protein concentration was 50 mg/l (range 25-72).

FIG 1—Serum C reactive protein concentrations in 27 patients with active microscopic polyarteritis (●) and polyarteritis nodosa (▲). Open symbols represent patients already receiving immunosuppressive treatment at time of referral. Horizontal bars are medians. Figure also shows median C reactive protein concentrations of 13 patients in complete remission. Labels a to d refer to text.

disease were the presence of glomerulonephritis; cutaneous or cerebral vasculitis; mononeuritis; polyarthralgia or polyarthropathy; episcleritis; myositis; fever; or evidence of gastrointestinal, lung, or ear, nose, or throat disease. Criteria for *partial remission* were clear cut suppression of the progression of disease activity; stabilisation of the renal abnormalities, both functional and urinary; and no worsening of other organ system disease activity. Criteria for *complete remission* were complete absence of disease activity; stable renal sediment (though proteinuria may persist for months or years in completely inactive renal disease); and no evidence of systemic inflammatory disease, such as arthralgia, myalgia, or fever.

Treatment—On admission to hospital induction immunosuppressive treatment was started with cyclophosphamide 3 mg/kg/day (2 mg/kg/day if over 55) and prednisolone 60 mg/day. Patients under 55 usually also received azathioprine 1 mg/kg/day. Plasma exchanges, each of

CHANGES IN SERUM C REACTIVE PROTEIN CONCENTRATION AND SEDIMENTATION RATE DURING INDUCTION OF REMISSION

Out of 18 of the 22 patients in whom remissions were induced, three had evidence of pulmonary haemorrhage at the time of referral with active disease. A further three patients developed bacteriological evidence of infection during their induction treatment (respiratory tract in two cases, skin in one case). In the remaining 12 patients there were no complications considered likely to cause an additional acute phase response. After the introduction of immunosuppressive treatment in these patients the average time for the serum C reactive protein concentration to fall to normal was 8.9 days (range 5-14). Clinical assessment of each of these patients at the same time showed that partial remission had been achieved in every case. By contrast, the erythrocyte sedimentation rate was still increased in all eight patients in whom it was measured (mean 86 mm in first hour, range 60-120) and did not return to normal (six patients) for a mean of 35 days (range 25-57). Figure 2 illustrates these observations in a single case.

In none of the eight episodes of relapse that were again followed by successful induction of remission was the relapse complicated by either pulmonary haemorrhage or infection. In these patients the serum C reactive protein concentration returned to normal a mean of 8.0 days (range 4-13) after the reintroduction or augmentation of immunosuppressive treatment. All the patients were then in partial remission by clinical criteria, although the sedimentation rate remained high in all five patients in whom it was measured.

SERUM C REACTIVE PROTEIN CONCENTRATION AND SEDIMENTATION RATE DURING COMPLETE REMISSION

Thirteen patients (12 with microscopic polyarteritis, one with polyarteritis nodosa) were in complete remission and free of infection and other complications for a mean of 48 (SD 18) months each (range 17-72) and during these periods were tested a mean of 18 times (range 9-42). Their C reactive protein concentrations remained almost entirely within the normal range (median <1 mg/l, interquartile range <1-1, range <1-26) (fig 1 d). Although the erythrocyte sedimentation rates sometimes fell in the normal range, they showed greater variation than the serum C reactive protein concentrations measured simultaneously and were often raised (mean 42 (SD 23) mm in first hour, range 12-135).

SERUM C REACTIVE PROTEIN CONCENTRATION IN DIFFERENTIAL DIAGNOSIS OF DETERIORATING RENAL FUNCTION

Eight patients underwent repeated percutaneous renal biopsy for deteriorating renal function in the absence of systemic features of the

concentration increases non-specifically in response to most forms of inflammation, infection, and tissue damage.⁷ It is synthesised by hepatocytes, probably in response to stimulation by peptide products of activated macrophages (interleukin 1, leucocyte endogenous mediator). Proteins closely resembling C reactive protein are present in all vertebrate species, and this stable evolutionary conservation together with the general nature of the acute phase response suggest that the protein has important functions. These are not yet known, however. Nevertheless, the empirical clinical measurement of serum C reactive protein concentrations provides a sensitive and useful index for monitoring the extent and activity of a variety of different diseases.^{10 12 13} We have extended the range of these applications in showing the close correlation between the serum concentration of the protein and the clinical course of polyarteritis, a serious group of disorders in which objective criteria of disease activity and for regulating treatment have been notably lacking.

We find that active polyarteritis diagnosed by generally accepted clinical criteria either at initial presentation or on relapse, in the presence or absence of immunosuppressive treatment, is invariably associated with a high serum concentration of C reactive protein. When the disease is in remission, occurring either spontaneously or with treatment, the concentration remains within the normal range, and during induction of remission the concentration falls in proportion to the clinical improvement. In the eight cases available for this study we also observed that the serum C reactive protein concentration differentiated between renal functional deterioration due to active glomerulitis (one case) and that due to progressive scarring (seven cases). This is a common clinical problem in patients with systemic vasculitis affecting the kidneys and poses therapeutic difficulties. The present, albeit limited finding, which we have also noted in some cases of Wegener's granulomatosis,¹⁴ may therefore help in resolving this dilemma. We do not yet know whether estimations of serum C reactive protein would also help to distinguish between continued inflammatory changes and chronic fibrosis in other systems—for example, lungs and nerves.

Increase of the erythrocyte sedimentation rate is another non-specific response to tissue damage and inflammation and has been widely used in monitoring patients with polyarteritis.³ As our results show, however, it responds much more slowly than C reactive protein to changes in disease activity and therefore does not necessarily reflect accurately the degree of inflammation at a particular time. Also rapid and precise assays for C reactive protein¹⁵ (Syva Co, Palo Alto, California; Beckman Instruments, Fullerton, California) confer significant advantages by comparison with the relative unreliability and great variance, albeit cheapness, of measurements of sedimentation rate.

Although we have shown the relation between serum C reactive protein concentration and vasculitic activity, we emphasise that the acute phase response is non-specific and that values of C reactive protein can be interpreted only in the light of full clinical information. Microbial infection and any other intercurrent complication must be excluded before ascribing a raised concentration to activity of polyarteritis alone. Nevertheless, provided that these facts are always borne in mind, the results that we present, although obtained only in patients whose disease included the kidneys, suggest that the frequent serial measurement of serum C reactive protein concentration may make a valuable contribution to the management of patients with polyarteritis.

This work was supported by MRC programme grant G979/51 to MBP. CRKH is an MRC training fellow. We thank Professor D K Peters, Dr A J Rees, and Dr C M Lockwood for permission to study their patients and Ms Benita Roberts for technical help.

FIG 2—Serial C reactive protein concentrations, measurements of erythrocyte sedimentation rate, and serum creatinine concentrations in 35 year old man with microscopic polyarteritis. Prednisolone, cyclophosphamide, and azathioprine started on day 0.

Conversion: SI to traditional units—Creatinine: 1 μmol/l ≈ 0.01 mg/100 ml.

disease. At the time of the procedure the serum C reactive protein concentration was raised in one patient (115 mg/l) and the biopsy sample showed evidence of acute necrotising glomerulitis. By contrast, the other seven patients had normal serum C reactive protein concentrations, and each biopsy showed glomerular scarring with no evidence of active renal disease. Sedimentation rate was increased in the patient with active glomerulitis and in five of those with glomerular scarring.

Discussion

C reactive protein was the first plasma protein shown to behave as an acute phase reactant—that is, its circulating con-

References

- 1 Fauci AS. The spectrum of vasculitis. *Ann Intern Med* 1978;89:660-76.
- 2 Scott DGI, Bacon PA, Elliott PJ, et al. Systemic vasculitis in a district

- general hospital 1972-1980: clinical and laboratory features, classification and prognosis of 80 cases. *Q J Med* 1982;**51**:292-311.
- ³ Cohen RD, Conn DL, Ilstrup DM. Clinical features, prognosis and response to treatment in polyarteritis. *Mayo Clin Proc* 1980;**55**:146-55.
- ⁴ Hind CRK, Paraskewakou H, Lockwood CM, *et al.* Prognosis after immunosuppression of patients with crescentic nephritis requiring dialysis. *Lancet* 1983;**i**:263-5.
- ⁵ Pepys MB. Acute phase phenomena. In: Cohen AS, ed. *The science and practice of clinical medicine: rheumatology and immunology*. New York: Grune and Stratton, 1979:85-9.
- ⁶ International Committee for Standardisation in Haematology. Reference method for the erythrocyte sedimentation rate (ESR) test on human blood. *Br J Haematol* 1973;**23**:671-3.
- ⁷ Pepys MB. C-reactive protein fifty years on. *Lancet* 1981;**i**:653-7.
- ⁸ Camilleri M, Pusey CD, Chadwick VS, Rees AJ. Gastrointestinal manifestations of systemic vasculitis. *Q J Med* 1983;**52**:141-9.
- ⁹ Ewan PW, Jones HA, Rhodes CG, Hughes JMB. Detection of pulmonary hemorrhage with carbon monoxide uptake. *N Engl J Med* 1976;**295**:1391-6.
- ¹⁰ Fagan EA, Dyck RF, Maton PN, *et al.* Serum levels of C-reactive protein in Crohn's disease and ulcerative colitis. *Eur J Clin Invest* 1982;**12**:351-9.
- ¹¹ Shine B, de Beer FC, Pepys MB. Solid phase radioimmunoassays for C-reactive protein. *Clin Chim Acta* 1981;**117**:13-23.
- ¹² de Beer FC, Hind CRK, Fox KM, *et al.* Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. *Br Heart J* 1982;**47**:239-43.
- ¹³ Mallya RK, Vergani D, Tee DEH, *et al.* Correlation in rheumatoid arthritis of concentrations of plasma C3d, serum rheumatoid factor, immune complexes and C-reactive protein with each other and with clinical features of disease activity. *Clin Exp Immunol* 1982;**48**:747-53.
- ¹⁴ Hind CRK, Winearls CG, Lockwood CM, Rees AJ, Pepys MB. Objective monitoring of activity in Wegener's granulomatosis by measurement of serum C-reactive protein concentration. *Clin Nephrol* (in press).
- ¹⁵ de Beer FC, Pepys MB. Solid-phase immunoradiometric assay for C-reactive protein using magnetisable cellulose particles. *J Immunol Methods* 1982;**50**:299-308.

(Accepted 31 January 1984)

Vitamin A treatment for night blindness in primary biliary cirrhosis

R P WALT, C M KEMP, L LYNESS, A C BIRD, S SHERLOCK

Abstract

Three patients with late stage primary biliary cirrhosis were found to have appreciable night blindness. Serum vitamin A concentrations were low in all three patients despite regular intramuscular supplementation in two. All patients responded dramatically to high dose oral supplementation, with full recovery of adaptation to dark and visual fields.

Oral rather than intramuscular vitamin A supplementation seems appropriate in the prevention of ocular complications of vitamin A deficiency in biliary cirrhosis.

Introduction

Vitamins that are soluble in fat are poorly absorbed in cholestatic liver disease, but routine measurements of vitamin A in 20 patients with primary biliary cirrhosis showed that three had pathologically low concentrations despite receiving intramuscular supplementation with vitamin A; two of these three patients had symptomatic night blindness. We report on these three patients.

Patients, methods, and results

We measured serum vitamin A concentrations by high pressure liquid chromatography¹ (normal range 0.7-3.1 $\mu\text{mol/l}$ (20-90 $\mu\text{g}/100\text{ ml}$)) and gave vitamin A supplements intramuscularly (Ro-A-Vit, Roche) or by mouth (vitamin A capsules, Macarthy's). We used a Goldmann perimeter to measure photopic function and an automated perimeter adaptometer to record the course and extent of cone and rod adaptation after an intense xenon flash.²

The table gives details of the patients when they presented initially with primary biliary cirrhosis.

Case 1—This woman presented in 1982 after noticing difficulty in driving at night. Her liver disease had worsened considerably (serum bilirubin concentration 660 $\mu\text{mol/l}$ (38.8 mg/100 ml)). Her visual field was constricted. Adaptation to the dark was absent (figure, curve A), and cone thresholds were raised by more than one log unit.

Dark adaptation curves (case 1) measured with flashing yellow-green test light ($\lambda=530\text{ nm}$) subtending a visual angle of 1° . Data points describe the log relative intensity needed for the test light to be just seen. The maximum intensity of the flash was designated as 0 log units; stimuli that were not seen at all are shown as +0.1. (Curve A, day 0; oral treatment started on day 4; curve B, day 11; treatment stopped on day 40; curve C, day 55; curve D, day 60; treatment restarted on day 61; curve E, day 74.)

Academic Department of Medicine, Royal Free Hospital School of Medicine, London NW3 2PF

R P WALT, MRCP, medical registrar
S SHERLOCK, DBE, MD, FRCP, professor

Departments of Visual Science and Clinical Ophthalmology, Institute of Ophthalmology, London WC1H 9QS, and Moorfields Eye Hospital, London EC1 2PD

C M KEMP, PHD, senior lecturer
L LYNESS, FRCS, senior registrar
A C BIRD, MD, FRCS, professor

Correspondence to: Dr R P Walt, Department of Therapeutics, University Hospital, Nottingham NG7 2UH.