

Erythrocyte sedimentation rate and C reactive protein in the assessment of polymyalgia rheumatica/giant cell arteritis on presentation and during follow up

VALERIE KYLE, TIM E CAWSTON, AND BRIAN L HAZLEMAN

From the Rheumatology Research Unit, Addenbrooke's Hospital, Cambridge

SUMMARY The erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were measured in 74 patients with polymyalgia rheumatica (PMR)/giant cell arteritis (GCA) on presentation, in the first month of treatment, and at long term follow up (up to 177 weeks). Before treatment the ESR was raised (>30 mm/h) in all cases and the CRP was raised (>6 mg/l) in 49/55 cases. The ESR was a better indicator of clinical disease activity except in patients who felt completely well at week 1. 'False positive' increases of ESR or CRP were rare. During relapses ESR was normal in 37/77 (48%) of cases and CRP in 41/73 (56%). It is suggested that ESR is the most useful laboratory parameter in assessing PMR/GCA.

The erythrocyte sedimentation rate (ESR) is usually raised in active untreated polymyalgia rheumatica (PMR)/giant cell arteritis (GCA) and returns to normal after treatment. It has traditionally been used both in making the diagnosis and assessing the response to steroids. The test, however, has some limitations. Although most studies report the ESR to be raised in 95-100% patients,¹⁻³ Ellis and Ralston found 22.5% of patients with PMR/GCA to have an ESR <30 mm/h,⁴ and there are well documented cases of biopsy positive GCA with a normal ESR.⁵⁻⁸ The ESR changes at different times of day, especially in the non-fasted state,⁹ and the range of the upper normal ESR in the elderly is quoted as up to 20 mm/h in some studies, but up to 40 mm/h in others.¹⁰⁻¹² Women may have higher level than men.¹² It is non-specific - the sedimentation rate increases with increasing concentrations of globulins and other plasma proteins, and in anaemia and microcytosis technical pitfalls may also affect the ESR recorded.¹³

C reactive protein (CRP) is synthesised by hepatocytes, and its synthesis and secretion rates increase within hours of acute injury or inflammation. It is a non-specific marker of tissue damage. It

has been proposed that CRP is a better test to use in assessing disease activity in PMR/GCA because it avoids some of the limitations of the ESR and also because it falls more rapidly in response to treatment. Eshagian and Goeken reported in 1980 that the CRP correlated better with disease activity than the ESR.¹³ Mallya *et al* also found that CRP reflected disease activity more accurately than ESR over the first two weeks of treatment in a study of 13 patients with GCA.¹⁴

Others have disagreed with this view. Park *et al* found the ESR correlated best with disease activity at varying stages of the condition in comparison with CRP and other acute phase proteins.¹⁵ Paolaggi *et al* did not examine CRP but found ESR better than other acute phase proteins during the follow up of GCA.¹⁶ A study in 1986 found that ESR, CRP, and plasma viscosity all rose during relapses¹⁷; no parameter predicted relapse.

The aim of this study was to assess ESR and CRP before and during treatment of PMR/GCA, to determine which correlated best with disease activity, and whether either parameter would predict relapse.

Patients and methods

Seventy four patients with active untreated PMR/GCA were included in the study. All fulfilled the diagnostic criteria of Jones and Hazleman.¹⁸ Thirty

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Correspondence to Dr Valerie Kyle, Rheumatology Research Unit, Unit E6, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

nine had PMR only, 18 GCA only, and 17 features of both PMR and GCA. There were 15 men, 12 of whom had PMR. Patients were assessed fully before treatment and ESR (Westergren) and CRP (Beckman rate nephelometer) measured. An ESR of >30 mm/h and a CRP >6 mg/l were regarded as abnormal. Temporal artery biopsies were positive in five of 22 patients with PMR and in 26 of 30 patients with GCA or PMR/GCA.

Patients were seen every one to two weeks for about two months then about every three months. Clinical assessment, ESR, and CRP were determined on each occasion. The follow up period was from four to 177 weeks, and 847 assessments were carried out.

Once treatment had started, patients were scored on a scale from 0 to 2 for a variety of clinical features (muscle pain, stiffness and tenderness, headache, visual symptoms, temporal artery tenderness, pulsation and thickening, other illness) to give an overall grading in relation to the previous visit. This was classed as follows: grade 1—relapse, either as a new or persisting event; grade 2—improvement but still not normal; grade 3—well; symptoms minimal. Coincidental illness was also recorded.

ESR and CRP during the follow up period were studied in two ways.

In a study of 63 of the patients (34 with PMR, 29 with GCA) assessments were made of the clinical state, ESR and CRP at 0, 1, and 2–4 weeks (most at two weeks) to study the hypothesis that CRP fell to normal more rapidly than the ESR after treatment of acute disease. Patients were allocated to either 'high' or 'low' prednisolone dosage for PMR and for GCA over this period. Patients with both PMR and GCA were classed as GCA for this part of the study. The initial prednisolone dose was 10–20 mg/day for PMR and 20–40 mg/day for GCA, after five days of 40 mg prednisolone for all patients with GCA.

Throughout the entire follow up period ESR and

CRP were recorded for each of the three subgroups PMR, GCA, and PMR/GCA. Particular attention was paid to absolute values and changes in relation to relapses (grade 1 visits) both before and during these episodes. When the patient experienced a relapse and increased the steroid dose to control symptoms before their clinic visit this was described as a 'home flare'.

STATISTICS

Analysis was carried out with χ^2 tests, Kruskal-Wallis tests, correlation testing, and analysis of variance.

Results

PRETREATMENT

The ESR was raised in all cases, with a mean of 71.8 mm/h (range 32–138). The mean levels and SE for each subgroup were PMR 70.21 (4.22), GCA 76.28 (4.96), PMR/GCA 70.59 (5.95) mm/h. These values were not significantly different.

CRP was raised in 49 of 55 patients; the six patients with CRP <6.0 mg/l all had an ESR >30 mm/h. The raised values ranged from 6 to 267 mg/l. This method does not measure normal values (which are quoted as <6.0 mg/l), but the means and SE for each subgroup of raised values were PMR 43.5 (6.3), GCA 79.4 (20.3), and PMR/GCA 54.9 (9.1) mg/l.

FOLLOW UP STUDIES

Patients were followed up for 4–177 weeks (mean 65.99, SE 5.53). The mean number of visits/patient was 11 (SE 0.72) with 847 patient visits in total. The mean values for each subgroup were not significantly different.

Eight patients who presented with PMR developed GCA, six within five weeks of starting treatment and two after six months or more. Four patients who presented with GCA developed PMR, all after more than four months' treatment. Patients are classed under the subgroup of presentation.

ESR and CRP in the first month of treatment

In the first month of treatment 20 patients were completely well (grade 3) at one week, but nine of these still had raised ESR and two a raised CRP. From two weeks onwards 52 were completely well, and by then only four had a raised ESR and eight a raised CRP. Table 1 shows the results for each subgroup.

After one week 24 grade 2 patients had improved but still had symptoms. Eight of these had a normal ESR and 16 a normal CRP. From two weeks onwards there were only 12 grade 2 assessments, of

Table 1 Grade 3 (completely well) patients with raised ESR* or CRP* at one week and at two to four weeks

At one week			At two to four weeks		
Completely well	Raised ESR	Raised CRP	Completely well	Raised ESR	Raised CRP
PMR*	9/25 4	1	PMR 29/39	3	6
GCA*	11/21 5	1	GCA 23/31	1	2
Total	20/46 9	2	Total 52/70	4	8

*ESR=erythrocyte sedimentation rate; CRP=C reactive protein; PMR=polymyalgia rheumatica; GCA=giant cell arteritis.

Table 2 Grade 2 (improved but still abnormal) patients with normal ESR or CRP at one week and at two to four weeks

At one week			At two to four weeks		
Improved	ESR normal	CRP normal	Improved	ESR normal	CRP normal
PMR 16/25	4	10	PMR 6/39	4	3
GCA 8/21	4	6	GCA 6/31	4	4
Total 24/46	8	16	Total 12/70	8	7

whom eight had a normal ESR and seven a normal CRP (Table 2).

The correlation between abnormal ESR and abnormal CRP values was then examined; of 24 patients with PMR with assessments at 0, 1, and 4 weeks, all had abnormal values initially. Table 3 shows the subsequent numbers with abnormal ESR and CRP. Analysis of these results gave $r=0.575$ ($p<0.01$). For 20 patients with GCA, where clinical assessment, ESR, and CRP were recorded at 0, 1, and 4 weeks, two patients had abnormal ESR at four weeks and two abnormal CRP concentrations at four weeks (Table 3). Correlation of these raised values gave $r=0.627$ ($p<0.01$).

Abnormal ESR and CRP at long term follow up

The ESR was abnormal (>30 mm/h) in 48% of new relapses (grade 1 visits) and CRP abnormal (>6.0 mg/l) in 41%. There was no significant difference in the percentage of abnormal values for each subgroup for either test, nor when ESR was compared with CRP (Table 4). On 13 occasions when the ESR was abnormal CRP was normal, and on nine CRP was abnormal and the ESR normal.

On visits when any abnormal symptoms and signs were recorded (grade 1 and 2 visits) the ESR was abnormal in 43% cases and CRP in 35%. There were no significant differences between subgroups (Table 5). There was a discrepancy between the ESR and CRP in 19% of clinically abnormal PMR visits, 45% GCA, and 19% PMR/GCA.

The ESR became abnormal on the visit immediately preceding a 'home flare', when the

Table 4 Percentage of relapses (grade 1 visits) with raised ESR or CRP for each subgroup

	Raised ESR (%)	Raised CRP (%)
PMR	42	47
GCA	59	29
PMR/GCA	55	38

patient was still clinically well, on nine out of 44 occasions (PMR 4, GCA 1, PMR/GCA 4). The CRP became abnormal on 10 out of 38 occasions. The abnormalities coincided in six cases.

Unexplained abnormalities in ESR or CRP, or both at long term follow up

On 17 occasions (less than 3% of all visits) the ESR was >30 mm/h with no apparent cause and on 27 visits the CRP was >6.0 g/l. Abnormalities of ESR or CRP during or immediately preceding a relapse, or coinciding with any abnormal symptoms or signs whether due to PMR/GCA or other disease, were excluded. One patient had an ESR of >70 mm/h on all but two occasions, even when well, but a normal CRP on all but four of his 12 visits. Apart from this case and one ESR reading of 53 mm/h, the unexplained abnormal ESR levels were all <45 mm/h.

ESR levels at long term follow up

During relapses (grade 1 visits) the mean ESR was 26.3 (SE 2.3) mm/h for PMR, 42.1 (6.91) for GCA, and 28.2 (2.9) for PMR/GCA. There was a significant difference between the levels ($F=4.4796$, 2 and 84 df, $p<0.02$) due to the differences between GCA and the other two subgroups. Thirteen of the 40 ESR levels greater than 30 mm/h during relapse had risen from normal (<30 mm/h) on the preceding visit (PMR 7, GCA 1, PMR/GCA 5). The mean rise was 14 mm/h. Twenty seven were already over 30 mm/h (PMR 12, GCA 9, PMR/GCA 6), one because of other illness.

Of the 45 normal ESR values, seven patients had increased their steroids before they attended hospital. In two cases the ESR was not determined.

Table 3 Number of patients with raised ESR and CRP over the first month of treatment

	Patients with PMR (n=24)			Patients with GCA (n=20)		
	At start	At 1 week	At 4 weeks	At start	At 1 week	At 4 weeks
ESR	24	12	1	20	9	2
CRP	24	7	4	19	5	2

Table 5 Occasions when abnormal clinical features were recorded and the ESR or CRP, or both, were raised

	Number of occasions (%)	
	ESR	CRP
PMR	58 (43)	53 (45)
GCA	17 (50)	9 (28)
PMR/GCA	28 (30)	17 (23)

CRP concentrations at long term follow up

Thirty two of 80 CRP concentrations measured during relapses were >6.0 g/l (PMR 20, GCA 5, PMR/GCA 7). Nineteen had been normal on the preceding visit (PMR 13, GCA 2, PMR/GCA 4). Thirteen were already abnormal (PMR 7, GCA 3, PMR/GCA 3). Of these, one from each subgroup had become abnormal only on the visit preceding the relapse visit. Of the 48 normal values, seven patients had already increased their steroids at home before the 'relapse' visit.

Thus during a clinical relapse 40/77 (52%) of ESR readings were abnormal (PMR 19/43, GCA 10/16, PMR/GCA 11/18) and 32/73 (44%) of CRP readings were abnormal (PMR 20/41, GCA 5/16, PMR/GCA 7/16), excluding episodes of intercurrent illness, or where the patient had increased the steroid dose before the blood test.

Discussion

In patients with active untreated PMR/GCA the ESR was always raised, but the CRP was occasionally normal. As cases with a normal ESR on presentation have been reported it seems reasonable to measure CRP in cases with a typical history where the ESR is normal. There is no indication, however, for using the CRP in preference to the ESR as a diagnostic test.

During the initial follow up period CRP fell to normal more rapidly than the ESR at one week in patients who were judged completely well, but both tests were equally accurate thereafter. In patients who had improved but were still clinically abnormal at one week CRP could have been misleading as it had fallen to normal in most cases, in contrast with the ESR. These results differ from previous studies which found the CRP to be better as a diagnostic test.^{13 14} The much smaller size of the other studies may partly explain the difference. In addition, most of the patients of Mallya *et al* appeared to recover completely over days, though details were not given. Although CRP may reflect early recovery in these

patients more accurately than does the ESR, this group is rarely a management problem. Correlation between abnormal values was reasonably good.

Results of a long term follow up showed that the ESR was raised in about 50% of new relapses and the CRP raised less frequently. Discrepancies occurred on a few occasions. This contrasts with the findings of Paulsen and Iversen, who found an ESR >25 mm/h in all relapses.¹⁹ On occasions when minor symptoms were present—that is, grade 1 or 2 visits, the ESR and CRP were abnormal in about 40% of cases, though again the ESR was raised more often. Discrepancies between the tests were more common in such episodes.

These results support the findings of an earlier retrospective study of 292 samples from this unit,¹⁵ but in this prospective study 847 samples from 74 patients followed up for up to 3½ years were assayed. A different method of CRP measurement was used. There are no other studies comparing ESR and CRP during the long term follow up of PMR/GCA.

Neither test was helpful in consistently predicting relapse. This is not unexpected in the later stages of follow up when the interval between visits was often three months, which is almost certainly too long to pick up incipient relapses by looking at changing trends in ESR. A rise in either CRP or ESR before a home relapse did occur, however, in about 25% of episodes, when the follow up interval was shorter. Unexplained abnormalities in either ESR or CRP were rare but occurred slightly more often in CRP measurements.

Overall, these results suggest that the ESR should continue to be used in preference to CRP in diagnosing PMR/GCA and in monitoring disease activity. During relapses, where an increase in steroid dose may be needed, the ESR is more likely to be raised than CRP, though normal levels of either do not exclude clinical flares. Neither test was very useful in monitoring minor degrees of disease activity, but these are less serious and may not require an alteration in treatment. Abnormal ESR or CRP findings are likely to be significant. Management should therefore be based primarily on the clinical picture, with the ESR the most useful laboratory parameter. CRP may be helpful in some cases if the ESR is normal despite clinically active disease, but routine measurement of both tests in follow up is unnecessary. The ESR measurement is also cheaper as capital outlay on both equipment and reagents is much more expensive for the measurement of CRP.

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