Acute phase proteins, C-reactive protein and serum amyloid A protein, as prognostic markers in the elderly inpatient

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Abstract

Aim: to study the clinical significance and potential utility of measuring serum amyloid A protein (SAA) compared with the classical acute phase protein, C-reactive protein (CRP).

Method: a 3 month prospective study on 66 women, mean age 83 years (range 69–106) and 33 men, mean age 84 years (range 69–95), admitted to the geriatric medicine unit at Hammersmith Hospital. CRP and SAA were determined on admission and at intervals throughout hospital stay; outcome end-points were death during the study, detection of infection, duration of admission and early re-admission to hospital after discharge.

Results: CRP and SAA responses were highly correlated (r = 0.75, P = 0.0001). However, the SAA response was greater than that of CRP in most individuals, with a median ratio of initial SAA to CRP of 2.2 in patients with infective pathology and 1.6 in those with inflammatory pathology. Median (range) SAA on admission was 98 (0.1–940) mg/ml in patients with infection and was twice that observed in patients with other causes of inflammation, median value 50 (0.6–699) mg/l. There was no difference between median CRP on admission in patients with infection or inflammation, median value 53 (0.1–235) and 51.5 (5–246) mg/l respectively. Initial and peak levels of CRP, but not of SAA, were significantly greater in patients who subsequently died, whereas high levels of both proteins predicted length of admission and early re-admission.

Conclusion: major elevations of the serum concentrations of CRP and SAA indicated serious disease and predicted poor outcome. Measurement of SAA as well as CRP enhanced the clinical utility of monitoring the acute phase response in 7% of patients with a diagnosis of infection.

Keywords: acute phase proteins, C-reactive protein, elderly inpatients, prognostic markers, serum amyloid A protein

Introduction

Specific signs and symptoms of disease are commonly absent in elderly patients [1] and standard laboratory tests are often unhelpful or misleading [2, 3]. Infection, a common cause of admission to hospital of old people can be particularly difficult to diagnose. It frequently manifests as a confusional state for which there may be many possible underlying organic and non-organic causes.

The value of measurements of serum C-reactive protein (CRP), the classical acute phase reactant, for monitoring patients of all ages is well established [4]. In particular CRP is a useful marker for infection in elderly patients and is superior both to other acute phase proteins and to the erythrocyte sedimentation rate [5–7]. Although the acute phase response is non-specific and on its own has no diagnostic significance, the sensitivity, speed and dynamic range of the CRP response to most forms of infection, inflammation and tissue injury combine to make it an exceptionally useful objective index of disease activity and response to therapy [8].

We have lately developed an automated immunoassay for serum amyloid A protein (SAA), another acute phase protein with a large dynamic range and possibly even more rapid response than CRP [9]. SAA is of interest as the precursor of AA amyloid fibrils as well as being an extremely sensitive acute phase protein [10],
and a candidate World Health Organisation International Reference Standard for SAA immunoassay has been prepared and is currently undergoing international evaluation (M. B. Pepys, S. Poole, R. Gaines Das, unpublished work). In the present study we compared SAA and CRP responses in elderly medical patients and investigated whether these analyses could provide prognostic information. An improvement in prediction of outcome, in hospital and after discharge, should lead to better patient management and cost containment.

Methods

Subjects
We studied 99 consecutive patients admitted during 3 months to the Division of Geriatric Medicine, Department of Medicine, Hammersmith Hospital, London. There were 66 women, mean age 83 years, range 69–106 and 33 men, mean age 84, range 69–95, comprising general practitioner referrals, admissions from the emergency room and transfers for rehabilitation. All consented verbally to participate in the study, which was approved by the ethics committee of the hospital.

Information about length of stay, death and re-admission after discharge were obtained from case notes and hospital computer records at the end of the study. The general practitioners of discharged patients were contacted to determine outcome in the community, including re-admission elsewhere.

Clinical diagnoses and outcome
Twenty-four patients died during the study and 60 were discharged; the remaining 15 were still in-patients when the analysis was completed. Follow-up information was available on 49 of the 60 patients discharged. The diagnoses on admission were established by retrospective analysis of the case records, and patients assigned to the following four diagnostic categories.

Category 1

Patients with definite infection established on clinical, microbiological or radiological criteria. Eleven patients with suspected infection, who received antibiotic therapy, but in whom infection was not necessarily confirmed were also included in this group.

Category 2

Patients with infection plus non-infective inflammation and/or tissue damage expected to provoke an acute phase response such as myocardial infarction, malignancy and trauma. This group included patients with fracture, those with severe bruising following a fall and those admitted for rehabilitation within 2 weeks of an operation.

Category 3

Patients with non-infective inflammation and/or tissue damage expected to provoke an acute phase response as above.

Category 4

The remaining patients without inflammatory pathology, comprising individuals admitted with stroke, ischaemic heart disease, congestive cardiac failure, gastrointestinal pathology and including those admitted for rehabilitation.

Immunoassays

Venous blood for estimation of CRP, SAA, haemoglobin and urea and creatinine was obtained from all patients within 24 h of admission. CRP was measured the same day using the Miles-Technicon RA1000 (Bayer Corporation) automated immunoturbidimetric method, (lower limit of sensitivity 2 mg/l). For statistical analysis samples containing < 2 mg/l were assigned an arbitrary value of 0.1 mg/l. If the CRP concentration was >3 mg/l or if an inflammatory condition was suspected, blood was subsequently taken daily whenever possible; otherwise sampling was performed twice weekly.

SAA was measured in each sample by automated enzyme immunoassay [9] on the Abbott IMx instrument (Abbott Laboratories, Abbott Park, IL, USA; lower limit of sensitivity 0.1 mg/l), using serum that had been stored at −20°C. Among normal healthy adults, 90% have CRP values < 3 mg/l and 99% have levels < 10 mg/l [11]; for SAA 82% have levels < 5 mg/l and 96% have levels < 10 mg/l [9].

Anaemia was defined as a haemoglobin level ≤11.5 g/dl for women and ≤12.5 g/dl for men and renal failure was defined as a urea ≥6.5 mmol/l plus a creatinine ≥125 μmol/l.

Statistical methods

Spearman rank correlation coefficients were calculated between SAA and CRP for both initial and peak levels. The significance of between-group differences was examined using the Wilcoxon rank sum test. The relationship between mortality and initial and peak values of SAA and CRP was further examined using logistic regression; the model was run with each of the SAA and CRP terms in turn and was adjusted for age.

The ratio of initial SAA to initial CRP was evaluated and its positive and negative predictive values for the diagnosis of infection also calculated. Sensitivity and specificity were calculated for peak values of CRP and SAA with respect to status (alive/dead) and for initial CRP and SAA values with respect to the diagnosis of infection.

With 100 patients we calculated that a 40% increase
Results
Twenty-four out of the 99 patients admitted died (Table 1). Median initial and peak CRP values were significantly greater in patients who died compared with those who survived (P = 0.03 and 0.01, respectively; Table 2). This was confirmed for peak CRP after adjusting for age (P = 0.02). The difference in initial CRP values between those who lived and died after adjusting for age was of borderline significance (P = 0.06). In contrast, there was no significant difference in either initial or peak SAA, between patients who lived or died (Table 2). Figure 1a gives the receiver operator curve for peak CRP, showing that a concentration above 60 mg/l achieved a specificity of 50% and a sensitivity of 65% in identifying those who died.

Table 3 shows the baseline characteristics in all patients admitted according to diagnostic category. Seventy out of the 99 patients were admitted with infection and/or inflammation that would be expected to provoke an acute phase response. Median (range) initial SAA in patients with infection and 'infection plus inflammation' was 98 (0.1-940) mg/l and 118 (3.4-421) mg/l respectively and these values were twice the median initial value of 50 (0.6-699) mg/l in patients with acute inflammation alone (Figure 2a). In contrast, there was no difference between median initial CRP in patients with infection, secondary infection or acute inflammation, with median values of 53 (0.1-235), 51 (0.1-174) and 51.5 (5-246) mg/l respectively (Figure 2b). The receiver operator curve showed that the sensitivity and specificity for initial SAA and initial CRP for detecting infection on admission (Figure 1b) was similar, with optimal values of 40 mg/l for detecting infection.

As expected there was a highly significant correlation between the initial values of SAA and CRP (R = 0.75, P = 0.0001) and between peak values of SAA and CRP (R = 0.82, P < 0.0001). However, their relative values varied between individuals (Figure 3). The SAA response was greater in most patients and median (interquartile range) ratio of initial SAA to CRP was 2.2 (1-4.2) in patients with infection, 1.6 (1.3-2.5) in those with inflammatory pathology and 1.6 (0.4-3.3) in patients with dual infective and inflammatory pathology. A ratio ≥2 had a positive predictive value of 56.8% for detecting infection, whereas a ratio < 2 had a negative predictive value of 59.2%. None of the diagnoses was associated with a persistent increase in only one reactant, although four patients admitted with infection (7%) had an initial increase in SAA only and two patients had an initial increase in CRP only (3%).

Excluding subjects who died, initial and peak values of SAA were significantly correlated with length of admission (R = 0.3 and 0.5 respectively, P < 0.01) as were initial and peak CRP values (R = 0.3 and 0.3 respectively, P < 0.01). Prediction of re-admission or subsequent general practitioner attendance in the 2
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Figure 1. Receiver operator curves for (a) peak serum amyloid A protein (SAA) and C-reactive protein (CRP) for the sensitivity and specificity of these tests in identifying those who died and (b) initial SAA and CRP in identifying those with infection versus all others. CRP, △, [values]; SAA, •, (values).

Figure 2. Initial levels of (a) serum amyloid A protein (SAA) and (b) C-reactive protein (CRP), according to diagnostic category. 1, infection; 2, infection plus inflammation; 3, inflammation; 4, other pathology. Horizontal bar represents median value.

Table 3. Baseline characteristics of patients according to diagnostic category

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Infection (group 1)</th>
<th>Infection + inflammation (group 2)</th>
<th>Inflammation (group 3)</th>
<th>Other (group 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>41</td>
<td>13</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Renal failure</td>
<td>12 (29%)</td>
<td>3 (23%)</td>
<td>5 (31%)</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>15 (36%)</td>
<td>7 (53%)</td>
<td>3 (18%)</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>(13)</td>
<td>Myocardial infarct (1)</td>
<td>Myocardial infarct (1)</td>
<td>Arrhythmia (1)</td>
</tr>
<tr>
<td>Chest</td>
<td>(12)</td>
<td>Malignancy (4)</td>
<td>Malignancy (4)</td>
<td>Cardiac failure (2)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>(2)</td>
<td>Trauma (8)</td>
<td>Trauma (9)</td>
<td>Rehabilitation (5)</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>(3)</td>
<td></td>
<td>Pancreatitis (1)</td>
<td>Transfusion (1)</td>
</tr>
<tr>
<td>Suspected infection</td>
<td>(11)</td>
<td></td>
<td>Intestinal perforation (1)</td>
<td>CVA (9)</td>
</tr>
<tr>
<td>Angina</td>
<td>(4)</td>
<td></td>
<td></td>
<td>Gastritis/ulcer (7)</td>
</tr>
</tbody>
</table>

CVA, cerebrovascular accident.
months after hospital discharge was examined. Follow-up information was available on 49 out of the 60 patients discharged during the study period. Eleven of these patients were discharged with persistently elevated or rising CRP and SAA for which no cause had been identified. Six out of these 11 patients were readmitted within 2 months compared with only six of the remaining 38 patients ($P < 0.05$). None of the four patients discharged with only one reactant rising was readmitted.

**Discussion**

These results confirm earlier work on CRP in elderly patients [5-7, 12] and extend it to SAA. High initial and peak values of both CRP and SAA provided unequivocal evidence of serious organic disease and predicted poor outcome, although SAA did not predict death. They are thus valuable guides to active investigation and treatment.

Twenty-four out of the 99 patients admitted died. This relatively high proportion probably reflects the mean age of the population under investigation which was also high (82 years, range 65–106). Infection was the most common indication for admission [5-7]. Cases were also admitted with suspected infection that was not confirmed, usually because antimicrobial therapy had already been started or appropriate specimens were not obtained, and these were included in group 1. The proportion of cases studied here with non-infective inflammation and/or tissue damage, such as myocardial infarction and malignancy, was relatively low, probably because at the Hammersmith Hospital most such patients are cared for by the respective specialist teams.

Initial and peak values of CRP, but not of SAA, were significantly higher in patients who died than in those who survived. High levels of both CRP and SAA were also predictive of length of hospital stay.

Figure 3. Serum amyloid A protein (SAA, □) and C-reactive protein (CRP, ○) response for (a) an 86-year-old man with chronic airway obstruction and indwelling urinary catheter for prostatic carcinoma admitted with increasing confusion, (b) an 89-year-old man admitted with cellulitis of both lower legs and treated with benzyl penicillin and flucloxacillin and (c) a 75-year-old woman with diabetes mellitus transferred for rehabilitation after femoral-popliteal by-pass performed 18 days previously. (a) Pseudomonas was cultured from the urine and antimicrobial therapy started. He subsequently developed pseudomembranous colitis (day 3), bronchopneumonia (day 13) and *E. coli* urinary infection (day 32). The CRP and SAA responses were similar and corresponded to his clinical course. Note that the acute phase response to the bronchopneumonia started two days before the clinical diagnosis was made. (b) Blood culture on day 4 yielded Clostridia. SAA levels were persistently greater than CRP and covered a wider dynamic range but showed a similar overall pattern. (c) Group D Streptococci and coagulase-positive Staphylococci had been cultured from her chronic leg ulcers and coliforms from her urine prior to transfer. The CRP response was persistently greater than that of SAA.
and early re-admission following discharge. These outcome measures are not straightforward in elderly subjects, in whom duration of admission may be much affected, for example, by availability of social services and other factors not considered here. Also re-admission and/or general practitioner visits may not closely reflect problems after discharge. Nevertheless, elevation of both acute phase proteins was a poor prognostic sign and the results emphasize the importance of monitoring levels of these proteins on admission, during management and before discharge.

The increase in SAA in patients with infective pathology was greater than that in patients with other pathology, while there was no difference in the CRP response. In addition the SAA:CRP ratio was greater in patients with primary infection compared with all other groups. This suggests that measurement of SAA in addition to CRP is a more useful guide to the presence of infection.

Although much useful information is obtained from CRP alone, our results indicate that the measurement of SAA provides extra value in at least 7% of patients with infection. Increase in both SAA and CRP predicted poor outcome, such as re-admission, better than one reactant alone, in that six out of 11 (52%) patients discharged with increases in both SAA and CRP were readmitted compared with none of the four patients discharged with only one reactant elevated. Seven percent of individuals with infection had increased concentrations of SAA on admission whilst CRP was below a concentration designated as ‘normal’, actually reflecting the limited sensitivity of about 2 mg/l in routine CRP assays. The median normal CRP value is 0.8 mg/l and concentrations can be as low as 0.07 mg/l in healthy subjects [11], so that CRP concentration must at least double before it even becomes detectable. In contrast, our SAA assay can detect and measure SAA at all points from the normal range upwards and thus provide a more sensitive marker of the acute phase response. Among the six patients with raised SAA on admission and ‘normal’ CRP, four had infection, one had inflammatory or tissue damaging processes and one, who subsequently died, had non-infective, non-inflammatory pathology. On the other hand, there were six cases (7%) who had raised CRP on admission and normal SAA: two had infections and both died, one had another inflammatory pathology and three had other diagnoses (two of these died).

CRP and SAA are very different proteins and their expression is differently regulated by the cytokine network, so it is not surprising that their behaviour differs in the complex situation of different individuals with multiple pathologies. Our results suggest that measurement of both these sensitive acute phase reactants enhances the utility of monitoring the acute phase response for clinical management and prognosis.

Key points
- Major elevations of the serum concentrations of C-reactive protein (CRP) and serum amyloid A protein (SAA) in elderly inpatients indicate serious disease and predict poor outcome.
- Measuring SAA as well as CRP enhances the value of monitoring the acute phase response in 7% of patients with a diagnosis of infection.

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References

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