C-reactive protein as measured by a sensitive enzyme-linked immunosorbent assay in patients with juvenile idiopathic arthritis

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C-reactive protein (CRP) is one of the indicators of disease activity and response to treatment in patients with inflammatory joint diseases. Turbidimetric and nephelometric methods are the approaches currently most common. These do not adequately measure CRP at concentrations below 5-10 mg/l; yet only about 2% of the blood donors had in our hands a CRP concentration ≥ 10 mg/l (1). In recent years enzyme-linked immunosorbent assays (ELISA) capable of detecting CRP concentrations of 0.5 mg/l or even less have become commercially available.

Two earlier studies have dealt specifically with the significance of CRP in juvenile idiopathic arthritis (JIA). Gwyther *et al*. (2) studied serum samples from 60 patients seen early in the course of their disease using a radial immunodiffusion technique which is slightly more sensitive than turbidimetry and nephelometry. CRP concentrations were found to be particularly high among patients with systemic onset of disease. CRP was also raised in cases with polyarticular onset, while in cases with pauciarticular onset only a modest increase was noted. Hussein *et al*. (3) studied serial specimens from 31 patients with long-lasting disease, using an ELISA somewhat less sensitive than the modifications currently available. CRP concentrations in active disease were significantly higher than in moderately active or inactive disease. In a considerable proportion of cases the CRP concentration remained below the detection level.

In the work described here we tested sera from 160 treated patients (101 girls and 59 boys) with JIA, using a sensitive ELISA. The mean age of the patients at diagnosis was 5.9 years (range 0.9 - 15.2 years), the mean duration of disease was 5.6 years (range 0 - 16 years) and the mean age at the time when the blood specimen for this study was taken was 11.5 years (range 1.8 - 25.3 years). In 93 patients the onset type was oligoarthritis and in 54 rheumatoid factor-negative polyarthritis; the remaining 13 patients had other types of JIA. For the purposes of the present study, a patient was considered to be in remission if there was no fever, no fatigue, no swollen joints, and no tender points for at least 4 months. Altogether 66 patients met these criteria; 58 patients were in remission with drugs and 8 patients without.

Serum samples were analysed in duplicate for CRP using a sandwich ELISA (UC CRP Elisa,Eucardio Laboratory, San Diego,California, USA) according to the manufacturer's instructions. The detection limit was 0.3 mg/l and the intra-assay coefficient of variation was 6%. About 11% (18/160) of the patients had CRP concentrations ≥ 10 mg/l. The median, however, was only 0.8 mg/l and the interquartile range 0.6 - 3.5 mg/l. Patients in remission had significantly lower CRP concentrations than those with active disease (Table I). Nonetheless,a considerable proportion of cases with active disease had in fact very low CRP concentrations; the cut-off point of the lowest quartile was as low as 0.6 mg/l. Patients with oligoarthirits had somewhat lower concentrations than those with polyarthritis, but this difference did not reach statistical significance.

Studies using sensitive ELISA have shown that CRP levels within the upper quartile/quintile of the "normal" range are associated with an increased risk of cardiovascular events, both in apparently healthy subjects and in subjects with pre-existing angina pectoris (4). Likewise, modestly but significantly increased CRP levels were found in women with early knee osteoarthritis, and higher levels, even if in the "normal" range, predicted progression of the disease (5). Thus, low-grade inflammation may be a significant aspect in atherosclerosis and osteoarthritis. The purpose of the study described here was to look for CRP concentrations in patients with JIA using a sensitive ELISA.

Control sera from healthy children were not available. Certain comparisons could be made, however, using CRP distributions among healthy adults. In a large population sample we found a median concentration of 1.0 mg/l for women and 1.6 mg/l for men (6). These figures match those reported by other investigators among control subjects in studies on atherosclerosis and osteoarthritis. Approximately 11% of our JIA patients had a CRP concentration of ≥10 mg/l and the cut-off point of the highest quartile was 3.5 mg/l. These figures are clearly higher than those recorded in our population sample of adults. On the other hand, the median concentration was only 0.8 mg/l, i.e. lower than that found among adults. Thus, at least half of the children with JIA under treatment or in remission without drugs evinced no CRP response as measured by a sensitive ELISA.

Table I. Distribution of C-reactive protein (CRP) concentration in patients with juvenile idiopathic arthritis.

	Number of patients	CRP concentration (mean)	mg/l (interquartile range)
Whole series	160	0.8	0.6 - 3.5
Patients in remission*	66	0.6	0.5 - 1.1
Patients with active disease*	94	1.6	0.6 - 5.7
Onset type			
Oligoarthritis†	93	0.7	0.6 - 2.0
Polyarthritis†	54	1.6	0.6 - 5.0

* Difference between groups: Mann-Whitney U test $p < 0.001$; † Difference between groups: Mann-Whitney U test $p = 0.09$.

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