Correlation between serum IL-6 and CRP levels and severity of head injury in children

Introduction

Infectious stimuli and trauma lead to a highly complex inflammatory reaction of the host, the so-called acute phase response. During acute phase response rates of the hepatic synthesis of several plasma proteins, the acute phase proteins, increase dramatically, while some others decrease. IL-6 is the most important mediator of acute phase protein synthesis in human hepatocytes [1]. Once IL-6 is released from the site of trauma or inflammation, it induces a wide range of systemic effects, including the acute phase response and production of acute phase proteins. It is well documented that patients with severe head injury (HI) are hypermetabolic, hypercatabolic and manifest several biochemical indications of acute phase response including the elevation of acute phase reactants [2–5].

The objectives of this study were to determine: (a) whether serum IL-6 and CRP levels were elevated in children with HI, (b) the fluctuation of IL-6 and CRP
during the course of hospitalization, (c) the relation between IL-6 and CRP levels and (d) the correlation between these two proteins and the severity of HI.

Patients and methods

In this prospective study we included children with HI admitted onto our PICU during the study period (1996–1997), with anticipated stays of at least 4 days. The term “HI” referred to any patient with altered level of consciousness after a trauma at the head with or without abnormal findings on CT scan. The patients ought to be admitted onto the PICU no more than 4 h after the injury and had to meet one of the two following criteria: 1) altered level of consciousness 2) abnormal motor responses (seizures, decorticate or decerebrate responses). Patients with other major injuries apart from the HI, patients treated with corticosteroids or patients who developed bacterial infection during their stay in the PICU were excluded from the study. The study has been approved by the Ethical Committee of the hospital. Their management in the PICU aimed: 1) to decrease cerebral oedema with hyperventilation, mannitol and sedation and 2) to treat the complications of HI.

Forty patients with cerebral oedema were treated with mannitol, 36 of them required mechanical ventilation (hyperventilation) under sedation. Eight children who experienced seizures and 28 were given antibiotic prophylaxis (cefotaxime plus dicloxacillin) because of open skull fractures. Thirty-eight of the patients (84.4%) made good recoveries or had moderate disabilities, three (6.7%) were severely disabled or vegetative at 1 year after the injury, according to the Glasgow Outcome Scale score [6], and 4 (8.9%) died. Blood samples were taken at 4, 12, 24, 48 and 72 h post-injury. Forty-five samples were taken per time point, except for the last time point (43 samples). Control samples of blood were taken from 10 normal children, who underwent adenoidectomy.

CRP was measured by immunonephelometry (using a Behring Nephelometer; Hoechst). Serum IL-6 was measured using a commercially available dual antibody sandwich enzyme-linked immunosorbent assay (Cytoscreen, BioSource, USA). This assay detects as little as 0.1 pg/ml with no cross-detection of other cytokines. Blood was collected for the IL-6 measurement in pyrogen-free glass tubes and centrifuged at 600 g for 10 min. The serum was removed and stored at −70°C in pyrogen-free plastic tubes until analysis.

Comparisons of biological parameters between the groups of patients were made using Student’s t-test for independent variables. To normalize the distribution of IL-6 values and to permit the use of the t-test, we used the log of serum level. The relationships between biological parameters were tested by linear regression and chi-square was used to test the correlation between IL-6 or CRP serum levels and outcomes of the patients.

Results

Forty-five children completed the study. Thirty-eight were boys and seven girls, with a median age of 9.2 years (range: 15 months to 14 years). Their initial GCS scores [7] ranged from 3 to 15 (median: 8.0); 24 had GCS of 8 or less and 21 GCS more than 8. Their admission peak 24-h PRISM score [8] was between 2 and 29 (median: 8.0); 14 of them had PRISM scores of 10 or more and 31 PRISM scores lower than 10.

Serum IL-6 values were elevated in all the head-injured children of our study. They reached the highest levels 4 h post-injury, decreasing over time, but they were still elevated 72 h after the injury (Fig. 1). The IL-6 levels in the controls were less than 0.1 pg/ml (below the sensitivity of the assay) (p < 0.001). IL-6 concentration in the serum of different groups of patients are presented in Figs. 2 and 3. The children in serious neurological condition (GCS ≤ 8) had significantly higher IL-6 values, than those with GCS scores higher than 8 at 4 and 12 h post-injury (**p < 0.01, *p < 0.05). Values are means ± SEM.

Fig. 1 Serum IL-6 levels of children with HI were significantly elevated above the levels of normal controls (> 0.1 pg/ml) at 4, 12, 24, 48 and 72 h post-injury (p < 0.001 in all time points). Results are shown as means ± SEM.

Fig. 2 Children with GCS scores 3–8 had significantly higher IL-6 values, than those with GCS scores higher than 8 at 4 and 12 h post-injury (**p < 0.01, *p < 0.05). Values are means ± SEM.