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Serum Intercellular Adhesion Molecule-I in Children with Chronic Liver Disease

Relationship to Disease Activity

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Intercellular adhesion molecule-I (ICAM-I) is a member of the immunoglobulin supergene family. It is expressed on the surface membrane of cells of multiple lineages at sites of inflammation. A soluble form of ICAM (sICAM-I) comprising the five extracellular Ig-like domains of ICAM-I has been detected in human serum and has been found to be increased in a variety of acute and chronic liver disorders. However, little is known about sICAM-I levels in children with chronic liver disease. Therefore, we measured sICAM-I in 23 children with chronic hepatitis, 14 children with cirrhosis, and 10 age- and sex-matched normal children by commercially available ELISA. We also correlated the sICAM-I levels with the histological activity index (HAI) score as determined from liver biopsies. Patients with chronic hepatitis had higher sICAM-I levels compared to controls (723 ± 272 ng/ml vs 282 ± 43 ng/ml, mean ± SD; $P < 0.05$). sICAM-I levels were also higher in patients with cirrhosis compared to controls (630 ± 218 ng, mean ± SD; $P < 0.05$). However, there was no significant difference between sICAM levels in patients with chronic hepatitis and cirrhosis. A significant correlation was found between the ICAM-I level and the histological activity index score in patients with chronic hepatitis ($r = 0.58$; $P < 0.001$) and in patients with cirrhosis ($r = 0.7$; $P < 0.001$). We also found that by using the cutoff level of 346 ng/ml, sICAM-I can be used as a screening test with high specificity (100%) and sensitivity (94%) to differentiate children with chronic liver disease from normal children. We conclude that sICAM is increased in children with chronic hepatitis and cirrhosis compared to controls. The degree of elevation correlates with the HAI score. sICAM may be used as a marker of the disease activity and may provide diagnostic and prognostic information in children with chronic liver disease. However, this needs to be further studied.

KEY WORDS: intercellular adhesion molecule; cirrhosis; chronic hepatitis.

Intercellular adhesion molecule-I (ICAM-I) is a member of the immunoglobulin supergene family. It is expressed on the surface membrane of cells of multiple lineages at sites of inflammation (1, 2). Shed-

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Table 1. Characteristics of Study Population

Characteristic	Patients		Controls
	Cirrhosis	Chronic hepatitis	
Age (yr)	6.7 ± 0.3	8.2 ± 0.3	7.3 ± 0.3
Sex (M/F)	8/6	13/10	6/4
Aspartate aminotransferase	41 ± 24	59 ± 28	20 ± 4
Alanine aminotransferase	44 ± 17	68 ± 31	21 ± 4
Total bilirubin (mg/dl)	1.1 ± 0.6	1.8 ± 0.9	0.6 ± 0.2
Prothrombin activity (%)	62 ± 5.4	78 ± 6.3	83 ± 4.9
Albumin (g/dl)	3.7 ± 0.6	3.4 ± 0.5	4.3 ± 0.4

ding of ICAM-I from these cells is enhanced by proinflammatory cytokines such as interferon (IFN), tumor necrosis factor (TNF), and interleukin-1 (IL-1). ICAM-I is believed to play an important role in many inflammatory and immune-mediated mechanisms, including lymphocyte recruitment and targeting, antigen presentation and recognition, and lymphocyte cytotoxicity (2–4).

A soluble form of ICAM (sICAM-I) comprising the five extracellular Ig-like domains of ICAM-I has been detected in human serum (5). sICAM-I has been found to be increased in a variety of acute and chronic liver disorders (6), and it was suggested that it could serve as a helpful marker in the diagnosis and therapeutic monitoring of inflammatory disorders (7). However, little is known about sICAM-I levels in children with chronic liver disease. Therefore, we measured sICAM-I levels in pediatric patients with chronic hepatitis and cirrhosis and correlated these levels with the histological activity index (HAI) score as suggested by Knodell et al (8), and modified by Desmet et al (9).

MATERIALS AND METHODS

Our study included 23 patients with chronic hepatitis (9 with chronic hepatitis B, 8 with chronic hepatitis C, and 6 with autoimmune hepatitis), and 14 patients with cirrhosis (7 with biliary atresia, 4 with Byler's disease, and 3 with α_1-antitrypsin deficiency). Diagnosis was made based on clinical, laboratory, and histological assessment. Ten healthy age- and sex-matched children attending the general pediatrics outpatient clinic for routine physical examination were recruited to serve as normal controls (Table 1). An Informed consent was obtained from the parents of patients and controls prior to enrollment into the study.

Percutaneous liver biopsy was done in all patients using a Menghini needle after a written consent was obtained from the parents. The biopsy samples from the 37 patients were blindly examined, and the HAI score was determined as suggested by Knodell et al (8), and modified by Desmet et al (9). Serum sICAM-I was measured in duplicate using a commercially available enzyme-linked immunosorbent assay (ELISA) (British Biotechnology Ltd., Oxford UK) as described by the manufacturer (2). One-way analysis of variance (ANOVA) with Tukey's studentized range test was used to determine the significance of difference among the controls, patients with chronic hepatitis, and patients with cirrhosis with regard to sICAM. Spearman correlation coefficients were used to determine the relationship between sICAM levels and the HAI score in the chronic hepatitis and cirrhosis groups. Data were expressed as mean ± SD. Results were considered significant at $P < 0.05$.

RESULTS

Patients with chronic hepatitis had higher sICAM-I levels compared to controls (723 ± 272 ng/ml vs 282 ± 43 ng/ml, mean ± SD; $P < 0.05$). sICAM-I levels were also higher in patients with cirrhosis compared to controls (630 ± 218 ng, mean ± SD; $P < 0.05$). However, there was no significant difference between serum ICAM-I levels in chronic hepatitis and cirrhotic patients (Figure 1).

A significant correlation was found between the ICAM-I level and the HAI score in patients with chronic hepatitis ($r = 0.58$; $P < 0.001$) and in patients with cirrhosis ($r = 0.7$; $P < 0.001$). A receiver operating characteristic (ROC) curve was derived. By using a cutoff level of 346 ng/ml, sICAM-I can be used as a screening test with high specificity (100%) and sensitivity (94%) to differentiate children with chronic liver disease from normal children.

DISCUSSION

The migration of circulating neutrophils, monocytes, and lymphocytes into perivascular tissues entails the interaction of specific ligands on their surface with receptors on endothelial cells. These ligands and their receptors have been defined as adhesion molecules (11). Cellular expression of these molecules is affected by cytokines, such as tumor TNF-α, IL-1, and IFN-γ. Tissue expression is increased during inflammatory processes such as hepatitis. Soluble forms

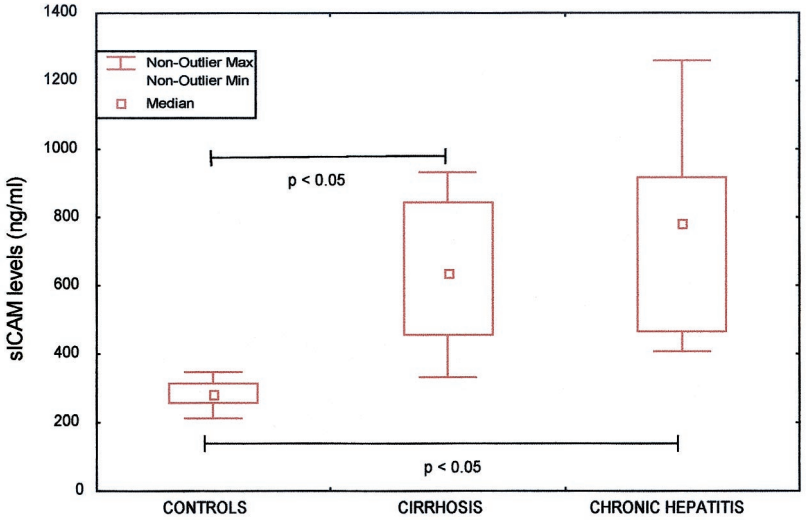

Fig 1. sICAM levels in controls, patients with cirrhosis, and patients with chronic hepatitis.

have been identified recently and their measurement may help in monitoring progression of inflammatory processes as well as response to therapy.

sICAM-I expression is significantly increased in patients with acute viral and drug-induced hepatitis, chronic active hepatitis, and active cirrhosis (6). Although treatment with corticosteroids reduces sICAM expression, patients with cirrhosis may continue to have increased levels (10). sICAM-I is increased in patients with chronic hepatitis C infection and was found to correlate positively with the grade of histological activity and to decrease in the patients who respond to interferon therapy (2). Although expression of sICAM-I is increased with progression of primary biliary cirrhosis, treatment with methotrexate has no effect on the expression of *s*ICAM or other adhesion molecules (11, 12).

sICAM-I was found to be increased in our pediatric patients with chronic hepatitis and cirrhosis compared to controls in a close relationship to the histological activity. We found that by using the cut off level of 346 ng/ml, sICAM-I can be used as a screening test with high specificity (100%) and sensitivity (94%) to differentiate children with chronic liver disease from normal children. These results suggest that measuring and monitoring serum ICAM-I levels may provide diagnostic and prognostic information and may be used as a marker of the disease activity. However, this needs to be further studied.

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