Serum hyaluronic acid concentrations in children with cirrhosis

Inci Nur Saltık-Temizel, Nurten Koçak, Hasan Özen, Hülya Demir
Hacettepe University, Faculty of Medicine, Department of Pediatrics, Section of Gastroenterology, Hepatology and Nutrition, 06100 Ankara, Turkey

Background: Liver disease is associated with increased levels of hyaluronic acid (HA). Aim: To evaluate serum HA concentrations in children with cirrhosis and its relation with liver function tests and Child-Pugh score. Methods: Twenty-two children with biopsy-proven liver cirrhosis were studied. All were assessed for the presence of ascites or encephalopathy and liver function tests were performed. Patients were categorized according to Child-Pugh criteria. Serum HA was measured using microELISA (normal 0-100 ng/mL). Twenty-two children with chronic hepatitis B and no cirrhosis were studied as controls. Results: Serum HA level in the cirrhotic children was 85.2 (72.8) ng/mL; levels were high (166.0 [46.3] ng/mL; range 115-246) in 8 (36.4%) patients. Three of 11 (27.2%) Child-Pugh class A patients, 3 of 8 (37.5%) class B patients, and 2 of 3 (66.7%) class C patients had elevated serum HA values (p=ns). Serum HA levels correlated with direct bilirubin level. The control group had lower levels (4.8 [2.3] ng/mL; p<0.05), which were in the normal range. Conclusion: Serum HA level may be useful as a diagnostic tool in children with cirrhosis. [Indian J Gastroenterol 2004;23:129-130]

Key words: Child, chronic liver disease, pediatric

Hyaluronic acid (HA) is a high-molecular-weight polysaccharide that is widely distributed in connective tissue. It is produced by fibroblasts and enters the circulation via lymph. It is taken up by hepatic sinusoidal endothelial cells (SECs), where it is degraded by hyaluronidase enzyme.

Liver disease is associated with increased levels of HA. Significant correlation between serum HA concentration, degree of liver fibrosis, and liver function tests has been found in primary biliary cirrhosis, alcoholic liver disease, and chronic hepatitis C. It has been suggested that serum HA level predicts response to interferon-alpha therapy in patients with chronic hepatitis C.

In children with liver cirrhosis, the relation between serum HA concentrations and liver injury is uncertain. We evaluated serum HA concentrations in children with cirrhosis and its relation with liver function tests and Child-Pugh score.

Methods
Twenty-two children (mean age 10.3 [5-14] years, range 1-17; 15 boys) with biopsy-proven cirrhosis were studied. All children were assessed clinically for the presence of ascites or encephalopathy. Liver function tests including prothrombin time were performed in all. Patients were categorized according to Child-Pugh criteria.

Liber biopsy had been performed in them within the last 6 months. The etiology of cirrhosis, based on biochemical and immunological blood tests and liver biopsy, was as follows: biliary atresia (4), Wilson's disease (4), autoimmune (2), idiopathic familial (2), progressive familial intrahepatic cholestasis (1), and cryptogenic (9). Twenty-two children with chronic hepatitis B and no cirrhosis (mean age 10.6 [4.5] years, range 4-18; 15 boys) were studied as controls.

Blood specimens (10 mL) were obtained after at least 4 hours of fasting and serum separated by centrifugation. The serum was stored at -20°C for measurement of HA level using microELISA (Corgenix; Colorado, USA). The normal range of HA levels is 0-100 ng/mL. Routine liver functions were studied by sequential multiple autoanalyzer at 37°C, with standards supplied by the manufacturer.

Statistical analysis
Results were expressed as mean (SD). Intergroup comparisons were done using Student's t test. The Pearson correlation coefficient was used to assess the degree of correlation between HA, liver function tests, and Child-Pugh scores. A p value <0.05 was considered statistically significant (two-tailed test of significance).

Results
The 22 patients were followed up for a mean period of 4.9 (3.4) years (range 0.5-12). Eleven patients were in Child-Pugh class A, 8 in B and 3 in C. On physical examination, 9 (41%) patients had ascites. The mean serum HA level was 85.2 (72.8) ng/mL (range 2-246) in children with cirrhosis, and 4.8 (2.3) ng/mL (1-9) in the control group. Serum HA level was higher than the upper limit of normal in 8 (36.4%) patients, of whom four had ascites. Seven of these 8 children were boys; 2 each had...
biliary atresia and autoimmune liver disease, one had Wilson's disease, and three had cryptogenic cirrhosis.

Three of 11 Child-Pugh class A patients, 3 of 8 class B patients, and 2 of 3 class C patients had raised serum HA values (p=ns). Serum HA levels had no relationship with age, duration of follow-up, presence of ascites, and serum levels of transaminases, albumin, and y-glutamyl transpeptidase or prothrombin time. Although only 3 of 8 patients had high conjugated bilirubin serum, HA levels significantly correlated with conjugated bilirubin (correlation coefficient 0.729; p=0.04). Only two of 14 patients with normal serum HA level had high conjugated bilirubin level.

**Discussion**

Hyaluronic acid is an unbranched high-molecular-weight polysaccharide that is synthesized primarily by the stellate (Ito) cells and cleared by hepatic SECs after binding specifically to a high-affinity receptor.

Fibrogenesis is associated with hepatic stellate cells proliferation, leading to excess HA production. The hepatic sinusoidal capillarization that occurs in cirrhosis coincides with reduction in the capacity of SECs to clear HA. The positive mechanisms for increase in HA concentration in liver cirrhosis are increased synthesis due to stellate cells proliferation and reduced clearance by SECs, with the latter predominating.

Studies in adult patients with various liver diseases have shown that there is significant correlation between serum HA concentration and the degree of liver fibrosis, and several liver function tests including serum albumin and bilirubin levels. In children with biliary atresia, serum HA might reflect the degree of liver fibrosis; however, there are no certain data about serum HA level in children with cirrhosis. In our study, children with cirrhosis had significantly higher mean serum HA level than the control group. We did not find any correlation between serum HA level and other liver function parameters except with conjugated bilirubin level. Plevris et al. found no difference in HA levels between different etiologies in adult cirrhotic patients, similar to our observation in children.

There are no confirmed prognostic factors for survival in children with liver disease. Malatack et al. found four prognostic factors, including serum cholesterol level, history of ascites, indirect bilirubin level and prothrombin time. We used the Child-Pugh score, which includes similar prognostic factors and also encephalopathy and albumin levels. Plevris et al. observed that serum HA levels increased with progression of liver cirrhosis as measured by the Child-Pugh classification. Murawski et al. observed higher serum HA levels in adult cirrhotic patients but found no correlation with Child-Pugh class. Plevris et al. reported that the specificity and sensitivity of serum HA level for diagnosing liver cirrhosis increased above the level of 300 mg/L. The highest serum HA level in our patients however was 246 mg/mL.

In conclusion, measurement of serum HA level may be useful as a diagnostic tool in cirrhotic children.

**References**


**Correspondence to:** Dr Saitik-Tomizel. Fax: +90 (31) 2311 7715. E-mail: slsaitik@hacettepe.edu.tr

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