Aminotransferase as a Prognostic Index in Infants with Liver Disease

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To assess the utility of the serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio in a group of infants with liver disorders, we retrospectively analyzed the charts of 73 infants with chronic liver disorders. Patients were included as having either a good outcome (n = 40) or a poor outcome (n = 33), based upon the clinical course. AST and ALT in serum were measured simultaneously at the time of initial presentation and at various follow-up visits during the first 13 months after birth. At presentation (mean age 1.65 months), there was no difference in the AST/ALT ratios between the good (1.61 ± 0.62; mean ± SD) and poor (1.65 ± 0.78) outcome groups (P = 0.81). However, over time, the AST/ALT ratio increased in patients in the poor-outcome group and decreased in patients in the good-outcome group. Calculating the AST/ALT ratio appears to be an easy, early, and reliable prognostic indicator for infants with hepatic disease, and may be a useful measure for evaluating liver-disease patients.

Advances in the diagnosis and treatment of pediatric liver disorders have markedly improved survival rates for children with liver disease (1). Unfortunately, a substantial number of children continue to die from complications of their primary hepatic pathology while awaiting liver transplantation. Given the limited number of donor organs, identification of the infants at greatest risk who might benefit from earlier hepatic transplantation could be of considerable utility.

The ratio between aspartate aminotransferase (AST, EC 2.6.1.1) and alanine aminotransferase (ALT, EC 2.6.1.2), AST/ALT, has been found to be a useful indicator of hepatic disease in adults (2). In adult patients with nonalcoholic liver disease, an AST/ALT ratio increasing to >1.0 suggests cirrhosis, whereas a ratio <1.0 is usually seen in patients with chronic hepatitis, survivors of acute viral hepatitis, and patients with chronic cholestatic syndromes (2–5). An AST/ALT activity concentration ratio >2.0 has been reported in adult patients with alcoholic liver disease (5, 6).

In an attempt to identify an easily measured and reliable index that would assist in the early evaluation of infants with liver disorders and offer a prognostic guide to their outcome, we assessed the utility of the AST/ALT ratio in the serum of a group of such infants.

Patients and Methods

We retrospectively analyzed the charts of 73 infants with chronic liver disorders, who had been referred to our division for evaluation and treatment between October 1976 and September 1988. Diagnoses were confirmed on the basis of appropriate clinical, microbiological, radiological, biochemical, and histological criteria. The study population included 42 infants with extrahepatic biliary atresia, 12 infants with cytomegalovirus (CMV) hepatitis, 11 with idiopathic neonatal hepatitis, six with alpha-1-antitrypsin deficiency liver disease, and two with arteriohepatic dysplasia (Alagille's syndrome). There were 39 boys and 34 girls.

Patients were assigned to either a good-outcome (n = 40) or poor-outcome (n = 33) group, based on their clinical course. Poor outcome was defined as evidence of cirrhosis, portal hypertension, esophageal varices, ascites, liver transplantation, or death. Patients in the good-outcome group had no signs of chronic liver disease or any of the findings used to define a poor outcome. Follow-up assessments were made from three months to 10 years later (mean 23 months).

AST and ALT activity concentrations were measured simultaneously in serum of each patient at the time of initial presentation and at various intervals at follow-up visits with an automated procedure (Abbott Bichromatic Analyzer, ABA-100; Abbott Labs., Abbott Park, IL) in our clinical chemistry laboratory under standard laboratory conditions (7). The serum AST/ALT ratios during the first 13 postnatal months were calculated from these serial values. We used Student's t-test (two-tailed) to compare values obtained for the two groups.

This study was approved by the Committee on Clinical Investigations and Publications of the Children's Hospital of Los Angeles.

Results

For the good-outcome group, serum AST values ranged

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from 15 to 637 U/L (reference range 20–55) and serum ALT from 13 to 1020 U/L (3–37). The calculated AST/ALT ratio for the good-outcome group ranged from 0.50 to 4.31 (mean 1.36, SD 0.62). For the poor-outcome group, the respective values ranged from 41 to 5850 U/L, 17 to 1890 U/L, and 0.46 to 4.34 (mean 1.70, SD 0.66).

At the time of initial presentation (ages one week to five months, mean 1.65 months), there was no significant difference in mean AST/ALT ratios between the good-outcome (1.61, SD 0.62) and poor-outcome (1.65, SD 0.78) groups (P = 0.81). However, if the AST/ALT ratios were followed serially over time, the ratio increased in patients in the poor-outcome group and decreased in patients in the good-outcome group (Table 1). Given the range of AST/ALT ratios, a single determination of the AST/ALT ratio during the first year of infancy was not predictive of outcome. By ages five to seven months, however, infants in the good-outcome group already tended to have an AST/ALT ratio <1.50 while infants in the poor-outcome group tended to have an AST/ALT ratio ≥1.50 (Figure 1).

Discussion

The present study demonstrates the utility of calculating and following serially the serum AST/ALT ratio in infants with liver disease. Through retrospective analysis, we were able to examine the AST/ALT ratios in patients in whom diagnosis and outcome were established. This way, we could exclude patients with myocardial injury, circulatory congestion, muscle injury, central nervous system disease, immediate postoperative states, and other nonhepatic conditions accompanied by increased serum aminotransferases (transaminases). AST and ALT catalyze the transfer of the alpha-amino groups of aspartate and alanine, respectively, to the alpha-keto group of ketoglutaric acid, resulting in the formation of oxaloacetic acid and pyruvic acid. Whereas AST is present in a wide variety of tissues (heart, skeletal muscle, kidney, and brain) in addition to liver, ALT is primarily found only in the liver (3). AST in the liver is present in both mitochondria and cytosol, with 80% of hepatic AST activity residing in the mitochondria (8). ALT in the liver is limited to the cytosol (3).

The AST/ALT ratio in the cytoplasm of the hepatocyte is 0.6, whereas the AST/ALT ratio in the total hepatocyte (including cytoplasm and mitochondria) is 3.0 (9). The isoenzymes of AST differ in cytoplasm and mitochondria (8).

Values for serum AST and ALT were abnormally high in all the infants at presentation. Although this may reflect the extent of hepatic necrosis, the increases do not correlate with outcome. Although declining values for serum AST and ALT may indicate recovery, they may also indicate a poor prognosis if there is a paucity of remaining hepatocytes to contribute to the serum enzyme pools. In most of these infants, serum AST and ALT were either slightly or moderately increased.

In general, the AST/ALT ratio was lower for infants in the good-outcome group compared with the poor-outcome group. This may be the result of the extent of hepatic injury and localization of transaminases within the hepatocyte. ALT is exclusively localized in the cytoplasm of the hepatocyte. In mild hepatic injury, only the hepatocyte membrane is damaged, releasing only cytoplasmic enzymes (including AST and ALT) but leaving hepatic mitochondrial membranes intact. Because the AST/ALT ratio in the hepatic cytoplasm is 0.6, a low AST/ALT ratio in serum is to be expected. However, with more severe hepatic injury, both hepatocyte cytoplasmic and mitochondrial membranes are damaged with pooling of enzymes from both sources. Because total hepatocyte AST/ALT is

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**Table 1. Changes in AST/ALT Grouped by Age and Outcome**

<table>
<thead>
<tr>
<th>Age, months</th>
<th>Good outcome</th>
<th>Poor outcome</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Ratio</td>
<td>SD</td>
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<tr>
<td>0–1</td>
<td>1.68</td>
<td>0.68</td>
</tr>
<tr>
<td>2–4</td>
<td>1.36</td>
<td>0.61</td>
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<tr>
<td>5–7</td>
<td>1.15</td>
<td>0.42</td>
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<tr>
<td>8–10</td>
<td>1.25</td>
<td>0.74</td>
</tr>
<tr>
<td>11–13</td>
<td>1.20</td>
<td>0.66</td>
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</tbody>
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NS, not significant (P <0.05).
Mitochondrial Aspartate Aminotransferase Determined by “Fast Protein Liquid Chromatography”

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We describe an improved separation of the isoenzymes of aspartate aminotransferase (EC 2.6.1.1), based on ion-exchange chromatography. Involving the “Fast Protein Liquid Chromatography” system (Pharmacia) with a MonoQ column, this rapid, reproducible method for quantifying the mitochondrial enzyme shows good resolution and sensitivity, and results correlate well with those by an established immunochemical method.

The mammalian aspartate aminotransferase (AspAT, EC 2.6.1.1) enzyme exists in two isoenzymic forms, mitochondrial (mAspAT) and cytosolic (cAspAT). Measurements of mAspAT may have diagnostic utility (1–6), but such determinations are not in routine use, in part because of inconvenient assay techniques and the lack of commercially available reagents.

The most nearly accurate and most sensitive assays are based on immunochemical techniques (6–9). Other procedures such as ion-exchange chromatography (2, 10), electrophoresis (11), and differential kinetics (12) have also been described, and their relative merits have been compared (13). A recently published improved electrophoretic method (14) yielded results correlating well with those by the immunochemical precipitation assay (7), but it is insufficiently sensitive for application to sera with normal or slightly increased mAspAT activity. Teranishi et al. (15) described a technique involving protease sensitivity, but this method apparently is highly imprecise near the normal reference interval.

Here we describe an improved separation of the isoenzymes based on the ion-exchange technique described by Sampson et al. (10) and later modified by Rabkin and Desjardins (2). We have made use of the high-performance separation of monodispersed particles ("Monobeads") and the "Fast Protein Liquid Chromatography" (FPLC) system to attain fast, reproducible separation with high recovery. Moreover, separation and quantification of the isoenzymes with this technique is independent of the species specificity of antibodies; thus the technique potentially is applicable to both human and animal studies.

Materials and Methods

Chromographic separations. We used the standard FPLC system (Pharmacia, LKB Biotechnology, Uppsala, Sweden) with a 5 × 50 mm column of MonoQ HR 5/5 ion-exchange resin. The column was equilibrated with buffer A: per liter, 50 mmol of Tris hydrochloride (pH 8.1 at 25 °C) and 50 mmol of NaCl. All samples were diluted threefold with buffer A, passed through a 0.22-μm (pore size) filter (Milllex-GS; Millipore, Molsheim, France), and 0.5 mL of filtrate was applied to the column. The column was eluted with 3 mL of buffer A and then with a linear gradient (0–100%) of buffer B (per liter, 50 mmol of the Tris hydrochloride buffer and 300 mmol of NaCl) in 7 mL. The

References