Alterations in Total Lactate Dehydrogenase and Its Isoenzyme-5 in Hepatic Disorders*

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ABSTRACT

Values for total lactate dehydrogenase (LD, EC 1.1.1.27) and LD isoenzyme-5 were determined in serum of 106 patients with benign hepatic disorders, 54 of whom had acute liver disorders, either acute hepatitis (39 patients) or acute circulatory disturbances (15 patients). Fifty-two had chronic hepatic disorders, either cirrhosis (25 patients) or chronic right heart failure (27 patients). Overall, values for LD were above normal for 86 percent of the 106 patients with benign hepatic disorders. In 83 percent of 30 patients with non-fulminant viral hepatitis, LD values were below 350 U per L, while in all nine patients with either fulminant viral or toxic hepatitis, and in all 15 patients with acute circulatory disturbances, LD values were above 500 U per L. In all 52 patients with chronic hepatic disorders, LD values were below 350 U per L. In patients with acute liver disorders, both the total LD and LD-5 proportions were sensitive for liver injury (87 percent and 91 percent, respectively). On the other hand, LD-5 proportion was much less sensitive than total LD in patients with chronic liver disorders (40 percent versus 85 percent). In conclusion, a difference was found in LD values and LD-5 ratios between patients with non-fulminant viral hepatitis and patients with other causes for acute liver injury. The LD-5 proportions are more sensitive for hepatic injury in patients with acute liver disorders than in those with chronic liver disorders.

Introduction

Increased values of lactate dehydrogenase (LD, EC 1.1.1.27) have been observed in serum of patients with benign liver disorders such as infectious hepatitis and cirrhosis of liver. Zimmernman and West observed that serum LD is an insensitive index of hepatic disease. Others observed a marked elevation of LD-4 and LD-5 isoenzymes in serum, where hepatocellular
ALTERATIONS IN TOTAL LE AND LE-5 IN HEPATIC DISORDERS

269

Damage was a prominent feature and concluded that increase in LD-4 and LD-5 may be more specific markers for hepatic involvement. Most groups with benign liver disorders described in the literature are relatively small. It is unclear whether or not there is any difference in the values of total LD and LD isoenzymes patterns between the acute and chronic hepatic disorders or if various liver disorders, either acute or chronic, might show a difference in LD patterns.

The present authors wished to determine total LD activity and the ratios of the isoenzyme LD-5 in serum of patients with acute and chronic hepatic disorders, to characterize which specific groups of patients are associated with increased total LD and LD-5 proportions, and to correlate the increase in total LD with the concentrations of LD-5 in serum.

Patients and Methods

One hundred and six patients were studied who were hospitalized in Beilinson Medical Center. Of these patients, 54 had acute and 52 had chronic hepatic disorders. Thirty-nine had acute hepatitis, most of them with viral hepatitis (34 patients) and five toxic hepatitis owing to drugs. Four patients out of the 34 with viral hepatitis had a fulminant hepatic failure defined as the onset of encephalopathy secondary to severe liver dysfunction within eight weeks of the onset of symptoms and in the absence of pre-existing liver disease.10 Fifteen patients suffered from acute circulatory disturbances, either acute liver congestion (10 patients) or shock (five patients). The 52 patients with chronic hepatic disorders had either cirrhosis (25 patients) or chronic right heart failure (27 patients).

After the blood samples for the LD activity and isoenzymes were obtained, they were kept at 4 to 8°C before the analysis, for no more than 24 hours.

Total serum LD was measured by the method of Wacker et al12 at 37°C in a centrifugal analyzer.* The normal reference interval in our laboratory is 100 to 225 U per L, and the coefficients of variation (CVs) for normal and abnormal serum LD values are 3.2 to 4.2 percent. The proportions of the LD isoenzymes were determined by electrophoresis on cellulose acetate plates† instrumentation. The normal reference interval for the LD isoenzymes, expressed as a percentage of the total LD, are: LD-1, 10 to 31 percent; LD-2, 35 to 53 percent; LD-3, 24 to 38 percent; LD-4, 0 to 10 percent; and LD-5, 0 to 10 percent. The CVs for determining the LD isoenzymes were as follows:

<table>
<thead>
<tr>
<th></th>
<th>LD-1</th>
<th>LD-2</th>
<th>LD-3</th>
<th>LD-4</th>
<th>LD-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within run</td>
<td>%</td>
<td>2.5</td>
<td>1.6</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Between day</td>
<td>%</td>
<td>3.5</td>
<td>3.5</td>
<td>6</td>
<td>7.8</td>
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</tbody>
</table>

The patients were divided into five groups based on total activity of LD in serum: group 1, within the normal reference interval, <225 U per L; group 2, activity mildly increased, 226 to 349 U per L; group 3, activity moderately increased, 350 to 499 U per L; group 4, activity highly increased, 500 to 999 U per L; and group 5, activity very highly increased, >1000 U per L.

The patients were divided into four groups based on the proportions of the LD-5; group A, within the normal reference interval, LD-5 per LD < 10 percent; group B, moderately increased, 11 to 20 percent; group C, highly increased, 20 to 40 percent; and group D, very

* Electro-Nucleonics, Fairfield, NJ 07006.
† Helena Kit (cat #5451), Helena Laboratories, Beaumont, TX 77704.
highly increased, >40 percent. The Student's t-test was used to compare between the mean and SD of LD activity in serum in the various groups of patients.

Results

In table I is shown total LD activity in the study population and the distribution of the patients according to LD activity in serum. Mean LD activity was significantly higher (p < 0.005) in the fulminant-viral and toxic-hepatitis groups of patients than in the acute non-fulminant viral hepatitis group. Twenty-five patients with acute non-fulminant viral hepatitis (83 percent), were found to have total LD activity below 350 U per L, while all nine patients with either toxic or fulminant viral hepatitis had LD values above 1000 U per L. Patients with acute circulatory disturbances, either acute liver congestion or shock, were also found to have significantly increased LD activity in serum in comparison with the acute non-fulminant viral hepatitis group of patients (p < 0.001). Activity of LD was, however, higher in the group of patients with shock in comparison with the group of patients with acute liver congestion. The values of LD in serum of the 10 patients with acute liver congestion were between 500 and 999 U per L, while all the five with shock, similar to the nine patients with fulminant-viral and toxic-hepatitis, were found to have LD values above 1000 U per L. Mean LD activity in serum of patients with chronic hepatic disorders, either cirrhosis or chronic right heart failure, was significantly lower (p < 0.01) in comparison with the three subgroups with acute hepatitis and with the two subgroups with acute circulatory disturbances. All the patients with chronic hepatic disorder were found to have LD activity in serum below 350 U per L.

In table II are shown the LD-5 proportions in the study population and the distribution of the patients according to the LD-5 per LD ratios. Mean LD-5 per LD was significantly higher in the fulminant-viral and toxic hepatitis groups of

<table>
<thead>
<tr>
<th>Total Lactate Dehydrogenase in the Study Population and the Distribution of the Patients According to LD Activity in Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LD, U/L +/-SD</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Non-fulminant hepatitis</td>
</tr>
<tr>
<td>Fulminant hepatitis</td>
</tr>
<tr>
<td>Toxic</td>
</tr>
<tr>
<td>Acute circulatory disturbances</td>
</tr>
<tr>
<td>Acute liver congestion</td>
</tr>
<tr>
<td>Shock</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Chronic right heart failure</td>
</tr>
</tbody>
</table>

Normal ranges
Group 1: < 225 U/L, within normal reference interval.
Group 2: 226 − 349 U/L, activity mildly increased.
Group 3: 350 − 499 U/L, activity moderately increased.
Group 4: 500 − 999 U/L, activity highly increased.
Group 5: > 1,000 U/L, activity very highly increased.
ALTERATIONS IN TOTAL LE AND LE-5 IN HEPATIC DISORDERS

patients than in the non-fulminant viral hepatitis group (p < 0.001). In 93 percent of patients with non-fulminant viral hepatitis, LD-5 proportions were below 20 percent, while in 78 percent of patients with fulminant-viral and toxic hepatitis, LD-5 proportions were above 40 percent. Most patients with acute circulatory disturbances were also found to have LD-5 proportions >20 percent. Mean LD-5 per LD was at its highest level in the group of patients with shock (65 ± 18 percent). Mean LD-5 proportions were significantly lower in the group of patients with chronic hepatic disorders in comparison with all groups with acute hepatic disorder. Sixty percent of patients with chronic liver disorder were found to have normal proportions of LD-5 in their serum.

Discussion

Total serum LD was found to be elevated in 23 of the 30 patients with non-fulminant viral hepatitis, and in all nine cases of either fulminant-viral or toxic-hepatitis. The LD-5 was a more sensitive index for liver injury as it was elevated in 34 of the 39 patients with acute hepatitis. This is in agreement with findings of earlier workers.6,7,8,11,14 In cases of cirrhosis, however, LD-5 was much less sensitive for hepatic involvement than total LD (28 percent versus 76 percent). Nathan et al7 reported a similar trend with 50 percent sensitivity for LD-5 and 60 percent for total LD. Ramdeo and Joshi8 and Trujillo et al11 reported, on the other hand, a higher sensitivity for the LD-5 parameter. Like Ramdeo and Joshi,8 the present authors found only moderately elevated levels of LD in non-fulminant hepatitis; in only five of the 30 patients, LD values were above 500 U per L.

On the other hand, in both groups of patients with fulminant-viral and toxic-hepatitis, total LD values were above 1000 U per L in all nine patients, and the LD-5/LD ratio was above 40 percent in seven of them. There may be some factors which affect the enzymatic pattern in serum in acute hepatitis and which may be responsible for the difference between the non-fulminant and fulmi-

| TABLE II |
|-----------------|-----------------|--------------------|-------|------|-------|
| Lactate Dehydrogenase Lsoenzyme-5 Proportions in the Study Population and the Distribution of the Patients According to the LD-5/LD Ratio |

<table>
<thead>
<tr>
<th>LD-5/LD, %+/−SD</th>
<th>Number of Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr. A</td>
<td>Gr. B</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fulminant hepatitis</td>
<td>16+/- 9</td>
<td>5</td>
</tr>
<tr>
<td>Fulminant hepatitis</td>
<td>49+/-10</td>
<td>-</td>
</tr>
<tr>
<td>Toxic</td>
<td>42+/- 9</td>
<td>-</td>
</tr>
<tr>
<td>Acute circulatory disturbances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute liver congestion</td>
<td>23+/- 7</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>65+/-18</td>
<td>-</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>9+/- 2</td>
<td>10</td>
</tr>
<tr>
<td>Chronic right heart failure</td>
<td>11+/- 3</td>
<td>13</td>
</tr>
</tbody>
</table>

Normal values:

- Group A: LD-5/LD < 10%, within normal reference interval.
- Group B: LD-5/LD 11 - 20%, moderately increased.
- Group C: LD-5/LD 20 - 40%, highly increased.
- Group D: LD-5/LD > 40%, very highly increased.
nant/toxic hepatitis. These include suddenness of liver cell injury, number of damaged cells, main site of injury in the liver lobule, and average severity of single cell damage. For example, hypoxia of the liver and many toxic liver injuries lead to acinarcental cell degeneration and necrosis, while cellular damage in viral hepatitis is more uniformly distributed within the lobule or even most marked periportally.

In ten patients with acute-liver congestion and in five with shock, LD values >500 U per L were found. In eleven of the 15 patients, increased LD-5 per LD ratio >20 percent were found. Ischemic hepatitis has been reported to occur in patients with cardiac failure or in patients with shock owing to gross hemorrhage or pericardial tamponade. A drop in systemic blood pressure has been shown to be the cause for centrilobular liver cell necrosis and hepatic enzyme rises of various intensity, ranging from reversible hepatitis-like rises to complete liver failure up to three days after the drop in blood pressure.

Though the mechanisms for liver injury in hepatitis and circulatory failure are different, the pattern of serum LD and LD-5 increase, in our study, was very similar. It is not possible to distinguish between the various etiologies according to the LD pattern only. In 27 patients with chronic right heart failure, a similar pattern was found of the total LD and LD-5 to that found in serum of patients with cirrhosis. The sensitivity of the LD-5 to liver involvement in patients with chronic heart failure was lower than that of total LD (52 percent versus 93 percent). The patterns of the LD isoenzymes in chronic heart failure were different from those found in the acute liver congestion group of patients in which total LD was much more increased (>500 U per L), and the LD proportions were above normal in all 10 patients.

Nathan et al7 described a sensitivity of 100 percent for both LD and LD-5 per LD in 11 patients with congestive heart failure, but it is not clear whether they had acute or chronic heart failure.

Conclusion

It is our conclusion that in acute liver disorders of either hepatitis or circulatory disturbances, both total LD and LD-5 proportions are sensitive for liver injury (87 percent and 91 percent, respectively). On the other hand, in chronic liver disorders of either cirrhosis or heart failure, LD-5 per LD is much less sensitive than total LD (40 percent versus 85 percent). A striking difference was also found in LD and LD-5 proportions between non-fulminant viral hepatitis group of patients and patients with other causes for the acute liver injury. In contrast, the patterns were quite similar in the two groups with chronic liver disturbances.

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ALTERATIONS IN TOTAL LE AND LE-5 IN HEPATIC DISORDERS

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