Increased α-Hydroxybutyrate Dehydrogenase in Serum from Children with Measles

Kenichi Kano and Tohju Ichimura

For treatment and prognostic evaluation of patients with measles, it is important to determine the source of the increase in serum α-hydroxybutyrate dehydrogenase (HBD; EC 1.1.1.27). Here we measured HBD and L-lactate dehydrogenase (LD; EC 1.1.1.27) activities in the serum of 18 children with measles and in 18 age-matched control patients with bronchopneumonia. HBD and LD activities in the measles patients were significantly higher than those in control subjects (P < 0.001). The HBD/LD ratio in the measles patients two to three days after the onset of rash was significantly lower than that in control subjects (P < 0.001). The low HBD/LD ratio was similar to the ratio found in lymphocytes. The number of peripheral lymphocytes decreased markedly after the onset of rash. Our results suggest that increased serum HBD and LD activity is common in measles infection and that the increase originates from the destruction of infected lymphocytes rather than from myocardial injury.

Additional Keyphrases: lymphocytes • lactate dehydrogenase

In measles patients, there is rarely any clinical indication of cardiovascular-system involvement (1). Woolbridge (2) reported that serum α-hydroxybutyrate dehydrogenase (HBD) and L-lactate dehydrogenase (LD; EC 1.1.1.27) activities were significantly increased in children with measles, including those who were dead on admission. He suggested that there might be a causal relationship between the measles virus, the myocardium, and sudden death. The HBD/LD ratio in measles patients, however, is not increased, as it is in patients with myocardial infarction (3, 4).

We investigated the incidence of increased HBD activity in serum as well as the mechanism of increase by serum enzymatic methods in patients with measles and compared these findings with those in bronchopneumonia patients without measles.

Materials and Methods

Subjects

The patients were 18 children with measles (8 girls and 10 boys) who were hospitalized at the Dokkyo University School of Medicine Hospital between August 1987 and July 1989 (mean age 4.6 years, SE 0.6). All patients were moderately dehydrated and had respiratory complications; 10 had pneumonia, 7 had bronchitis, and 1 had laryngitis. Eleven patients in whom we measured complement fixation titer for measles showed a fourfold or greater increase; the remaining 7 patients were diagnosed as having measles by clinical findings.

The age-matched control group consisted of 18 children without measles with bacterial pneumonia (9 girls and 9 boys) who were hospitalized between August 1987 and November 1989 (mean age 4.5 years, SE 0.7). 4 had respiratory syncytial virus, 3 had influenza A virus, and 1 had para influenza type 2 virus.

Children in both groups were in good health with no cardiac, hepatic, renal, hematologic, or muscular diseases before infection developed, and no child had received any intramuscular injection.

Methods

We measured HBD, LD, aspartate aminotransferase (AST; EC 2.6.1.1), alanine aminotransferase (ALT; EC 2.6.1.2), creatine kinase (CK; EC 2.7.3.2), fructose-bisphosphate aldolase (aldolase; EC 4.1.2.13), and α-aminolase (EC 3.2.1.1) concentrations in serum at two- to six-day intervals with an automated analyzer (Model 710; Hitachi, Tokyo, Japan).

We isolated lymphocytes and erythrocytes from the peripheral blood of five healthy young adult volunteers (ages 20–25 years) by the Hypaque-Ficoll technique (5). We homogenized the cells in 0.1 mol/L phosphate-buffered saline by using ultrasonde at 35 W at 4 °C for 30 s. We measured HBD and LD activities in the lymphocytes and erythrocytes in the supernates of the cellular homogenates.

For all 18 children with measles, we obtained an electrocardiogram (ECG) two to three days after the onset of rash and again four to six days later.

Results are expressed as mean and SE, and statistical evaluation was done with the Student's unpaired t-test.

Results

Serum HBD activity was markedly increased in all 18 measles patients (mean 563.4 U/L, SE 19.4), as was the LD activity (1408 U/L, SE 54.3). HBD activity exceeded 400 U/L in 15 of the 18 measles patients (83%) and was >600 U/L in 5 of 18 (28%). LD activity exceeded 800 U/L in all 18 measles patients and was >1500 U/L in 6 (33%). In the control group, HBD did not exceed 400 U/L (mean 203.8 U/L, SE 10.5) and LD did not exceed 800 U/L (mean 473.6 U/L, SE 23.9) in any subject.

Figure 1 shows the sequential change in HBD activity in measles patients with increased and normal CK activity. HBD activity gradually increased when the rash appeared, reached a peak (613.9 U/L, SE 28.7) two to three days later, and then returned almost to the normal range. A similar pattern was observed for LD activity (Table 1).

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1 Nonstandard abbreviations: HBD, α-hydroxybutyrate dehydrogenase; LD, L-lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatine kinase; and ECG, electrocardiogram.

Received May 21, 1991; accepted February 14, 1992.

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Figure 2 shows the sequential change in the HBD/LD ratio in measles patients. The HBD/LD ratio began to gradually decrease after the rash appeared, reached its minimum in two to three days, and then returned to that shown by the control subjects. The minimum HBD/LD ratio in measles patients was significantly \( P < 0.001 \) less than the mean HBD/LD ratio in the control group (0.387, SE 0.003, vs 0.430, SE 0.004). The lowest HBD/LD ratio (0.387, SE 0.003) approached the ratio found in lymphocytes (0.370, SE 0.010). The HBD/LD ratio in erythrocytes was 0.493 (SE 0.011). The number of peripheral lymphocytes significantly \( P < 0.01 \) decreased one to three days after the onset of rash, then gradually increased, and became normal in approximately seven days.

Table 1 shows the mean serum enzyme activities before and after the onset of rash. AST activity was slightly increased in measles patients and followed a time course similar to that of HBD (Figure 1). ALT activity was normal in 17 of the 18 measles patients, and slightly increased in 1. CK activity was increased in 9 of the 18 measles patients (622.8 U/L, SE 149.3) and normal in 9. Measles patients were separated into two groups by CK activity: in one group CK activity remained within the normal range, and in the other group it increased when the rash appeared and peaked at two to three days (Figure 3). There was no difference between patients with normal and increased CK activity in the time course of serum HBD activity or in HBD/LD ratio (Figures 1 and 2). The increased CK fraction comprised MM, not MB, in all four patients in whom it was measured (Figure 3). Aldolase activity was increased in the 14 measles patients (10.2 U/L, SE 0.6) in whom it was measured and showed a time course similar to that of HBD activity (Table 1). \( \alpha \)-Amylase activity was within the normal range in 9 of the 12 patients in whom it was measured and slightly in-

<table>
<thead>
<tr>
<th>Days before or after the onset of rash</th>
<th>No. of patients</th>
<th>LD (250–520)</th>
<th>AST (5–40)</th>
<th>ALT (10–45)</th>
<th>Aldolase (2–6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2 to -1</td>
<td>3</td>
<td>556.3 (33.9)</td>
<td>35.0 (4.2)</td>
<td>12.7 (1.5)</td>
<td>3.8 (1.0)</td>
</tr>
<tr>
<td>0-1</td>
<td>8</td>
<td>987.0 (72.8)</td>
<td>49.9 (4.0)</td>
<td>14.8 (1.9)</td>
<td>6.8 (0.7)</td>
</tr>
<tr>
<td>2-3</td>
<td>8</td>
<td>1 585.3 (72.2)</td>
<td>66.4 (8.2)</td>
<td>19.0 (2.8)</td>
<td>10.3 (0.9)</td>
</tr>
<tr>
<td>4-6</td>
<td>10</td>
<td>1 175.0 (72.2)</td>
<td>42.2 (5.2)</td>
<td>22.7 (3.4)</td>
<td>9.7 (0.7)</td>
</tr>
<tr>
<td>7-10</td>
<td>9</td>
<td>834.9 (42.0)</td>
<td>26.2 (1.5)</td>
<td>13.0 (1.2)</td>
<td>4.8 (0.4)</td>
</tr>
<tr>
<td>11-15</td>
<td>3</td>
<td>561.3 (67.8)</td>
<td>21.0 (1.5)</td>
<td>13.0 (1.2)</td>
<td>3.5 (1.1)</td>
</tr>
</tbody>
</table>

increased in 3. AST, ALT, CK, and α-amylase activities in all control patients were within the normal range. Aldolase activity was increased in 2 of the 15 control subjects.

Table 2 shows enzyme-activity data for five measles patients in whom LD isoenzymes were determined two to three days after the onset of rash. LD-3 and LD-4 fractions were increased (LD-3 >LD-4) in all five patients. LD, HBD, and aldolase activities were increased in all patients, but AST and CK activities were increased in only two of the five patients. ALT activity was normal in all patients, and amylase activity was normal in four of the five patients.

Figure 4 shows the biochemical course for one patient with measles (first patient in Table 2). HBD, LD, and aldolase activities in serum were markedly increased two to three days after the onset of rash, but CK, ALT and amylase activities were not increased.

An ECG abnormality consisting of minor T-wave changes was present in 4 of the 18 measles patients. No patient had clinical evidence of myocarditis, congestive heart failure, significant arrhythmia, or myocardial infarction.

Discussion
To our knowledge, only one report (2) in the English literature describes increased serum HBD in children with measles. Woolridge (6) observed high HBD and LD activities in all of 14 children with measles; activities were markedly increased in two children who died. Marked ECG abnormalities were also reported for these two patients, but myocardial injury was not confirmed by autopsy. Although a high HBD/LD ratio was reported for patients with myocardial infarction (3,4), the HBD/LD ratio in measles patients is low. In another study (6), as well as here, the LD-1 activity, which reflects myocardial injury, was within normal limits. Furthermore, Leibovicci et al. (7) reported that the incidence of ECG abnormalities in young adults with measles was only 0.7%, and Bokcin (8) reported no cardiac causes of death in 454 measles mortalities in the United States. Thus, the markedly increased serum HBD in all measles patients cannot be explained as being of cardiac origin.

The HBD/LD ratio was significantly (P <0.001) lower and HBD activity was significantly (P <0.001) higher two to three days after the onset of rash in our measles patients than in the control group. Both low HBD/LD ratio and increased HBD activity were found in patients with liver disease and infectious mononucleosis (4). Because ALT activity and LD-5 concentration, which reflect hepatic function (9), were within normal limits in the measles patients (Tables 1 and 2 and Figure 3), the increase in total HBD was not of hepatic origin.

Both high HBD/LD ratio and increased HBD activity were reported in patients with muscular dystrophy (4). CK activity in measles patients was increased by 50% (Figure 1), and markedly increased HBD activity was found in measles patients with normal CK activity (Table 2 and Figures 1 and 4). Therefore, markedly increased serum HBD in all measles patients cannot be explained as being of muscular origin.

The HBD/LD ratio in peripheral lymphocytes was low (0.370, SE 0.010) and similar to the minimum HBD/LD value found two to three days after the onset of rash. Increased HBD and LD activities are common in measles infection, along with the well-recognized lymphopenia (5), which was also seen in our measles patients.

<table>
<thead>
<tr>
<th>Table 2. Enzyme Activity (U/L) in Serum from Five Measles Patients in Whom LD Isoenzymes Were Measured</th>
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<tbody>
<tr>
<td>LD isoenzymes, %</td>
</tr>
<tr>
<td>1575</td>
</tr>
<tr>
<td>1429</td>
</tr>
<tr>
<td>1357</td>
</tr>
<tr>
<td>1764</td>
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<td>1665</td>
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</tbody>
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* Normal reference ranges for children ages one to nine years given in parentheses.
The increased CK activity in serum was reported to reside in the BB fraction (15) or the MM fraction (7, 15). Here, CK was increased in 9 (50%) of the 18 measles patients, and the increased fraction was MM, not MB, in all four patients in whom CK isoenzymes were measured (Figure 3). Leibovic et al. (7), because of observing myoglobin in urine, suggested that increased CK and aldolase activities in measles patients originated partly from rhabdomyolysis. Aldolase activity was increased in all 14 measles patients in whom it was measured. Because lymphocytes contain aldolase along with HBD and LD (16), it was suggested that the increased aldolase activity originated from muscle and infected lymphocytes.

In conclusion, our results suggest that the increased HBD and LD activities observed in measles patients result mainly from destruction of infected lymphocytes.

We thank Professor T. Furukawa (the Second Department of Pediatrics, Dokkyo University School of Medicine, Tochigi) for allowing us to include data from his patients.

References