Increased Lactate Dehydrogenase in Serum in Measles Infection

Norio Sugaya,1 Yoshinao Takeuchi,2 and Takashi Kanno3

We determined lactate dehydrogenase (LD; EC 1.1.1.27) in serum from 75 sequential measles patients and 105 control patients. In the measles patients, LD was increased to 1147.9 ± 43.8 (mean ± SE) U/L, markedly more than in the control group (517.2 ± 15.0 U/L, p < 0.001). Both LD-3 and LD-4 isoenzymes were increased, but the concentration of LD-5 was normal. Patients with high LD values (>1500 U/L) had longer hospital stays than did those with lower values (p < 0.01). Our results suggest that increased LD in serum is a common finding in measles infection and presumably originates from lymphocytes.

Although measles is usually diagnosed from the typical clinical picture, the patient's presentation does not always rule out other diagnostic possibilities. Aside from a leukocyte count to demonstrate leukopenia, there are no widely available immediate laboratory aids in diagnosing measles infection (1).

In Japan, a low vaccination rate (60–70%) among young children resulted in a measles epidemic in 1983–84. Activities of lactate dehydrogenase (LD; EC 1.1.1.27) in serum were frequently increased, being extremely high in some patients, similar to activities seen in malignant disorders (2).4

To investigate whether the incidence of increased LD activity in serum can be correlated with measles infection and serve as an adjunct to clinical findings, we evaluated the incidence of increased LD in serum as a manifestation of measles infection in a large group of children with measles, and sought to clarify the origin of this increase by isoenzyme analysis.

Subjects and Methods

Subjects

The subject group consisted of 75 children with measles who were originally hospitalized with respiratory complications: 29 with pneumonia, 42 with bronchitis, and four with laryngitis. Patients were chosen from among children hospitalized at Nippon Kokan Hospital during April 1980 to May 1984. The diagnosis of pneumonia or bronchitis was based on roentgenographic findings; laryngitis, on the patient's history and physical findings. Thirty-four of these patients had moderate to severe diarrhea.

In 61 of the patients, the complement fixation titers for measles demonstrated a fourfold or greater increase; the remaining 14 patients were diagnosed as having measles by clinical criteria. All were allegedly in good health before the measles infection, with no cardiac, hepatic, or muscular diseases. None had received measles vaccination.

In 50 of the patients, we measured acute (day 3–5 of illness) and convalescent (two to three weeks later) complement fixation titers of influenza A and B, adenovirus, respiratory syncytial virus, and Mycoplasma pneumoniae in addition to the hemagglutination inhibition titers of parainfluenza virus type 1–3. Of these, only respiratory syncytial virus infection was demonstrated (in two patients). Acute and convalescent titers of hepatitis B surface antigen, hepatitis A antibody, Epstein-Barr virus antibody (viral capsid antigen IgG, IgM, and Epstein-Barr nuclear antigen), and cytomegalovirus antibody (IgG and IgM) were measured in 28 of the 75 patients, but no significant changes were demonstrated.

The control group consisted of 105 patients admitted with bronchitis or gastroenteritis during September 1983 to May 1984: 23 with bronchitis, 34 with bronchitis and gastroenteritis, and 48 with gastroenteritis. Among the 57 (23 + 34) with bronchitis were 12 with respiratory syncytial virus infection, four with parainfluenza type 3 virus, and eight with influenza A virus. All were confirmed by serology and virus isolation. Of the 82 (34 + 48) with gastroenteritis, 15 were diagnosed as having rotavirus infection on the basis of fecal testing with an enzyme-linked immunoabsorbent assay.

In both groups, we measured LD, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and gamma-glutamyltransferase (GGT) at three- to five-day intervals. We also determined, at various levels, LD isoenzymes in serum from 15 children with measles and 12 control patients. Serum amylase (EC 3.2.1.1) and creatine kinase (EC 2.7.3.2) were measured in 31 and 25 children with measles, respectively.

Methods

Activities of liver-derived enzymes in serum were determined in the clinical chemistry laboratory at Nippon Kokan Hospital with a sequential multichannel continuous-flow analyzer (Clinolyzer; Nippon Denahi Co., Tokyo, Japan) by well-established methods (3, 4).

For each patient, we compared the highest values measured between days 1 and 10 of illness. Normal reference intervals for children are LD 250–520 U/L, AST 20–50 U/L, and ALT 10–40 U/L.

The distribution of the five LD isoenzymes was measured by a commonly used procedure involving agarose gel electrophoresis (5) and densitometric scanning. Reference intervals (mean ± SEM) for LD isoenzymes in children at our hospital are LD-1 30.1 ± 0.5, LD-2 34.5 ± 0.4, LD-3 25.7 ± 0.3, LD-4 5.9 ± 0.3, and LD-5 3.5 ± 0.3 (n = 90).

Statistical Methods

We used Student's t-test for all statistical comparisons of mean values, and the chi-square test to evaluate differences.
between observed frequency of LD increases in measles patients vs control subjects. Data were expressed as mean ± SEM.

Results

Table 1 gives the mean age and age distribution of both groups of subjects. There was no significant difference between the measles and control groups with regard to mean age. The distributions of LD values for both groups are shown in Table 2. Compared with the high normal values of the controls, LD was significantly increased in the measles patients (p < 0.001). In 69 of the 75 patients with measles (92%), LD exceeded 700 U/L in 15 (20%), it was greater than 1500 U/L. In the control group, LD exceeded 700 U/L in only 12.4% of the cases, and in no case was LD greater than 1500 U/L. The difference between the frequency of increased LD (>700 U/L) in the measles vs control patients (92.0% vs 12.4%) was statistically significant (p < 0.001).

Figure 1 illustrates sequential changes of LD in 12 patients with measles. Similar patterns were observed in a great majority of the patients. LD activity gradually began to increase with the appearance of rash, peaking in three to five days, then returning to within the normal range in 10 to 14 days.

LD measured in eight patients during the prodromal phase ranged from 347 to 875 U/L (mean 641.5, SEM 64.4 U/L), a mildly increased value.

There was no statistically significant difference in LD activity between measles patients with pneumonia and those with bronchitis, nor was LD activity affected by the presence of diarrhea. Although the LD values did not correlate well with the severity of clinical symptoms, hospital stay was substantially (p < 0.01) longer for those with LD >1500 U/L, than for those with LD <1500 U/L: 18.5 ±1.8 days (n = 15) vs 12.3 ±0.5 days (n = 60). In the former group, persistent cough (5/15), appetite loss and fatigue (6/15), and diarrhea (4/15) were the main reason for the prolonged hospitalization.

LD isoenzymes were measured in 15 patients with measles and analyzed both as relative percentage and as absolute activities. When total LD peaked, the relative percentages (mean ± SEM) were as follows: LD-1 18.9 ±1.4, LD-2 32.8 ±1.2, LD-3 35.5 ±1.1, LD-4 9.7 ±1.1, and LD-5 2.8 ±0.5. Compared with the normal mean values, a marked increase of LD-3 was characteristic (p <0.001), and LD-4 was slightly above normal (p <0.001); LD-1 showed a moderate decrease (p <0.01). The percentages of LD-2 and LD-5 were not significantly different from normal. The absolute activities of LD isoenzymes were greatest for LD-2 and LD-3. Nine of the 15 patients with very high total LD showed a “flip” in the normal LD-2 to LD-3 ratio; i.e., the LD-3 concentration exceeded that of LD-2.

We also measured LD isoenzymes in 12 control patients whose total LD exceeded 700 U/L. When total LD peaked, the relative percentages (mean ± SEM) were as follows: LD-1 28.8 ±0.8, LD-2 36.3 ±0.6, LD-3 27.7 ±0.8, LD-4 4.7 ±0.4, and LD-5 4.0 ±0.4. These were not significantly different from the normal mean values for LD isoenzymes.

Figure 2 shows the LD isoenzyme patterns of two representative patients with measles. In the two-year-old, total LD was as high as 2259 U/L two days after the onset of rash. LD-2, LD-3, and LD-4 were all increased, with a predominance of LD-3. After three days, total LD decreased slightly to 1935 U/L, primarily reflecting a rapid decrease in LD-4. After 14 days, LD fell to within the normal range and the isoenzyme pattern was also normal. The nine-year-old patient was hospitalized one day before the appearance of rash, at which time the total LD and isoenzyme pattern were normal. Afterwards, the total LD began to increase steadily, and LD-3 was markedly increased three days after the onset of rash.

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**Table 1. Comparison of the Measles and Control Groups**

<table>
<thead>
<tr>
<th>Range</th>
<th>Measles</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age n</td>
<td>Age n</td>
<td></td>
</tr>
<tr>
<td>1-11 mo</td>
<td>10</td>
<td>46</td>
</tr>
<tr>
<td>12-23 mo</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>2-3 yr</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>4-12 yr</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Mean</td>
<td>23 mo</td>
<td>17 mo</td>
</tr>
</tbody>
</table>

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**Table 2. Distribution of LD values**

<table>
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<tr>
<th>LD, U/L</th>
<th>Measles</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;700</td>
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<td>92</td>
</tr>
<tr>
<td>700-1000</td>
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</tr>
<tr>
<td>1000-1500</td>
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<tr>
<td>1500-2000</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>2000-2500</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Mean ±SEM (and range) of LD activity: *1147.9 ±43.8 (490–2279) U/L; 517.2 ±15.0 (295–1247) U/L, significantly different (p <0.001).
AST activity was slightly increased in the 75 patients (82.2 ± 6.5 U/L), as was ALT activity (43.1 ± 6.7 U/L). GGT activity was normal in 73 of the 75 patients, slightly increased in two. AP activity was normal in all patients. Creatine kinase activity was within the normal range in 22 of the 25 measles patients in whom it was measured, slightly increased in three. Amylase activity was also normal in 29 of 31, slightly increased in two. The number of peripheral lymphocytes decreased markedly immediately after the onset of rash; in most cases, they had gradually increased, becoming normal by approximately six days afterwards.

Discussion

In 20% of the measles patients, LD activity was >1500 U/L, a condition encountered only infrequently in routine pediatric practice. Moreover, an LD increase to >700 U/L was much more common in the measles patients than in the control group (92.0% vs 12.4%, p <0.001). In pediatric practice, increased LD activity in serum during measles is generally regarded as a nonspecific manifestation of pulmonary insult or dehydration.

To our knowledge, only one report dealing with increased serum LD in children with measles has been published. Olilsaegers et al. (6), observing high values for LD in uncomplicated nonhospitalized measles patients, reported that the proportion of LD isoenzymes followed the normal pattern and that the increased LD probably was ascribable to the cytoplasmic enzyme leaking through the cell wall.

In our patients, the relative percentages of both LD-3 and LD-4 were increased, with LD-3 predominating. Because LD-5, which reflects hepatic function (2), was within normal limits in all cases, the increase in total LD is not of hepatic origin. In contrast, the five LD isoenzymes in the control group were increased equally.

LD-3 in serum originates mainly from the pancreas (2), the lungs (2, 7), and the lymphocytes (2, 8, 9). The measles patients in this study had normal amylase activities and no symptoms or signs referable to the pancreas. With rare exceptions (10, 11), LD activities are within normal limits in patients with bronchitis or pneumonia (12, 13), as was also shown in our control subjects. Pulmonary infarction and embolism are rare in children and are usually postoperative complications (14).

The fact that measles virus has been shown to infect human lymphocytes in vivo, and peripheral lymphocytes in vitro, suggests that the virus has a predilection for these cells (15). Perhaps by the time that the rash appears, infected lymphocytes are destroyed by immunological reaction or directly by measles virus, thus releasing intracellular LD, which is reflected in the increase of LD in serum of measles patients.

In conclusion, because of the high incidence and markedly increased values of LD, we believe that increased LD in serum is a common finding in measles infection, together with the well-known leukopenia (16, 17). Moreover, our results suggest that the origin of the increased LD is destruction of the infected lymphocytes.

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References