Clinicopathological Study on Liver Dysfunction in Measles

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We analyzed the clinical course of eight patients with liver dysfunction in measles. All of the patients showed an elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH), but no jaundice. These levels returned to normal about 3 weeks after the onset of the rash. A percutaneous liver biopsy was done in two cases. Histological examination showed slight necrosis of liver cells but no significant changes in portal area. On electron microscopy, virus particles were not detected. We detected measles virus RNA in the liver specimen by RT-PCR, which suggests that the measles virus affects liver cells directly in measles.

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Key words: measles virus, hepatitis, young adults, liver biopsy, RT-PCR

Introduction

Measles is an acute febrile illness predominantly affecting children and is usually a benign self-limiting disease. Several complications have been described in measles, including respiratory tract infection, pneumonia, otitis media, ileocolitis, myocarditis, encephalitis and subacute sclerosing panencephalitis (SSPE) (1). Hepatitis in measles is reported commonly in the European and American literature (1-4). Liver dysfunction has occurred frequently in young adults (3-7). However, such cases in Japan are relatively rare (6, 8, 9). Hepatic involvement as a consequence of measles infection is poorly understood. The pathogenic mechanism of liver dysfunction in measles has not been fully investigated. Only a few satisfactory studies on the histological analysis have been reported to date (10, 11). Here, we describe the clinicopathological study of eight patients with liver dysfunction in measles.

Materials and Methods

Eight patients who were hospitalized due to liver dysfunction in measles were studied (Table 1). Their age ranged from 15 to 29 years with a mean age of 21.1 years. Three were male and five female. The diagnosis of measles was established by a history of typical prodrome and suggestive signs on physical examination and the elevation of immunoglobulin M (IgM) antibody against measles (enzyme immunoassay: EIA method). All patients denied having had previous measles infection or vaccination. In addition, results of serologic tests for hepatitis B surface antigen, anti-hepatitis A virus, Epstein-Barr virus, cytomegalovirus and rubella were all negative.

Results

All patients had fever, rash and cough. The duration of fever averaged 6.6 days. The period of rash averaged 5.4 days. There were no severe complications such as pneumonia, encephalitis, myocarditis or jaundice. The clinical course in all patients was uneventful.

Liver function test

The results of the liver function test are summarized in Table 1. All of the patients showed an elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH). Maximum AST values ranged from 46 to 2,910 IU/l, that of ALT from 79 to 2,550 IU/ml and that of LDH from 659 to 5,350 IU/ml. In most cases, there was a mild to moderate disturbance of AST, ALT and LDH. The serum level of LDH was markedly high as compared with that of transaminase. Severe liver dysfunction (AST>500 IU/ml) was detected in two patients. Bilirubin was within normal limits in all cases. Alkaline phosphatase was elevated in two cases. γ-glutamyl transpeptidase (γ-GTP) was elevated in four cases. Serum AST and ALT levels increased with the development of rash, reaching a maximum 7 to 12 days after the start of rash. Serum LDH increased at the time of the appearance of rash, and reached a maximum 2 to 3 days earlier than the peak of AST and ALT. These high levels gradually returned to normal.
Liver Dysfunction in Measles

Table 1. Clinical and Laboratory Findings of 8 Patients on Admission

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Duration</th>
<th>Maximum values of liver function tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fever (days)</td>
<td>T-Bil (mg/dl)</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>F</td>
<td>8</td>
<td>0.96</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>F</td>
<td>5</td>
<td>0.93</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>F</td>
<td>6</td>
<td>0.68</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>M</td>
<td>8</td>
<td>0.66</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>M</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>M</td>
<td>7</td>
<td>0.3</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
<td>F</td>
<td>8</td>
<td>0.6</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>F</td>
<td>8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Figure 1. Histological findings of the liver in case 3. (A) Slight necrosis of liver cells and cellular infiltration are observed in liver parenchyma. No piecemeal necrosis, cellular infiltration or fibrosis in portal area is observed (HE stain, ×200). (B) The hepatocytes are pleomorphic, and acidophilic bodies are present (HE stain, ×400).

Figure 2. Electron microscopy (case 3). No measles virus particles are seen (×5,000).

about 3 weeks after the onset of rash. Serum LDH isozymes were analyzed in 4 of the 8 patients; subunits 2 or 3 were mainly elevated in 2 cases. Subunit 5, in which the elevation is dependent upon liver dysfunction, was mainly elevated in 2 cases.

Liver biopsy

Percutaneous liver biopsy was undertaken in 2 of the 8 patients (Cases 2 and 3) at the recovery stage. Light microscopy revealed slight necrosis of liver cells in the parenchyma, but there was no piecemeal necrosis, cellular infiltration or fibrosis in portal area in all cases (Fig. 1). On electron microscopy, measles virus particles were not detected in any cases (Fig. 2). For the detection of measles virus RNA, RT-PCR was performed with the primer “MFP 1” (5'-GGC AAT TGA GGC AAT CAG ACA-3') and “MFP 2” (5'-CTT GAG AGC CTA TGT TGT ACG-3') in liver specimens by a method described previously (12). Measles virus was found to be positive in case 3 (Fig. 3).
Liver dysfunction in measles was first recognized in 1960 by Berry (2). He reported a 29-year-old woman with measles who had an elevation of AST with the development of rash, and also pointed out the many clinical similarities between measles, infectious mononucleosis and hepatitis A. Since then hepatitis in measles has been often reported in the European and American literature (1-4). It occurs more frequently in adolescents and young adults (5, 7, 13). The presumption is that the incidence of liver dysfunction in measles is much lower than 80% (7). However, such cases are relatively rare in Japan (6-8), because hepatic involvement as a consequence of measles has been rarely recognized.

Hepatitis is usually detected by the presence of a transient elevation of serum AST or ALT values during the acute phase of illness. Hepatocellular dysfunction is much more frequent (4). Overt jaundice is very uncommon and has been reported only in a few cases (4, 7, 13, 14). Also, in our cases, jaundice was not observed. In general, liver dysfunction in measles is usually mild and is associated with a good prognosis (4, 6, 13). Gavish et al (7) indicated there is a clear correlation between the severity of hepatic involvement and the occurrence of secondary bacterial infection. In contrast, Eto et al (8) reported that the severity of liver dysfunction did not correlate with the severity of measles. Although two cases had severe liver dysfunction (AST>500 IU/ml) in our study, they recovered uneventfully and had no long-term sequela. Hashimoto et al (9) reported a case of severe liver dysfunction (AST 9,630 IU/ml, ALT 4,120 IU/ml) with measles requiring plasma apheresis. Their rare case would suggest that we be more careful about liver function in the follow-up of measles infection.

It is characteristic for measles patients to have a markedly higher serum LDH level than transaminase level (8). From our findings of LDH isozymes, the elevation of serum LDH in measles is not necessarily dependent upon liver dysfunction. Fournier et al (15) reported that the measles virus was infected with lymphocytes in SSPE patients. We speculate that the serum LDH level is increased due to the destruction of infected lymphocytes in measles infection.

There have been very few satisfactory reports on the histological analysis in hepatitis in measles. Monif and Hood (10) reported abnormal liver histology consisting of lymphocytic infiltration with small foci of hepatocellular necrosis in a child who died of severe ileocolitis complicating a measles infection. Modai et al (11) described mild and nonspecific changes in the sinusoids. The present histological results are consistent with the previous reports. The pathogenesis of the complication of liver dysfunction in measles has been only partially elucidated. From the findings of liver specimen that virus particles were not detected on electron microscopy and staining with anti-measles antibodies was negative, a few investigators suggested that liver damage in measles might be mediated by some immunological mechanism rather than by direct viral insult, as described in hepatitis B (11, 13). However, we detected measles virus RNA in the liver specimen of case 3 by RT-PCR. Moench et al (16) showed that the ductal epithelium of the liver in fatal measles was stained with anti-measles antibodies. These results raise the possibility that the measles virus invades the liver in measles infection with liver dysfunction. Further study is necessary to determine whether the measles virus affects liver cells directly.

Hepatitis can be present during the course of many viral infections, including those due to hepatitis A virus, Epstein-Barr virus, cytomegalovirus, yellow fever virus, coxsackie viruses, varicella, herpes simplex virus and echovirus (1). While measles immunization has been decreasing in Japan, hepatitis in measles is probably more extensive in adults. It is important for physicians to be aware that liver dysfunction may be one of the complications in a measles infection of young adults.

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References

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