Elevated IgA antibodies to Epstein-Barr virus in children with chronic active Epstein-Barr virus infection.

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Abstract

Anti-Epstein-Barr virus (EBV) antibodies were tested in 11 children with chronic active EBV infection. Anti-virus capsid antigen (VCA)-IgG antibody titers ranged from 1:640 to 1:10,240. Anti-VCA-IgM antibody was consistently positive in 5 of the 11 patients; anti-VCA-IgA antibody was consistently positive in 6 of the 10 patients; anti-early antigen (EA)-IgG antibody was consistently positive in 10 of the 11 patients and anti-EA-IgA antibody was consistently positive in 4 out of the 7 patients. Anti-EBV nuclear antigen (EBNA) antibody was not detected in two patients. Consistently positive anti-VCA-IgA- and anti-EA-IgA- antibody may be a characteristic feature of abnormal antibody responses in severe chronic active EBV-infection in childhood.

KEYWORDS: IgA antibody, Epstein-Barr virus, chronic active EBV-infection

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Anti-Epstein-Barr virus (EBV) antibodies were tested in 11 children with chronic active EBV infection. Anti-virus capsid antigen (VCA)-IgG antibody titers ranged from 1:640 to 1:10,240. Anti-VCA-IgM antibody was consistently positive in 5 of the 11 patients; anti-VCA-IgA antibody was consistently positive in 6 of the 10 patients; anti-early antigen (EA)-IgG antibody was consistently positive in 10 of the 11 patients and anti-EA-IgA antibody was consistently positive in 4 out of the 7 patients. Anti-EBV nuclear antigen (EBNA) antibody was not detected in two patients. Consistently positive anti-VCA-IgA and anti-EA-IgA antibody may be a characteristic feature of abnormal antibody responses in severe chronic active EBV-infection in childhood.

Key words: IgA antibody, Epstein-Barr virus, chronic active EBV-infection

It is well known that elevated IgA antibody against virus capsid antigen (VCA) of Epstein-Barr (EB) virus is one of the characteristic features of nasopharyngeal carcinoma. VCA-IgA antibody may also be transiently detectable in the course of acute infectious mononucleosis (1). EB-virus infection may become a chronic active state in both adults and children. Several immunological abnormalities such as defective natural killer (NK) cell activity, EB-virus specific cytotoxic T lymphocyte (CTL) activity, and lymphokine production have been reported in patients with chronic active EB-virus infection (3-6). Akaboshi et al. (2) noted that elevated IgA antibodies to EB-virus were found in children with recurrent parotitis caused by EB-virus. Though a few VCA-IgA antibody positive cases of chronic active EB-virus infection have been described (7-9), only little research had been done on the significance of IgA antibodies to EB-virus in chronic active EB-virus infection.

We examined EB-virus antibodies specifically IgA antibodies to EB-virus in 11 children and infants with chronic active EB-virus infection. The diagnostic criteria (10) for chronic active EB-virus infection are; 1) chronic or recurrent infectious mononucleosis-like symptoms lasting for a period of at least one year and often longer,
Table 1  Clinical data of patients with chronic active Epstein-Barr virus infection

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at onset (y-m)</th>
<th>Liver (cm\textsuperscript{a})</th>
<th>Spleen (cm\textsuperscript{b})</th>
<th>Lymphnode (cm\textsuperscript{b})</th>
<th>Rash</th>
<th>Fever</th>
<th>Complications and clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>M</td>
<td>0- 1</td>
<td>6.5</td>
<td>6.0</td>
<td>2.0</td>
<td>+</td>
<td>+</td>
<td>Pneumonitis, remission at 12 m after onset</td>
</tr>
<tr>
<td>2.</td>
<td>Y</td>
<td>0- 3</td>
<td>5.0</td>
<td>9.0</td>
<td>3.0</td>
<td>+</td>
<td>+</td>
<td>Pneumonitis, active more than 4 y after onset</td>
</tr>
<tr>
<td>3.</td>
<td>K</td>
<td>12- 0</td>
<td>4.0</td>
<td>15.0</td>
<td>2.0</td>
<td>-</td>
<td>+</td>
<td>NHL, dead at 13 m after onset</td>
</tr>
<tr>
<td>4.</td>
<td>K</td>
<td>8- 5</td>
<td>1.5</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>Hemolytic anemia, active more than 3 y after onset</td>
</tr>
<tr>
<td>5.</td>
<td>M</td>
<td>2- 6</td>
<td>7.0</td>
<td>12.0</td>
<td>7.0</td>
<td>+</td>
<td>+</td>
<td>HD, dead at 6 y after onset</td>
</tr>
<tr>
<td>6.</td>
<td>R</td>
<td>2- 4</td>
<td>5.0</td>
<td>9.0</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>Hemolytic anemia, active more than 2 y after onset</td>
</tr>
<tr>
<td>7.</td>
<td>F</td>
<td>7- 6</td>
<td>1.0</td>
<td>5.0</td>
<td>0.5</td>
<td>+</td>
<td>+</td>
<td>Chronic hepatitis, active more than 2 y after onset</td>
</tr>
<tr>
<td>8.</td>
<td>M</td>
<td>5-11</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>+</td>
<td>+</td>
<td>Fever and arthritis, active more than 4 y after onset</td>
</tr>
<tr>
<td>9.</td>
<td>M</td>
<td>12- 1</td>
<td>10.0</td>
<td>12.0</td>
<td>2.0</td>
<td>-</td>
<td>+</td>
<td>VAHS, CMV-pneumonitis, dead at 26 m after onset</td>
</tr>
<tr>
<td>10.</td>
<td>R</td>
<td>10- 0</td>
<td>3.0</td>
<td>1.0</td>
<td>1.0</td>
<td>+</td>
<td>-</td>
<td>Chronic active hepatitis, active more than 14 m after onset</td>
</tr>
<tr>
<td>11.</td>
<td>Y</td>
<td>11- 0</td>
<td>9.0</td>
<td>6.0</td>
<td>2.0</td>
<td>-</td>
<td>+</td>
<td>VAHS, dead at 2 m after onset</td>
</tr>
</tbody>
</table>

\textsuperscript{a}: Length below costal margin.  
\textsuperscript{b}: Size in diameter.  
Abbreviations: y, year(s); m, month(s); NHL, non Hodgkin's lymphoma; HD, Hodgkin's disease; VAHS, virus associated hemophagocytic syndrome; CMV, cytomegalovirus.

2) an unusual pattern of anti-EB-virus antibodies with raised anti-early antigen (EA) and/or absent anti-EB-virus nuclear antigen (EBNA) titers, and 3) no evidence of any prior immunological abnormality or of any other recent infection by which to explain the condition.

The patients characteristically had a lymphoproliferative syndrome similar to Duncan disease (X-linked lymphoproliferative syndrome, XLP), however no familial involvement was observed and the disease occurred in both males and females (Table 1). The age of the patients at onset varied from one month to 12 years. None of the patients had characteristic symptoms of acute infectious mononucleosis in their past history. One patient entered into remission 12 months after onset of the disease, two patients died from malignant lymphoma and two patients died from virus associated hemophagocytic syndrome and cytomegalovirus pneumonitis (Table 1).

All serum samples were obtained during the active state of the disease and some of them were frozen and stored at -80°C for 1 to 2 years before anti-EB-virus antibodies were tested. Anti-VCA-antibodies and anti-EA-antibodies were tested by an indirect immunofluorescence technique (11, 12), and anti-EBNA-antibody was tested by an indirect immunofluorescence with complement method (13).

At the time when the patients were diagnosed as suffering from chronic active EB-virus infection, anti-EB-virus antibody titers were as follows. High titers of anti-VCA-IgG antibodies were detectable in all cases.
IgA Antibodies to EBV in Chronic EBV Infection

Some of the anti-EB-virus IgA antibody positive cases, reported by Akaboshi et al. (2), might be clinically diagnosed as chronic active EB-virus infection. IgA antibodies to EB-virus are not detectable in normal EB-virus seropositive individuals and are transiently detectable during the course of acute infectious mononucleosis (1). Tosato et al. (14) described the immunological state of chronic active EB-virus infection appear "frozen" in a state typically found only briefly during the convalescence from acute EB-virus infection. Consistently positive IgA antibodies to EB-virus may indicate that an active stage of EB-virus infection as high as in the acute stage of acute infectious mononucleosis persists in patients with chronic active EB-virus infection. Three out of 6 IgA antibody positive cases died from malignant lymphoma and virus associated hemophagocytic syndrome with pneumonitis, while all 4 IgA-antibody negative cases are still alive, one of them in complete remission. We would like to emphasize that the elevated IgA antibodies to EB-virus is probably a characterisitic immunological abnormality in severe types of chronic active EB-virus infection.

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