Seroconversion to Human Herpesvirus 6 and Human Herpesvirus 7 Among Brazilian Children with Clinical Diagnoses of Measles or Rubella

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We collected acute-phase and convalescent-phase serum samples from Brazilian patients who presented with exanthem of unknown origin and evaluated these samples by means of an immunoblot assay for seroconversion to human herpesvirus 6 (HHV-6) or human herpesvirus 7 (HHV-7). Measles or rubella had been clinically diagnosed in all of these patients, but their sera were negative for antibodies to both measles virus and rubella virus. Twenty percent of the patients clearly seroconverted to HHV-6 after manifestation of the exanthem, and 8% seroconverted to HHV-7. All seroconversions to HHV-6 occurred in children aged ≤5 years; a 41% frequency of seroconversion to HHV-6 was noted among children between 3 months and 23 months of age, whereas seroconversions to HHV-7 were detected during infancy and through adulthood. Our data indicate that primary infections due to HHV-6 or HHV-7 can be misdiagnosed as measles or rubella.

Measles, rubella, and exanthem subitum (ES) are common exanthems of children. The major etiologic agent of ES is human herpesvirus 6 variant B (HHV-6B) [1]. More recently, human herpesvirus 7 (HHV-7) has also been associated with ES [2]. The differential diagnosis of measles, rubella, and ES is aided by the fact that the classic presentation of each disease is distinct; however, atypical presentations are not uncommon and can lead to misdiagnosis [3–5].

Differential diagnosis may also be confounded by either of the following factors: (1) inaccurate or incomplete information from a parent, particularly if the patient presents with a rash after the classic prodrome of ES or measles (which increases the difficulty of accurate diagnosis based on clinical symptoms); and (2) widespread measles and rubella vaccination programs, which have left many clinicians unfamiliar with the signs of naturally occurring infections.

Both measles and rubella pose serious public health problems, are notifiable diseases in most industrialized countries, and are preventable through vaccination. Therefore, it is important to better understand the extent to which infections due to HHV-6 and HHV-7 are associated with exanthematous illness.

We collected paired serum samples from patients with presumptive diagnoses of measles or rubella who were seronegative for measles and rubella viruses; we tested these samples for antibodies to HHV-6 and HHV-7.

Materials and Methods

Serum samples. Acute-phase and convalescent-phase sera were collected from 6,165 children and adults with suspected measles or rubella in 1992 and 1993 as part of the Measles and Rubella Surveillance Program in the State of São Paulo, Brazil. The diagnoses were based on a clinical picture of generalized rash of ≥3 days’ duration; a fever (temperature, ≥38.3°C); and either cough, coryza, or conjunctivitis. Serological assays for measles and rubella were performed at the Adolfo Lutz Institute in São Paulo. Eleven percent (673) of these individuals seroconverted to rubella virus, and 2% (100) seroconverted to measles virus. One hundred and eighty-one serum pairs from seronegative patients were tested for antibodies to HHV-6 and HHV-7.

Samples were selected on the basis of the following criteria: (1) availability of information regarding patient age, date of the onset of rash, and date of acute-phase and convalescent-phase serum collection; and (2) availability of sufficient volumes of acute-phase and convalescent-phase serum to perform multiple tests. Acute-phase serum was collected when the patient presented with an exanthem (mean day of collection, day 3 after the onset of rash; range, 0–19 days) and convalescent-phase serum was collected an average of 11 days later (range, 1–54 days). Patients’ ages ranged from 13 days to 29 years. All samples were collected after appropriate consent was obtained.
patients in this sample set had convalescent-phase sera that were positive for antibodies to HHV-6, and 60% had convalescent-phase sera that were positive for antibodies to HHV-7. Increased convalescent-phase reactivity. In toto, 94% of the HHV-6. No evidence of seroconversion to HHV-6 was detected in individuals >5 years of age and in 7% (10 of 138) of samples from patients >5 years of age. Seroconversion to HHV-7 or HHV-6 was observed in 8% (14 of 181) and in 20% (37 of 181) of patients past the age at which maternal antibody persists, the acute-phase serum was compared with the acute-phase sample, the change was regarded as increased reactivity.

Results

The following results were obtained for a population of 181 individuals composed of 43 patients >5 years of age and 138 patients ≤5 years of age. Seroconversion to HHV-7 or HHV-6 was observed in 8% (14 of 181) and in 20% (37 of 181) of the patients in each group, respectively (table 1). Seventy-four percent of the patients in this population had antibodies to HHV-6 in their acute-phase sera, and 49% had antibodies to HHV-7. Ten percent of the samples had increased convalescent-phase reactivity to HHV-6; 2% had increased reactivity to HHV-7, relative to the acute-phase sample. Seroconversion to HHV-7 was detected in 9% (4 of 43) of the samples obtained from individuals >5 years of age and in 7% (10 of 138) of samples from those ≤5 years of age.

Table 1. Percentage of 181 Brazilian patients seropositive for antibodies to human herpesvirus 6 and human herpesvirus 7, as determined by immunoblot assay.

<table>
<thead>
<tr>
<th>Serum sample, reactivity</th>
<th>HHV-6*</th>
<th>HHV-7*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute-phase reactivity</td>
<td>74 (134)</td>
<td>49 (89)</td>
</tr>
<tr>
<td>Convalescent-phase reactivity</td>
<td>94 (171)</td>
<td>57 (103)</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>20 (37)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Increase in reactivity with respect to acute sera</td>
<td>10 (18)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Negative</td>
<td>6 (10)</td>
<td>43 (78)</td>
</tr>
</tbody>
</table>

NOTE. HHV-6 = human herpesvirus 6; HHV-7 = human herpesvirus 7.
* Percentage (number of patients).

Immunoblot assay. Immunoblot assays for antibodies to HHV-6B and HHV-7 were performed as previously described [6, 7]. The acute-phase and convalescent-phase samples from each individual were tested in adjacent wells of an immunoblot manifold. Paired serum specimens that showed no reactivity in the acute phase and clearly visible reactivity in the convalescent phase were regarded as seroconversions. If an unambiguous, visible increase in color intensity was observed when the convalescent-phase sample was compared with the acute-phase sample, the change was regarded as increased reactivity.

Discussion

Infection with HHV-6 and HHV-7 was clearly associated with exanthem in 20% and 8%, respectively, of the two groups of patients with exanthem of unknown origin. The increased reactivity detected between acute-phase and convalescent-phase serum samples may in some cases indicate that the exanthem resulted from the reactivation of HHV-6 or HHV-7. However, it is possible that the children <6 months of age still retained some maternal antibodies, which could explain the weak acute-phase reactivity observed in these samples. With respect to those children past the age at which maternal antibody persists, the acute-phase serum may have been collected from some patients who were already producing virus-specific IgG. If either of these hypotheses is correct, then the percentage of children who seroconverted to these viruses would be higher.

Improper diagnosis of antibiotic sensitivity following unnecessary administration of antibiotics during a misdiagnosed case of primary HHV-6 infection has been discussed [reviewed in 8]. Our results suggest that an important issue is the misdiagnosis of primary infection due to HHV-6 or HHV-7 as cases of measles or rubella. Similar results were obtained for children in England who had presumptive cases of measles or rubella but whose illnesses were actually due to primary HHV-6 infection [9].

Our results demonstrate the need to include primary or reactivated infection due to HHV-6 and HHV-7 in the differential diagnosis of illnesses associated with rash. Accurate diagnosis is important because of the potential effect of measles and rubella on patients as well as on their contacts. Convenient tests for measles and rubella are commercially available; commercial diagnostic assays are needed for the accurate detection of antibodies to HHV-6 and HHV-7.

References


ANSWER TO THE ARCANUM (SEE PAGE 1116)

SERIOUS INFECTIONS CAUSED BY DIPHTHEROIDS

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References


