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.
were positive for antibodies to HHV-6, and 60% had convalescent-phase sera that were positive for antibodies to HHV-7. In toto, 94% of the HHV-6. No evidence of seroconversion to HHV-6 was detected in individuals >5 years of age; however, 14% (6 of 43) showed versions occurred between 3 months and 23 months of age; to HHV-7 was detected in 9% (4 of 43) of the samples obtained to HHV-7, relative to the acute-phase sample. Seroconversion from individuals >5 years of age and in 7% (10 of 138) of samples from those years of age.

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.

Of the 138 children ≤5 years of age, 27% (37 of 138) seroconverted to HHV-6, and 41% (36 of 87) of these seroconversions occurred between 3 months and 23 months of age; these ages are within the expected range for acquisition of HHV-6. No evidence of seroconversion to HHV-6 was detected in individuals >5 years of age; however, 14% (6 of 43) showed increased convalescent-phase reactivity. In toto, 94% of the 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.

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


NOTE. HHV-6 = human herpesvirus 6; HHV-7 = human herpesvirus 7. * Percentage (number of patients).
5. Brown DW, Ramsay ME, Richards AF, Miller E. Salivary diagnosis of unspecified Corynebacterium. (Courtesy of Dr. Frank Witebsky.)

Figure 1. Small gram-positive coccobacilli with a beaded appearance are clustered in a pattern resembling a picket fence (arrow), which is typical for Corynebacterium jeikeium. (Courtesy of Dr. Frank Witebsky.)

The name "jeikeium" is an acronym commemorating Drs. Johnson and Kaye, who described a series of infections due to corynebacteria in 1970 [1]. As often occurs with emerging pathogens, clinical descriptions characterizing these infections had been published earlier, including the first series of cases of endocarditis due to diphtheroids [2], but it took a long time to recognize that these entities were caused by a unique yet unspeciated corynebacterium.

Jackman et al. recently proposed the name Corynebacterium jeikeium species nov. for corynebacteria cataloged by the CDC (Centers for Disease Control and Prevention) as group JK after careful molecular and chemotaxonomic studies indicated unifying features belitting a distinct taxon [3]. Before this DNA technology was available, the Special Bacteriology Section of the CDC developed an alphabetized catalog (Group A, B, C, etc.) for unspeciated organisms that were grouped according to this scheme. Initially cataloged by the CDC into two separate groups, J and K, elution profiles obtained by gas liquid chromatography [4] established the fact that these two groups of organisms had identical features, and they were subsequently referred to as Corynebacterium group JK. Quite serendipitously, Dr. Johnson’s and Dr. Kaye’s initials also correspond to these letters.

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ANSWER TO THE ARCANUM (SEE PAGE 1116)

SERIOUS INFECTIONS CAUSED BY DIPHTHEROIDS

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Figure 2. The title and authors of the original article on Corynebacterium jeikeium as they appeared in the Annals of the New York Academy of Sciences in 1970. The article consisted of eight tables in an article of eight pages that described infections due to a heterogeneous group of diphtheroids. Organisms were grouped according to this scheme. Initially cataloged by the CDC into two separate groups, J and K, elution profiles obtained by gas liquid chromatography [4] established the fact that these two groups of organisms had identical features, and they were subsequently referred to as Corynebacterium group JK. Quite serendipitously, Dr. Johnson’s and Dr. Kaye’s initials also correspond to these letters.

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