

ASSOCIATION OF HUMAN HERPESVIRUS 6 INFECTION WITH EXANTHEM SUBITUM IN BELEM, BRAZIL

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SUMMARY

Recent human herpesvirus 6 (HHV-6) infection was detected in cases of exanthem subitum (ES) involving four children, aged 10 to 24 months, between April and August 1994, in Belém, Brazil. By using the indirect immunofluorescence antibody assay (IFA), significant increases (at least eight times) in antibody concentrations were noted from the acute to the convalescent serum samples, with titers ranging from <1:10/1:80 to <1:10/1:640 (patients 3 and 2, respectively). All children had high fever (over 39°C) for three days, followed by generalized, maculo-papular skin rash. A physical examination of the children also revealed concomitant, cervical lymph node swelling and tonsillar pharyngitis in two of them.

KEYWORDS: Human herpesvirus 6; Exanthem subitum.

INTRODUCTION

HHV-6 was first isolated by SALAHUDDIN et al.¹² from peripheral blood mononuclear cells of patients with lymphoproliferative disorders and AIDS. This agent was originally named human B-lymphotropic virus, mainly because of its cytopathic effect in cultures of lymphocytes.

Since its discovery, HHV-6 has been associated with a variety of clinical disorders, the strongest aetiological evidence being related to exanthem subitum (ES) or roseola infantum¹⁴. This is a common disease of infancy, characterized by high fever (39-40°C) of abrupt onset, for a few days, and the appearance of a maculo-papular skin rash when the fever subsides. Symptoms are usually mild, but central nervous involvement has been reported as a complication⁶. Virus isolation has also been recorded in cases of systemic lupus

erythematosus⁴, chronic fatigue syndrome¹, hepatitis², malignancy and lymphoproliferative lesions⁶, febrile convulsions^{5,8} and other illnesses.

Studies carried out to date in Brazil have mainly focused on the prevalence of HHV-6 antibody among urban and remote Amazonian communities^{3,7}. The former detected seroprevalence rates of 76.5% and 77.2% for Brazilian and Japanese immigrants, respectively, whereas the latter investigations indicated that 10% of Amerindians have antibody to HHV-6.

The present report deals with the first cases of ES to be recorded in Belém, Brazil, involving children less than three years of age, and whose paired sera showed significant increase in antibody titers, from acute to convalescent samples, when these were tested for the presence of HHV-6 antibody by the IFA.

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PATIENTS AND METHODS

The four patients attended the General Virology Unit of the Instituto Evandro Chagas during the period April - August, 1994; two were female, aged 10 and 11 months, and two were male, aged 16 and 24 months (Table 1). All presented with fever and exanthem, whereas two of them also had tonsillar pharyngitis and cervical lymph node swelling. Acute sera were obtained from all children and, seven to 26 days later, a second, convalescent sample was collected; these specimens were kept frozen at -20°C until their examination.

All sera were assayed at serial, twofold dilutions (from 1:10 to 1:1280) for the presence of antibodies to HHV-6, using an immunofluorescence-based commercial kit made by Biotrim International Ltd., Dublin, Ireland. This technique uses human lymphocytes infected with HHV-6 as the cell substrate.

Using standard serological procedures, all paired serum samples were tested for the presence of antibody to rubella (hemagglutination inhibition, HI, and enzyme-linked immunosorbent assay, ELISA), measles (HI and ELISA), infectious mononucleosis (Paul Bunnell-Davidson test), toxoplasmosis (indirect immunofluorescence assay, IFA) and arboviral infections (HI). This latter group included Oropouche,

Mayaro and Dengue viruses. Sera were also tested for the presence of parvovirus B19 antibody by using an IFA commercial kit provided by the same manufacturers of the previously mentioned HHV-6 reagents.

RESULTS

Clinical symptoms and serological results are summarized in Table 1. The fever of all 4 children was high (39-40°C) and of three days duration. When it subsided, a maculopapular rash appeared on the face, subsequently spreading rapidly down to the trunk and then to the extremities (2-3 days) (Fig. 1). It faded quickly, usually lasting 1 day in each area of the body. Cervical and postauricular lymphadenopathy were noted in three children, and two of them showed tonsillar pharyngitis.

Seroconversions (at least eightfold increase in antibody levels) for HHV-6 were detected in the four paired sera, with increases in titers ranging from < 1:10 to 1:80 in patient 3 and from < 1:10 to 1:640 in patient 2.

No evidence of recent infection with rubellavirus, measles, Epstein-BARR virus, arboviruses, parvovirus B19 or *Toxoplasma gondii* was detected. Neither faecal samples nor throat swabs were obtained for attempts to isolate enterovirus.

TABLE 1

Clinical and laboratorial findings in cases of exanthem subitum associated with HHV-6 infection in Belém, Brazil.

	Patients			
	1	2	3	4
Age (months)/Sex	11/F	24/M	16/M	10/F
Onset of symptoms	15/04/94	07/05/94	13/06/94	07/08/94
Duration of symptoms in days				
Fever	3	3	3	3
Rash	3	3	2	2
Lymphnode swelling	5	5	-	5
Tonsillar pharyngitis	3	-	-	3
Serology				
Titer of acute serum	1:40	<1:10	<1:10	1:40
Titer of convalescent serum	1:640 ⁽¹⁴⁾	1:640 ⁽²⁶⁾	1:80 ⁽¹⁶⁾	1:320 ⁽⁷⁾

() Interval-time, in **days**, between collection of acute and convalescent-phase serum samples.



Fig. 1 - Patient nº 4 with maculo-papular rash on the face and trunk.

DISCUSSION

To our knowledge, this is the first report of cases of ES in the Amazon region (and probably the first in Brazil) with a diagnosis made on both clinical and laboratorial data. The seroconversions for HHV-6 detected in all cases, and the typical ES clinical picture, leaves no doubt that all the children were infected by this herpesvirus. As no specimens could be obtained for enterovirus isolation, we cannot entirely rule out the possibility of these agents being associated with the aetiology of the exanthematous illnesses. This seems to be very unlikely, however, as, in addition to the laboratorial results indicating recent HHV-6 infection, the clinical features resembled those which are widely recognized as being typical of ES^{10, 15}. LINNAVUORI et al⁸ and UEDA et al¹³ in Finland and Japan, respectively, also established the diagnosis of recent HHV-6 infection, in cases of ES, on the basis of seroconversion. It may be noted that most investigations carried out in various parts of the world, reported the occurrence of HHV-6 infection in children less than 2 years of age, as is the case in our study^{9, 11, 14, 15}. Again, serosurveys

conducted in Japan¹³ have demonstrated high seropositivity rates for HHV-6 among children aged 10 to 11 months, suggesting that primary infections mainly occur within the first year of life.

Although febrile convulsions are reported to often occur in the course of ES, with incidence varying from 0.6% to 50%⁵, these were not observed in our four patients, who recovered completely one week after the onset of symptoms.

Although of a preliminary nature, our findings suggest that HHV-6 may be an important agent of exanthematous illness in infancy and childhood in this region of Brazil. Alerting local physicians as to the importance of this viral agent as a human pathogen, and the availability of rapid and sensitive techniques for routine laboratorial diagnosis are issues to be pursued. In addition, further and broader studies are necessary (possibly including genotyping of virus strains), in order to better understand both clinical and epidemiological features of HHV-6 infection in this region.

RESUMO

Exantema súbito associado a infecção pelo herpesvírus humano tipo 6 em Belém, Brasil

Infecção recente por herpesvírus humano tipo 6 (HHV-6) foi detectada em casos de exantema súbito envolvendo quatro crianças com idades de 10 a 24 meses, no período compreendido entre abril e agosto de 1994, em Belém, Brasil. Utilizando-se a técnica da imunofluorescência indireta, aumentos significativos (de pelo menos oito vezes) foram observados nas concentrações de anticorpos das amostras de soro, da fase aguda para as da convalescente, com títulos variando de < 1:10 / 1:80 a < 1:10 / 1:640 (pacientes 3 e 2, respectivamente). Todas as crianças apresentaram febre alta (acima de 39°C) por três dias, seguida de exantema máculo-papular generalizado. O exame físico realizado nas crianças revelou concomitância de adenomegalia cervical e amigdalite em dois desses indivíduos.

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