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Clinical Impact of Primary Infection with Roseoloviruses

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Abstract

The roseoloviruses, human herpesvirus-6A -6B and -7 (HHV-6A, HHV-6B and HHV-7) cause acute infection, establish latency, and in the case of HHV-6A and HHV-6B, whole virus can integrate into the host chromosome. Primary infection with HHV-6B occurs in nearly all children and was first linked to the clinical syndrome roseola infantum. However, roseolovirus infection results in a spectrum of clinical disease, ranging from asymptomatic infection to acute febrile illnesses with severe neurologic complications and accounts for a significant portion of healthcare utilization by young children. Recent advances have underscored the association of HHV-6B and HHV-7 primary infection with febrile status epilepticus as well as the role of reactivation of latent infection in encephalitis following cord blood stem cell transplantation.

Introduction

Roseoloviruses include human herpesvirus-6A -6B and -7 (HHV-6A, HHV-6B and HHV-7), which constitute the *Betaherpesviridae* subfamily of human herpesviruses along with human cytomegalovirus (HCMV). HHV-6 was first isolated from immunocompromised adults in 1986 by Salahuddin and colleagues [1]. Initially two distinct variants of HHV-6 were identified, HHV-6A and B with HHV-6B causing disease in developed countries. The two variants were officially classified as separate viruses in 2012[2].

As with all human herpesviruses, following primary infection HHV-6 and -7 establish latent or persistent infection in different cell types, have the ability to reactivate, and may be intermittently shed in bodily fluids [3]. Unlike other human herpesviruses, HHV-6A and

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HHV-6B are also found integrated into the host genome (ciHHV-6). Integration has been documented in 0.2-1% of the general population and along with latency has confounded the ability to correlate the presence of viral nucleic acid with active disease [4].

The syndrome known as roseola infantum was reported as early as 1809 by Robert Willan in his textbook “On cutaneous diseases” [5]. This clinical entity is also commonly referred to as exanthem subitum and early published descriptions of the disease still hold true. It is an illness that affects children by the age of three and is marked by the abrupt development of high fever lasting 3-5 days. The hallmark maculopapular rash appears as the fever subsides, and there may be few, if any, associated symptoms. Despite knowledge of this common disease of infancy, the etiologic agent was not identified until 1988 by Yaminishi and colleagues [6]. They demonstrated both the presence of circulating virus in peripheral blood mononuclear cells (PBMCs) during acute roseola and subsequent seroconversion during convalescence in four infants in Japan. It was nearly a decade later before our understanding of the full clinical spectrum of HHV-6 primary infection was expanded past roseola.

Recognition of primary infection with HHV-6 is important because the high prevalence of infection and its association with fever leads to substantial healthcare utilization. Primary infection in childhood is also strongly associated with neurologic complications, and reactivation of the latent virus under immunosuppressive conditions has been associated with significant morbidity. This review discusses the spectrum of clinical disease associated with roseolovirus primary infection, highlighting recent advances.

Epidemiology

The ubiquitous nature of infection with HHV-6 is evidenced by the fact that all newborns have passive maternal antibody to HHV-6 which typically wanes by 4-6 months of age, with primary infection occurring fairly soon thereafter [7-9]. The young age of primary HHV-6 infection was demonstrated in a prospective study by Hall and colleagues of children with fever seen in the emergency department (ED) in Rochester, NY [7]. Utilizing viral isolation and seroconversion, HHV-6B was identified as the causative agent of illness in 159 of 1553 children less than 24 months of age, while only one child out of 100 at 25-36 months of age had fever due to primary HHV-6B infection. The peak age of infection was 6-9 months [7]. Zerr and colleagues conducted a population-based prospective cohort study of HHV-6 primary infection in children from birth through two years of age in Seattle, WA. Based on persistent shedding of HHV-6B DNA in saliva, they noted a peak incidence of primary infection from nine to 21 months of age among children in the community, which is slightly older than the ED-based study. This shift in age of acquisition is also reflected in a 40% cumulative incidence of infection by 12 months of age, but the vast majority of children (77%) still acquired the virus by 24 months of age [10].

While HHV-6A DNA has been identified in umbilical cord blood mononuclear cells and in approximately one third of individuals with ciHHV-6, its role in subsequent active disease has not yet been established [11]. Clinical disease in North America, Europe and Asia has almost exclusively been linked to HHV-6B infection [2]. This contrasts with one region of

sub-Saharan Africa, where HHV-6A DNA was detected in a majority of infants in an HIV-1 endemic region [12].

Transmission

The exact modes of transmission of HHV-6 have yet to be definitely determined. It is presumed that HHV-6 can be transmitted from the saliva of asymptomatic adults and older children because of the rapid and reliable transmission of virus to susceptible infants and the lack of recognized outbreaks [3]. It does seem clear that close contact is required for transmission, supported by the observations that having older siblings and parents who share saliva are associated with virus acquisition, but attending daycare is not [10, 13]. Recently, transmission of HHV-6 via respiratory droplets has been suggested by the identification of viral DNA in nasal mucosa and olfactory bulb specimens. Olfactory-ensheathing cells, specialized glial cells present in the nasal cavity, are also capable of being infected in vitro with HHV-6A suggesting that the olfactory pathway may be a route of entry of HHV-6 into the CNS [14].

Congenital infection with HHV-6 also occurs in approximately 1% of newborns [11]. While this rate is similar to congenital transmission of CMV, 86% of congenital infections are transmitted via chromosomally-integrated virus (ciHHV-6) while a minority (14%) is transmitted through presumed transplacental infection [15]. Chromosomal integration with germline transmission is a mechanism unique to HHV-6 and has not been demonstrated for HHV-7 or any other human herpesvirus. Infants with ciHHV-6 have measurable HHV-6-specific antibody, but it is unknown whether this is protective, whether the virus is actively replicating and the long term effects of congenitally-acquired HHV-6[4, 15, 16].

Clinical presentation

Symptoms

The most common finding in children with HHV-6 primary infection is fever (Table 1). Compared to other febrile illnesses in children under two years of age evaluated in an emergency department setting, HHV-6 infection has been shown to cause a significantly higher mean temperature (39.6°C compared to 38.9°C), with the great majority of children exhibiting temperatures greater than 39°C. In the study in Rochester NY, fevers remained high for the first three days with 15% of children remaining febrile for six or more days. Children with primary HHV-6 infection also presented earlier into the illness for medical care than children with other febrile illnesses (2.1 vs. 2.9 days) [7].

While studies from Japan have strongly linked HHV-6 to the clinical syndrome of roseola, this may be a reflection of study design and subject inclusion criteria [6, 17]. Prospective studies in the US have revealed that the classic syndrome of roseola accompanies only a minority of primary HHV-6B infections. The hallmark rash of roseola was observed in only 6% of the children at initial presentation when febrile and in another 17% at the time of defervescence in the study by Hall and colleagues [7]. Similarly, rash was only present in approximately 20% of children during primary HHV-6 infection in the community based

study in Seattle, WA [10]. This highlights that roseola infantum is identified in less than a quarter of children with primary HHV-6 infection in the United States.

Fever, fussiness and rhinorrhea are present in over half of children with primary HHV-6B infection while diarrhea, rash and roseola are all significantly more common during primary HHV-6B infection than other periods of illness [10]. Additionally, febrile children with HHV-6B infection are less likely to present with cough or other symptoms of lower respiratory tract infection [7].

Healthcare Utilization

HHV-6B primary infection is a common cause of acute medical care visits accounting for 10% of physician office visits and 10-17% of acute febrile ED visits in children up to 36 months of age [7, 10, 18, 19]. Remarkably, primary infection has been identified in 24% of children from six to nine months of age presenting to the ED with an acute febrile illnesses (Figure 1) [7]. Additionally, children with primary HHV-6B infection are more likely to present with signs of serious systemic illness, irritability, and inflamed tympanic membranes and are commonly diagnosed with a presumed serious bacterial infection or otitis media, often resulting in unnecessary antibiotic use. Hospitalization due to concern for serious infection has been documented in one-third of children less than six months of age with primary infection seen in an ED [7, 18]. These data indicate that acute HHV-6B infection is associated with a high level of healthcare utilization. While the majority of children have a relatively benign clinical course, the acute clinical presentation may be concerning to both parents and healthcare providers alike.

Complications

Case reports and small case series have linked primary HHV-6 infection with a wide range of potential complications including myocarditis, rhabdomyolysis, thrombocytopenia, Guillain-Barre syndrome and hepatitis/fulminant hepatic failure [20-22]. Many of these studies used the presence of HHV-6 DNA in the target organ, PBMCs, or other body fluids as evidence of active HHV-6 infection. However, detection of viral nucleic acid can represent active infection, latent infection or ciHHV-6. While such laboratory studies are not widely available, active replication of the virus or protein production should be identified to correlate infection with the clinical syndrome observed. The absence or presence of HHV-6-specific antibody can then be used to help determine whether there is a primary infection or reactivation, respectively.

Neurologic Complications and Sequelae

Seizures

Neurologic complications, manifested as seizures or encephalopathy, have long been associated with roseola. However, the true prevalence of seizures complicating HHV-6 primary infection has been difficult to determine due to the wide variation in study designs and populations. A literature review encompassing studies from 1994 to 2004 found that 17% of children seeking medical attention with primary HHV-6 infection had seizures as a complication [23]. Children from 12-15 months of age may be at particular risk with a

documented rate of febrile seizures of 36% among children presenting to the ED with acute HHV-6B infection. Overall, primary HHV-6B infection accounts for approximately 25 to 33% of the febrile seizures observed in children less than 24 months of age in the emergency department setting [7, 24]. Additionally, data form the United Kingdom identified HHV-6B & HHV-7 infection in 17% of cases of suspected encephalitis or severe febrile seizures in young children [25].

While the majority of febrile seizures are considered to have a benign clinical course, 5-8% meet criteria for status epilepticus, and an estimated 5,000 to 10,000 cases of febrile status epilepticus (FSE) occur annually in the United States. Febrile seizures are the most common cause of status epilepticus in previously healthy children, accounting for over 70% of status epilepticus during the second year of life [26, 27]. The long term consequences of FSE are still not completely understood. There is a potential but controversial link to the future development of intractable temporal lobe epilepsy and hippocampal sclerosis, which is the most common reason for epilepsy surgery in adults [28, 29]. Recent data from the multicenter prospective study, Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT), has substantially expanded our current understanding of FSE [30]. This study has provided ongoing detailed evaluation of 200 children from ages one month through five years who presented with FSE in order to study the casual relationship between FSE and temporal lobe epilepsy. HHV-6 and HHV-7 virologic studies were performed to determine the frequency of roseolovirus-associated FSE and to determine if roseolovirus-associated FSE is more likely to cause subsequent hippocampal injury and temporal lobe epilepsy. There were 44 cases of primary roseolovirus infection and 14 cases of reactivation as determined by serology and reverse transcriptase PCR. Together, HHV-6B and HHV-7 accounted for one-third of the cases of FSE in the study with HHV-6B causing the majority. There were no differences in acute temporal lobe (hippocampal) injury between children with HHV-6 or HHV-7 infection and those without at the time of infection, and the subsequent development of hippocampal sclerosis is still under active investigation. Therefore, while roseoloviruses may cause hippocampal injury, it appears they may be no more likely than other viruses to do so during the acute illness [30]. HHV-6B has been found in temporal lobe specimens of patients with intractable temporal lobe epilepsy, but the causal relationship between HHV-6B reactivation and hippocampal injury remains undefined [31-33].

Encephalitis and other neurologic disorders

HHV-6B reactivation is an established cause of limbic encephalitis in immune compromised persons following hematopoetic stem cell transplantation, as initially described by Wainwright and colleagues [34] (*please refer to the accompanying review by Zerr and Hill*). More recently, the receipt of cord blood stem cells has been highly associated with HHV-6 reactivation and encephalitis [35, 36]. HHV-6B, and rarely HHV-7, primary infection has also been associated with encephalitis in immune competent individuals [37]. There appears to be a distinct geographic distribution, with the highest incidence occurring in Japan. Surveys estimate that 60 cases of roseola per year are complicated by encephalitis in Japan, making it the second most common cause of infection-related encephalitis. Severe neurologic sequelae such as acute necrotizing encephalitis, hemorrhagic shock and acute

encephalopathy with biphasic seizures complicate nearly half of those cases [38, 39]. Evidence suggests that this may be a cytokine-mediated disorder [40]. HHV-6B has also been implicated in triggering potentially fatal neurologic deterioration in children with an underlying mitochondrial disorder involving polymerase gamma gene (POLG) mutations, suggesting that underlying host factors may contribute to the severity of HHV-6-associated neurological disease [41].

HHV-7 Primary infection

HHV-7 was first isolated from $CD4^+$ lymphocytes in 1990 by Frenkel and colleagues and subsequently found to be a distinct virus closely related to HHV6-A and HHV-6B and an additional cause of roseola [42]. Infection is highly prevalent worldwide and also causes universal infection in childhood. However, HHV-7 tends to infect slightly older children when compared to primary HHV-6B infection. A small case series identified 8 cases of primary HHV-7 infection out of 250 children presenting to the ED with fever. The median age of presentation was 26 months and only one child was less than 13 months old. The clinical presentation was indistinguishable from that of HHV-6B infection, and notably six of the eight children presented with seizures [43]. Suga and colleagues in Japan also found that HHV-7 infection was comparable to HHV-6 in a slightly older child, although seizure activity was only observed in one of fifteen cases of HHV-7 primary infection [44]. While these studies are relatively small in size, it appears that HHV-7 primary infection has the potential for severe complications similar to HHV-6. Recent evidence has also linked delayed HHV-7 primary infection with severe neurologic complications, including encephalitis and Guillain-Barre syndrome [45].

Summary/Research Priorities

Primary infection with roseoloviruses is nearly universal in early childhood. While the majority of infections are self-limited, the large number of infections coupled with the characteristic fever leads to significant healthcare utilization and possible antibiotic misuse. New methods for sensitive, specific and timely diagnosis of acute infection could potentially mitigate some of the healthcare expenditures and antimicrobial overuse (*please refer to the accompanying review on diagnostics by Hill et al*). Additionally, the universal nature of infection with roseoloviruses, along with the recognition of ciHHV-6, creates unique challenges in investigating the true burden of disease and research is most urgently needed to determine methodology and criteria for distinguishing a causal relationship between roseoloviruses and pathology. Although primary infection has been directly linked to a spectrum of neurologic complications, most notably febrile status epilepticus, the full spectrum of complications and their clinical burden remain important research questions. The identification of potential biomarkers to predict individuals at high risk for complications and the possible benefits of antiviral treatment in select populations are related research priorities.

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Highlights

- HHV-6B primary infection occurs in nearly all children by three years of age.
- HHV-6 can integrate into the host genome and be passed via germline transmission.
- Only a quarter of HHV-6B primary infections manifest as roseola infantum in the US.
- HHV-6B or HHV-7 account for 1/3 of febrile status epilepticus cases in children.
- Delayed HHV-7 primary infection may be associated with more severe neurologic complications.

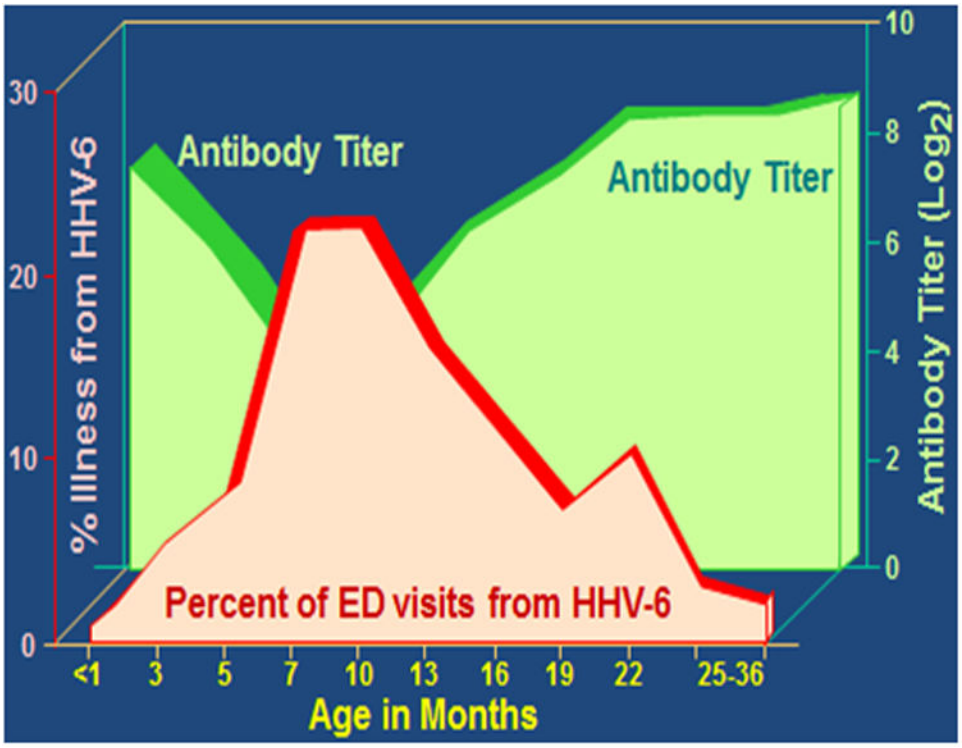

Figure 1.

HHV-6 Antibody Titer in 0-36 Month Old Children and Acquisition of Primary Infection. Data from N Engl J Med, Hall CB et al., Human Herpesvirus-6 Infection in Children: A Prospective Study of Complication and Reactivation. 331: 432-8. Copyright (1994) Massachusetts Medical Society. Reprinted with permission.

Table 1

Signs and Symptoms Associated with Primary HHV-6 Infection.

	Range	Vianna et al.[46]	Zerr et al.[10]	Caserta et al.[43]	Hall et al.[7]	Asano et al.[17]	Pruksananonda et al.[18]
Year Published	1992-2008	2008	2005	1998	1994	1994	1992
Number of Subjects	626	97	130	29	160 (1094 evaluated)*	179	34
Inclusion Criteria		Children with rash and/or roseola	Out-patient cohort	Children with fever	Children evaluated in the Emergency Dept.	Children with rash and/or roseola	Children evaluated in the Emergency Dept.
	% of patients with symptom(s) when reported						
Asymptomatic	6		6				
Fever (T>38° C)	58-98	94	58	100	100 [87 (T>39)]	98	100 [65 (T>40)]
Rash (generalized)	18-48	91	31	48			18
Roseola	17-24		24		17		
Gastrointestinal Symptoms (general)	3-34			34	30		3
vomiting	8-21	21	8				21
diarrhea	24-68	24	26			68	27
Upper Respiratory Symptoms	3-41				41		3
rhinorrhea	56-66	61	66				56
Lower Respiratory Symptoms	24						24
Cough	27-62	62	34				27
Cervical Adenopathy	31-34	34				31	
Pharyngeal Papules	65					65	
Tonsillitis	29	29					
Conjunctivitis	26	26					
Acute Otitis Media/Inflammed Tympanic Membranes	8-62	8			30		62
Eyelid Edema	30					30	
Fussiness/Irritability	69-82		70	69			82
Seizures	0-17	1	0	17	13	8	3
Bulging Anterior Fontanelle	26					26	
Prompted Outpatient Visit	39		39				

	Range	Vianna et al.[46]	Zerr et al.[10]	Caserta et al.[43]	Hall et al.[7]	Asano et al.[17]	Pruksananonda et al.[18]
Prompted Hospitalization	13-17			17	13		

*None of the additional 582 infants with non-febrile illness evaluated in the Emergency Department or the 352 infants without an acute illness seen in ambulatory clinics had evidence of primary HHV-6 infection.