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Clinical impact of primary infection with roseoloviruses

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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.

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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 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 three to five 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 four to six 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 six to nine 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. On the basis of 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 ED 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 versus 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