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COMMENTARY

The Eruptive Fevers at Sixes and Sevens

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Abstract: Sixth Disease (roseola infantum) and its primary causative agent, HHV-6, share names that numerically concur. This article examines and answers the question of whether that correspondence is by design or coincidental by briefly reviewing the history and nomenclature of the HHV viruses and the classic febrile rashes of childhood while highlighting some clinical and microbiologic features of HHV-6 infection.

Keywords: HHV-6, HHV-7, human herpesviruses, roseola infantum, sixth disease, Kawasaki disease, viral taxonomy, nomenclature, emergency medicine, historical coincidence

Background

Human herpesvirus type 6 (HHV-6) is a large, enveloped, double-stranded DNA virus that infects leukocytes by binding the CD46 and CD134 receptors,[1–4] inducing chemokine and cytokine release.[5–7] Viral transmission is thought to occur primarily within families[8,9] through saliva,[8,10] and the majority of children in the US are infected by the age of two.[9] It is estimated that HHV-6 infection accounts for about 10–20% of emergency department (ED) visits among infants and young toddlers with a febrile illness,[11–13] and up to 40% of the subset of those patients who are admitted to the hospital. In addition to fever, common presenting signs and symptoms include rash, upper respiratory symptoms, severe neutropenia, cough, lymphadenopathy, vomiting, diarrhea, irritability, seizures, Koplik/Nagayama's spots, otitis, and a bulging anterior fontanelle.[6,9,11,12,14–17] The acute clinical course is usually self-limited,[12] but in some cases there are complications such as recurrent seizures, status epilepticus,[17] encephalitis,[18–20] and rarely rhabdomyolysis[21] or myocarditis.[22]

About 10–30% of presenting HHV-6-infected children will develop the classic pink roseola rash after rapid defervescence[9,11,12] that we label exanthem subitum and that triggers the diagnosis of roseola infantum or Sixth Disease.[23] In the ED, these cases sometimes raise the question of whether HHV-6 and Sixth Disease were named after one another. It sounds plausible enough, if not likely. At least one popular medical website recently said that Sixth Disease is so named "because the human herpesvirus (HHV) type 6 most often causes the illness".

History of Discovery and Nomenclature

The question then turns to whether the disease was named after the virus, or *vice versa*, or else whether the paired sixes were, in fact, just a historical accident. As most pediatricians know, Sixth Disease derives its name from its sixth position on the list of "eruptive fevers"—ie, febrile rashes—of childhood that clinicians had compiled[24–26] in the early 1900's based on the order in which the illnesses were first clinically described. The first five were measles, scarlet fever, rubella, a somewhat mysterious "Fourth Disease",[24] (identified by some as staphylococcal scalded skin syndrome[27,28]) and erythema infectiosum, a.k.a. Fifth Disease.[29,30] The term "Sixth Disease" dates to at least as far back as the 1930's.[29,31–34] The HHV-6 virus, on the other hand, was not discovered until five decades later, in 1986, by a group of researchers at NIH[35] headed by the

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virologist Robert C. Gallo, who also proved that HIV was the causative pathogen in AIDS.[36,37] The clinical entity was, therefore, named well before the pathogen.

The Gallo group initially named the virus the human B-lymphotropic virus (HBLV), because it was shown to target and morphologically convert human B-cells, but the next year[38] they proposed renaming it HHV-6. The proposed name change again raises the question of whether it related to the virus's role in Sixth Disease. And, again, this may sound plausible, except that the cause of Sixth Disease was unknown in 1987. The NIH group recommended the change because they had learned by then that the virus targeted T-cells as well as B-cells. Since it was the sixth human herpesvirus to be isolated, after herpes simplex viruses 1 and 2, varicella-zoster virus, Epstein-Barr virus and cytomegalovirus, (ie, HHV-1 through HHV-5, respectively),[39] the new virus was named[40] HHV-6, in compliance with the nomenclature guidelines put forward by the International Committee for Taxonomy of Viruses (ICTV).[41,42]

It was not until the following year, 1988, that the virus was shown to be the causative agent of Sixth Disease by researchers in Osaka.[43] Dr. Gallo was kind enough to confirm through a personal communication that the proposed HHV-6 designation had nothing to do with roseola or Sixth Disease. Thus, the virus and the disease it causes were named independently. It is just an odd historical coincidence that they both happened to be sixth on their respective lists when they were. (The error on the medical website has subsequently been corrected.)

Later Developments

Since the 1980's, the list of identified human herpesviruses has grown. There are currently eight of them, including HHV-7, and the Kaposi's Sarcoma herpesvirus,[44] a.k.a. HHV-8. In addition, the two main variants of HHV-6 have been named A and B.[45,46] The variant thought to cause the majority of HHV-6 clinical disease in infants and toddlers in the U.S.[47] and Japan,[48] including Sixth Disease, was called HHV-6B, although febrile rashes and encephalitis have also been described with infantile HHV-6A infection in some other parts of the world,[18,20,49,50] and the two viruses share ~90% sequence identity.[51] In addition, HHV-6, like most other herpesviruses, has been found to cause latent infection[52] that can manifest later in life.[53–56] Unlike most other herpesviruses, however, both HHV-6 variants demonstrate the capacity to integrate directly into the host genome[57] and transmit via germline[58,59] from parent to offspring. This vertical transmission occurs in about 1% of the population[60–62] and is called inherited chromosomally integrated HHV-6 (iciHHV-6). Mother-to-child transmission of either variant has also been found to sometimes occur transplacentally.[63]

As for the century-old numbered list of eruptive fevers of childhood, some have, over the decades, envisioned Kawasaki syndrome to be the Seventh Disease,[64–67] and while HHV-7 is not (yet?) believed to be its causative agent, more recent studies have indicated that approximately 30% of Kawasaki patients have elevated blood levels of the virus's DNA in the acute phase of the illness.[68,69] This may arise from reactivation of prior infection rather than acute infection, but in either case it represents another historical coincidence.

While it is clear that the numerical agreement was unintended in both Sixth Disease/HHV-6 and Seventh Disease/HHV-7, the occurrence of two such coincidences back-to-back suggests a real effect at work. In particular, the earlier a disease is discovered or described, the earlier its pathogenesis is likely to be explored,[70] and, similarly, the earlier a novel potential pathogen is identified, the earlier the search for a possible associated disease can begin.[71,72] Either case may result in temporal cross-correlation.[73] Hence, all else being equal, a pathogen and its associated disease may have a higher-than-random chance of appearing at the same ordinal position on their discovery lists.

Conclusion

The numerical correspondence between the names of Sixth Disease and its primary causative agent, HHV-6, arose by historical coincidence rather than by design. Both the disease and virus are part of nomenclature systems that add category members in the order of their date of discovery, and both happened to be the sixth members added to their respective categories. However, since the order in which diseases are discovered may correlate to some degree with the order in which they are studied and their pathogens identified, it is possible that the concurrence is not due entirely to chance.

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Disclosure

The author reports no conflicts of interest in this work.

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