Multilane Highway to Congenital Infection

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(See the article by Caserta et al., on pages 1296–303.)

Congenital infections are an important clinical and societal problem that can be devastating for children and their families. Although many congenital infections are asymptomatic, some are associated with overwhelming consequences requiring long-term support that can include physical care and addressing learning and other developmental difficulties.

Advances in medical care have allowed identification and prevention or treatment of some congenital infections. For example, primary maternal syphilis is likely to cause fetal death, and latent maternal syphilis may result in no fetal or neonatal disease or in an easily missed latent infection that ultimately causes devastating disease if not treated. Universal screening and treatment of pregnant women for syphilis is asymptomatic, some are associated with febrile convulsions. These are remarkable demonstrations of the value of attending to congenital infections.

One of the most important congenital infections in the United States is cytomegalovirus (CMV) infection. As discussed recently in these pages [1, 2], congenital CMV infections can lead to significant learning disabilities and cause a significant portion of cases of early childhood sensorineural hearing loss. The latter problem is particularly vexing because hearing loss associated with congenital CMV infection may not develop for months or years, thus escaping detection by standard neonatal hearing tests. Screening and treatment programs for congenital CMV infections are in evaluation internationally.

CMV is a member of the betaherpesvirus subfamily (the Betaherpesvirinae). The other human betaherpesviruses, human herpesvirus (HHV)-6 and HHV-7, share a number of biological properties with CMV, including lymphotropism and a propensity to infect children [3]. Two major forms of HHV-6 have been identified, variants A and B. The clinical spectrum of HHV-6A remains to be defined. HHV-6B is highly prevalent, causes most cases of the early childhood disease roseola (exanthem subitum or sixth disease), and has been associated with diverse diseases in immunocompromised patients. Approximately 20% of children from 6 to 12 months old who are admitted to emergency departments with febrile illnesses are experiencing primary HHV-6B infections. Primary infections with HHV-7 cause a small percentage of roseola cases and have been associated with febrile convulsions at a rate higher than that for HHV-6. Congenital transmission of HHV-7 has not been detected. Approximately 1% of children are congenitally infected with HHV-6, a frequency similar to that for CMV [4]. Fifty-seven occurrences of congenital infection were detected among the >5600 children examined; all were asymptomatic. For perspective, this sample size would not have allowed reliable detection of a symptomatic case of CMV infection (~1% of children congenitally infected with CMV are symptomatic). Thus, the contribution of HHV-6 to congenital disease remains to be determined, and the modes of transmission have not been fully defined.

In this issue of the Journal, Caserta et al. [5] describe a large-scale study to examine the prevalence of HHV-6 and HHV-7 nucleic acids in blood samples and cervical swabs from pregnant women, to detect possible associations with congenital transmission of these viruses. Their article is the most recent chapter in an ongoing study of the natural history of pediatric HHV-6 and HHV-7 infections by Dr. Caserta, Dr. Hall, and associates. This work has proven to be valuable in its illumination of the spectrum of disease associated with these viruses and in understanding enough of their habits to make
better sense of observations of their behavior in other contexts.

The approach was to sample blood and the cervix in women at various points during pregnancy and, in some cases, to also test postpartum placental samples or blood samples from the infants for the presence of HHV-6 and HHV-7 DNA. Testing at different stages of pregnancy is important, because the timing of infection might influence the likelihood and type of damage to the fetus and neonate. Although HHV-7 DNA was detected in ~70% of the blood samples tested, consistent with the findings of previous work, there was no evidence of congenital transmission of the virus. Two paths for congenital transmission of HHV-6 were identified. Two of the 5 children with evidence of congenital transmission of HHV-6 may have been infected via a conventional infectious process in utero, from mothers in whom virus was detected intermittently and at low levels. The other 3 children had congenital infections that were likely due to transmission of germline-integrated HHV-6 genomes. Two of these children probably acquired the virus from their mothers, who were consistently positive for HHV-6 DNA at high levels (~1 × 10^5 genomic copies/μg of DNA) throughout pregnancy. For one child born to a mother who was negative for HHV-6 by polymerase chain reaction (PCR) during and after pregnancy, similarly high levels of HHV-6 DNA were detected in the placenta and in the neonate’s peripheral blood mononuclear cells. The placenta was also positive by reverse-transcriptase PCR for a spliced HHV-6 transcript, indicative of some level of viral activity. The possibilities are either that the child acquired a high HHV-6 DNA load via germline transmission from the father or that the child had a fulminant infection at the time of birth. Clinical manifestations were not reported. Clark et al. [6] have described a healthy individual with chromosomally integrated HHV-6 in whom viral gene transcription was also detected.

Germline transmission of viruses is not a common event. Although numerous endogenous retroviruses are woven into the fabric of the human genome and have some biological activity, they are not functional viruses. Indeed, by their very nature, viruses are entities that explicitly employ modes of transmission that are physically disconnected from the host genome. Thus, a minimal virus is a genome that can be replicated and is packaged in a manner that allows its transmission from cell to cell and from organism to organism. Although some viral genomes integrate into the host genome as part of their pathogenic process (e.g., papillomaviruses), the integrated forms play no direct role in organism-to-organism transmission.

Several years ago, HHV-6 was found to be integrated into the genomes of some individuals with lymphoma, leukemia, and multiple sclerosis [7, 8]. Approximately 1% (0.2%–5% in various studies) of the population harbors chromosomally integrated HHV-6 genomes [9]. In situ hybridization revealed the presence of the viral genome at the ends of specific chromosomes. In one case, the virus was integrated at the tip of chromosome 22 in a mother, at the tip of chromosome 1 in a father, and at both locations in their daughter [10]. Insufficient examples have been studied to determine whether the virus has a preference for particular chromosomes. That the integrations map at the tips of chromosomes may relate to the fact that arrays of sequences similar to those found at mammalian chromosomal telomeres are also present at the termini of HHV-6 genomes. In some individuals with high HHV-6 loads, viral DNA has not been detected in every cell [11]. It remains to be determined whether this is due to (1) the insertion of viral genomes into the chromosomes of many, but not all, cells at a time after conception, (2) the sensitivity of the detection method [6], or (3) the loss of portions of or entire integrated viral genomes from a subset of cells during development after a germline transmission event. Ward, Clark, and colleagues recently published a series of articles in which they demonstrated transmission of chromosomally integrated HHV-6 through stem cell transplantation [12] and illustrated the likelihood of chromosomally integrated HHV-6 being the basis for false-positive assignments of HHV-6 as the cause of some cases of encephalitis [13].

The observations on chromosomally integrated HHV-6 raise several important questions.

What is the nature of viral gene expression in cells that harbor chromosomally integrated HHV-6 genomes? Viral transcripts have been detected in some individuals, but it is not known what fraction of cells might be actively transcribing viral genes, in which tissues this might occur, whether subsets of viral genes might be expressed in some cells under pathological conditions, or whether the transcripts lead to the expression of viral proteins. Can the integrated genomes be resurrected to produce infectious virus?

What are the short- and long-term clinical implications of chromosomally integrated HHV-6 genomes? Does lifelong limited expression of viral genes from integrated genomes lead to an immunological tolerance of HHV-6 antigens that may affect control of exogenous infection with the virus? Is it possible that, in populations of cells harboring chromosomally integrated HHV-6 genomes, a subset of cells are in pathologically relevant states of active replication that might be controlled by an antiviral [14]?

We are left with the biologically plausible possibilities that congenital infections with HHV-6 may have consequential outcomes and that there may be very different short- and long-term outcomes depending on whether the infection was transmitted via a classic infectious process or via the novel germline chromosomal integration mechanism for HHV-6 transmission. Stay tuned.

References

1. Ogawa H, Suzutani T, Baba Y, et al. Etiology of severe sensorineural hearing loss in chil-

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