An Old Rose and its Newly Revealed Thorns

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(See the major Article by Yang et al, on pages 361–9.)

To paint a rose, the artist must “forget all the roses that were ever painted.”

H. Matisse

As physicians and biomedical scientists, we daily experience the tension between things we know, things we do not know, and the ever-rising tide of new information, most of which arrives with uncertain significance and robustness. New information sometimes collides with things we have long known, in ways that can obstruct learning.

In this issue of the *Journal of Infectious Diseases*, Yang and colleagues [1] measured the prevalence of human herpesvirus 6 (HHV-6) DNA in archived explanted livers obtained from children whose need for liver transplantation was due to liver failure of unknown etiology (LFUE). LFUE is a severe condition, with only a 25% survival rate in the absence of a transplant [2]. Approximately 20% of pediatric liver transplants are due to LFUE [3]. In children younger than 3 years of age, the authors found elevated levels of human herpesvirus 6 (HHV-6) DNA in 13/27 (48%) LFUE cases versus 2/27 (7.4%) (P = .0009) livers of children whose livers failed for identified reasons. The relationship was significant in children up to the age of 6 years. Given that HHV-6 has an antiviral susceptibility profile similar to that of human cytomegalovirus, including susceptibility to ganciclovir, valganciclovir, cidofovir, and foscarnet [4], this striking result suggests an immediately accessible path to development of improved care for children presenting with LFUE, and raises the question of whether the virus might have related activity in adults. The work provides yet another reminder of the extraordinary value of well-documented archives of clinical specimens.

In considering these results, let us suspend for a few minutes our prior understanding that HHV-6 is a lymphotropic virus whose dominant pathology is roseola and related mild and self-limiting febrile/rash illnesses of young children. There is more to the story.

**ROSEOLOVIRUSES?**

“HHV-6” is often used to collectively refer to 2 distinct but closely related viruses, HHV-6A and HHV-6B [5]. Along with the somewhat more distantly related HHV-7 and some simian homologs, these viruses are members of the *Roseolovirus* genus within the betaherpesvirus subfamily (the Betaherpesvirinae) of the herpesvirus family (the *Herpesviridae*) [6]. The polymerase chain reaction (PCR) methods employed by Yang et al did not enable discrimination between HHV-6A and HHV-6B; for reasons described in their article, it is likely that most, if not all, of the viruses detected were HHV-6B.

**BEYOND LYMPHOCYTES: ROSEOLOVIRUS HOST AND TISSUE TROPISMS, AND SPECTRUM OF DISEASE**

All 3 human roseoloviruses can infect lymphocytes, but each employs a different primary host cell receptor and infects different subsets of T cells. An important point relative to the study of Yang et al is that while they are indeed lymphotropic viruses, all 3 viruses can also infect non-lymphoid cells, enabling each to infect a different, but overlapping, spectrum of cells, tissues, and organs.

It is well established that early life primary infections with the human roseoloviruses are common, with HHV-6B seroprevalence exceeding 80% before 4 years of age [7]. Common manifestations of HHV-6B and HHV-7 primary infections include fever/rash illnesses related to roseola, as well as more severe conditions such as febrile status epilepticus [8–10]. It is also well established that during the induced immunosuppression associated with organ transplantation, roseolovirus activity is associated with end-organ diseases, including cognitive dysfunction, encephalitis, encephalopathy, pneumonia, and hepatitis [11]. Outside the context of transplantation, and with varying levels of evidence, activity of these viruses (mostly HHV-6B) has also been associated with drug-induced hypersensitivity syndrome (also known as drug rash with eosinophilia and systemic symptoms [DRESS]), cardiomyopathy, multiple sclerosis, Hashimoto’s thyroiditis (HHV-6A), and, recently, Alzheimer’s disease (HHV-6A and HHV-7) [7, 12, 13]. Examination of affected tissues has made it clear that these viruses can be active in diseased tissues without producing a viremia that can be
distinguished from their normal background levels in circulating lymphocytes.

While, in most instances, HHV-6 is transmitted vertically as an infectious virus, approximately 1% of humans harbor inherited chromosomally integrated HHV-6A or HHV-6B (iciHHV-6) [6, 14, 15]. This enables a form of horizontal transmission via germline cells that results in the virus genome being present in every cell of individuals with iciHHV-6. While uncommon, iciHHV-6 can complicate diagnosis and has been associated with adverse clinical outcomes. iciHHV-6 is not a factor in the work of Yang et al.

A NEWLY ILLUMINATED THORN: HHV-6 AND LFUE

The study by Yang et al did not emerge from a vacuum. Rather, it extends from and expands upon a body of work that has demonstrated the ability of HHV-6A and HHV-6B to infect and damage solid organs, including the liver, in the absence of meaningful viremia. As mentioned above, HHV-6 has been associated with hepatitis in liver transplant recipients [16]. Bonnafous and colleagues recently showed that HHV-6A reactivated from a liver obtained from an iciHHV-6A–positive donor, and caused a fatal infection in the liver’s recipient [17]. In a 2002 study from Japan [18], Ishikawa and colleagues found HHV-6 DNA in livers obtained from 5 of 5 (100%) pediatric and 2 of 6 (33%) adult patients with fulminant hepatitis; using in situ methods, HHV-6 DNA, RNA, and proteins were detected in hepatocytes and ductal epithelial cells in the liver of one of the children. Multiple lines of evidence have now demonstrated that HHV-6 is a likely contributor to liver failures that can lead to the need for pediatric liver transplants.

WHAT TO DO?

Early detection and treatment of HHV-6–associated pediatric liver failure offer the opportunity to reduce, if not eliminate, the need for liver transplants in children with liver failure of unknown etiology. In addition to reducing the short- and long-term transplant-related trauma experienced by those individuals and their families, more livers would be available for transplantation into children with other causes of liver failure.

For this to come to pass, several things will need to be done to further validate the etiologic association and to establish effective approaches to clinical management:

• Given the absence of diagnostically useful levels of viremia during LFUE, the risk-benefit relationships and methods for obtaining liver biopsies from pediatric liver failure patients need to be assessed. As an alternative, surrogate markers for HHV-6 involvement in liver failure need to be identified.

• As part of defining standardized thresholds for action, quantitative PCR assays need to be implemented that are calibrated relative to the recently introduced World Health Organization international standard for HHV-6B DNA [19].

• Suggestion of antiviral efficacy against HHV-6 has been seen in liver transplant recipients [16]. Clinical trials should be conducted to evaluate the clinical efficacy of antiviral therapy in controlling HHV-6–associated liver failure. Multicenter trials can accelerate the process.

Changes in illumination can indeed enhance our understanding of the character of a rose.

Notes

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References


