COMMENTARY

Going viral and the fatal vulnerability of neurons from immunity, not from infection

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Clinicians are often faced with life and death choices in treating patients with viral infections. Often, consideration focuses on viral eradication with antiviral therapies, akin to bacterial antibiotics or to immune-based strategies, involving either active immunization or passive immunization with neutralizing antibodies. However, clinicians often consider that the immune response to a virus in the brain is as damaging as the viral infection itself. It is common to use immune suppression—often with corticosteroids—during viral encephalitis, side by side with antiviral approaches. In PNAS, Kulcsar et al. study mosquito-borne alphaviruses that cause fatal encephalomyelitis in horses and humans (1). The authors provide a rationale for the dual and contradictory strategies of treatment with antivirals alongside immune suppression.

Kulcsar et al. (1) show that death in infection with neuroadapted Sindbis virus results from immune-mediated damage to infected neurons, not by the infection itself. Death ensues from entry of T cells to the central nervous system. The absence of the immune-suppressive cytokine, IL-10, leads to earlier onset of paralysis and increased death. One of the fascinating conclusions in this study is that immunity to infected neurons was more critical in survival than the viral infection itself. This finding reinforces earlier conclusions from studies on Sindbis-mediated neuronal death (2, 3). Here, Kulcsar et al. (1) identify some of the key culprits in this immune-mediated fatal pathology from viral infection.

Normally, lymphocytes are excluded from the central nervous system, although some degree of immune surveillance is present. Lymphocytes enter the central nervous system under conditions of inflammation. The key molecule involved in homing to the brain is α4 integrin (4–6). It is known that blockade of α4 integrin is quite effective in attenuating the inflammation seen in the quintessential autoimmune disease of the central nervous system, multiple sclerosis (4–6) (Fig. 1). Perhaps surprisingly, blockade of α4 integrin, via administration of anti-α4 integrin antibodies, impedes lymphocyte migration to the brain in viral encephalitis because of Borna Virus (7). Following administration of anti-α4 integrin antibody, significant clinical improvement was seen without influencing viral levels (7). This benefit in viral encephalitis is altogether surprising, considering that the major "Achilles heel" of therapy of multiple sclerosis with α4 blockade is the development of the viral disease known as progressive multifocal leukoencephalitis, caused by the John Cunningham virus. Thus, acute intervention in viral encephalitis with α4 integrin blockade may be protective, whereas chronic use of such blockade may render individuals susceptible to another form of viral encephalitis (4, 5, 7).

Kulcsar et al. (1) show that a major role in the pathology of fatal alphavirus infection is mediated by Th17 and dual Th1/Th17 T cells. Th17 cells expressed the Th1 transcription factor Tbet, along with granzyme, IL-22, and GM-CSF. GM-CSF production was higher in IL-10–deleted mice. Absence of IL-10 in infected mice resulted in early neurologic manifestations and increased death.

Clinicians treating viral encephalitis must understand that there are two competing facets of the pathology of brain infection. First, the viral invasion of the brain produces its own damage and pathology to neurons. This finding was most notably seen in poliomyelitis, where the motor neuron undergoes a series of pathologic changes leading to paralysis and death. It was never clear that damage to motor neurons was a result of viral infection or from subsequent immune attack. Certainly in polio the inhibition of the virus with active and passive immunization was of great benefit (8, 9). Preventing the virus from ever gaining access to the brain and spinal cord was one of the stark conclusions from the pioneering work of researchers in the 1940s and 1950s.

Such research of course lead to the eradication of this scourge—the tragic polio epidemics of summers past—via active immunization to polio. However, we clinicians still treat deadly viruses that infect the brain. Repeatedly, when on ward rounds when we treat acute viral infections of the brain, we fall back on immune suppression as a life-saving measure rather than active or passive immunization. This strategy of immune suppression remains a great paradox. It is a source

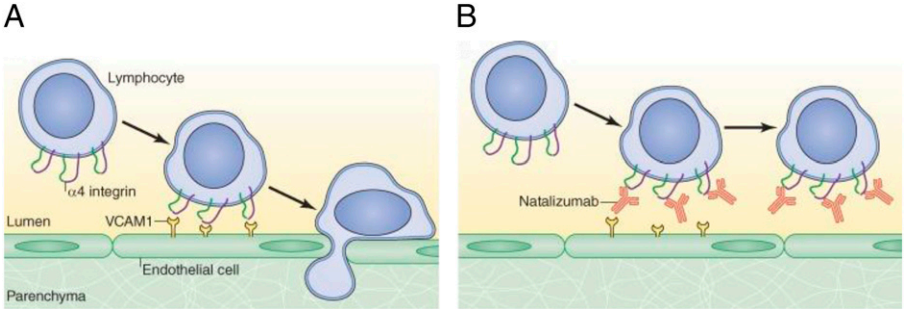

Fig. 1. Natalizumab blocks lymphocyte homing in multiple sclerosis. (*A*) α4 integrin binds to vascular cell-adhesion molecule 1 (VCAM1) on inflamed brain endothelium. This interaction gives lymphocytes access to the central nervous system. The presence of immune cells in the brain is a prominent feature of multiple sclerosis and viral encephalitis. (*B*) Natalizumab, a humanized antibody to α4 integrin, blocks binding of lymphocytes to VCAM on inflamed brain endothelium, thereby preventing lymphocyte entry into the central nervous system. Blockade of entry to the central nervous system is protective in some forms of viral encephalitis (7). Reprinted from ref. 5.

Author contributions: L.S. designed research, performed research, and wrote the paper.

The author declares no conflict of interest.

See companion article on page 16053 in issue 45 of volume 111.

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www.pnas.org/cgi/doi/10.1073/pnas.1420310111

of continued long and heated discussions among clinicians and continued puzzlement when we see a patient "going viral" in the medical sense. The study of Kulcsar et al. (1) helps clarify the molecules and cells involved in fatal viral attacks on the brain, providing a strong rationale for why we give immune suppression in the face of viral attack.

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