SCANNING THE LITERATURE

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Future Possibilitites for Early Treatment & Vaccines

Ben-Nathan D, Lustig S, Tam G, Robinzon S, Segal S, Rager-Zisman B. Prophylactic and therapeutic efficacy of human intravenous immunoglobulin in treating West Nile virus infection in mice. J Infect Dis 2003; 188:5–12.

West Nile virus (WNV) is a mosquito-borne disease found most commonly in Africa, West Asia, and the Middle East, where up to 40% of the human population possesses antibodies. It is an emerging disease in the United States. Humans infected with WNV develop a febrile illness that can progress to meningitis or encephalitis. In mice, WNV causes central nervous system infection, paralysis, encephalitis, and death. Currently, no specific therapy or vaccine has been approved for human use. We examined the prophylactic and therapeutic efficacy of pooled human plasma (PP) and intravenous immunoglobulin (IVIG) for treatment of WNV-infected mice. Full protection was achieved when the infected mice were treated with pooled plasma or IVIG obtained from healthy Israeli blood donors that contained WNV-specific antibodies. Similar treatments using PP or IVIG obtained from US blood donors had no protective effect. Recovery of the lethally infected mice was dependent on the dose and time of IVIG administration. These results indicate that antibodies play a major role in protection and recovery from WNV infection and that IVIG can be used as first-line therapy.

Comments: Antibody-mediated or humoral immunity may be effective in treating or preventing WNV infections in mice. WNV is endemic in the Middle East, and blood donors in Israel have anti-WNV titers of 1:1600, whereas US blood donors have 1:10. This is concentrated in intravenous immunoglobulin (IVIG) and less so in pooled plasma (PP) from various donors. To establish standards, the first experiment compared IVIG and PP from Israel and the US to non-immune and immune mouse serum (titers of 1:3200). Mice were infected intraperitoneally with 20-200 times the lethal dose that kills 50% of mice (LD50). Treatment with immune mouse serum, IVIG or PP from Israel, resulted in 100% survival. Treatment with non-immune mouse serum, IVIG or PP from the US, did not. Next, the effect of single or serial treatments with IVIG or PP was tested. This showed that serial injections of IVIG or PP from Israel increased survival with each injection. Five daily injections protected 100% of mice. A single high dose of IVIG also conferred protection, but if it was delayed by 2 days, it only delayed death. Two high-dose treatments were needed early in the course to confer 100% survival. Finally, this protective effect was dose dependant. Importantly, all treated mice that survived became immune, with antibody titers of 1:3200 against WNV, the same titers that occur in surviving, untreated mice.

There are some important distinctions between this study and WNV infections in humans, of course. The mice were infected with huge doses of virus and treated very early in their course of disease. The survival rate is much higher in natural infections. Mosquitoes cannot deliver such a high dose of virus in their bite, especially to an animal as large as a human. Also, most human cases are asymptomatic, and suspicion for infection only occurs in the most severe cases. Treatment is usually delayed until WNV is suspected and infection has already taken hold. Therefore, this treatment may not be as effective in human cases.

However, the implications of this study are important for a number of reasons. First, it shows that antibodies can slow or stop viral replication, even across the blood-brain barrier. Second, it proposes a prophylaxis and treatment for early cases of WNV. Finally, it creates the possibility of a vaccine against it. Since WNV and Japanese encephalitis are members of the same antigenic complex, it may be possible to create a vaccine to WNV much like the one that exists for Japanese encephalitis. Also, since many infections are subclinical and asymptomatic, perhaps "herd immunity" will prevent another epidemic like last year's season. Hopefully, we will not need to test this theory in the coming months.

Novel Detection of NVW

Carson P, Steidler T, Patron R, Tate JM, Tight R, Smego RA Jr. Plasma Cell Pleocytosis in Cerebrospinal Fluid in Patients with West Nile Virus Encephalitis. Clin Infect Dis 2003; 37:e12–5

We describe 4 patients with West Nile virus encephalitis who all displayed previously unreported plasma cell pleocytosis of the cerebrospinal fluid (CSF). Three patients recovered but had varying degrees of mild neurologic disability on discharge from the hospital, and 1 patient died. The finding of significant numbers of plasma cells in CSF may serve as a useful early diagnostic clue for West Nile virus encephalitis.

Comments: WNV is usually diagnosed by serology in the CSF or serum. However, most laboratories are overworked, and confirmatory results take too long to guide empiric therapy when it is most helpful. This article reviewed patients prospectively for encephalitis and then reviewed cases confirmed to be from WNV. Four patients were confirmed with WNV in this study, and their CSF specimens were reviewed by two independent pathologists. All the patients had plasma cells visible in their CSF as part of their CSF lymphocytosis from the virus. Up to 40% of the lymphocytes in the CSF were plasma cells, an effect not seen in the patients' sera. This effect has not been described with many other viruses and it may be a useful early screening test for WNV infection. Further study must be done to determine its usefulness in treatment and survival. But this may provide a useful initial test for empiric management of symptomatic WNV infection.