The clinical response of West Nile virus neuroinvasive disease to intravenous immunoglobulin therapy

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Abstract

The aim of the study was to determine whether intravenous gamma globulin (IVIG) treatment is effective in patients with West Nile Virus (WNV) neuroinvasive disease. We contacted hospital based infectious disease experts in Israeli hospitals to identify patients with WNV neuroinvasive disease who were treated with IVIG. The main outcome measure was neurological response after treatment. There were 12 patients who received IVIG and four improved within 48 h. Three patients died, 6 had partial recovery, and 3 recovered completely. Eleven of the 12 patients were infected with Israeli genotypes that are highly homologous to Europe/Africa viruses. The rapid response in some patients suggests that IVIG is effective, and might be used to treat patients with WNV neuroinvasive disease with IVIG.

Introduction

The West Nile virus (WNV) is an arthropod-borne flavivirus that is associated primarily with epidemics of flu-like febrile illness. Neurologic manifestations are uncommon with overlapping clinical syndromes including encephalitis, meningitis and acute flaccid paralysis.1 WNV has been endemic in Israel since the 1950s usually causing a mild, self-limiting disease but an isolated epidemic occurred in the year 2000 with 428 hospitalized cases of neurological disease and 42 deaths.2 The observation of a patient with chronic lymphocytic leukemia and WNV encephalopathy who made a prompt and complete recovery after receiving high dose intravenous immunoglobulin (IVIG)3 lead to the finding that immunoglobulin preparations in Israel contain high titers of antibodies to WNV (1:1600).4 Since then, case studies have continued to suggest that IVIG therapy can be effective in some patients including immunosuppressed post-transplant patients.5 Recent reviews have called for randomized controlled trials4 and a multicenter randomized, placebo-controlled trial sponsored by the National Institute of Health is in progress.5 The results of such studies are urgently needed because of the high morbidity and mortality rates of neuroinvasive WNV. Nevertheless until results of randomized controlled trials are available, an accumulated series of cases can provide a higher degree of evidence than isolated case reports. In this report, we summarize the clinical course of all patients known to have received intravenous immunoglobulin for WNV neuroinvasive disease in Israel until the end of 2007. We also characterized the prevalent genotypes found in mosquitoes (highly correlated with human infection) according to time and place in order to determine if there is a relationship to the outcome according to the various genotypes.

Materials and Methods

We contacted the Infectious Disease consultants of Israeli Hospitals to request details of the clinical course of patients with serious WNV neuroinvasive disease who received treatment with at least one day of high dose intravenous immunoglobulin. Details of 12 patients were compiled from case notes. Ten cases have been reported previously and were not included.

Serological tests

Serological testing was performed in the Ministry of Health’s National Center for Zoonotic Viruses, at the Central Virology Laboratory by using an IgM-capture enzyme-linked immunosorbent assay (ELISA). Diagnosis of primary WNV infection was made on the basis of clinical symptoms and signs, together with laboratory confirmation of the presence of immunoglobulin M (IgM) antibodies, with or without IgG antibodies, and low IgG avidity. Diagnosis was also made on the basis of a significant rise in antibody level between paired samples (≥4 fold), and a specific reaction calculated from the reaction to viral antigen over the reaction to mock antigen (≥2 fold).6,7 All tests were developed in house and performed with a local WNV isolate (as antigen) either genotypically similar genotype to the New York 1999 strain or a genotype similar to both the New York 1999 and to the Romania 1997 strain.8

Virus isolation and identification

For identification of the circulating WNV genotypes in the country, RNA was extracted from mosquito pools, as part of the yearly routine mosquito surveillance program. RNA was then amplified by Real-Time RT-PCR with specific primers of the ENV gene.9 Virus isolates were identified by standard RT-PCR methods,10 amplified, sequenced,11 and the gene compared with published sequences in the Gene bank.

Results

There were 12 patients who received IVIG; three patients died, 6 had partial recovery, and 3 recovered completely (Table 1). Eleven of the 12 patients were infected with Israeli genotypes that are highly homologous to Europe/Africa viruses. A standard dose of IVIG of 0.4g/kg/day was used, for a variable number of days (Table 1). The effects of therapy were often dramatic and occurred within 48 hours in 4 patients.

Discussion

The major finding of our study is the prompt response to treatment with IVIG observed in some patients with WNV neuroinvasive dis-
ease. Our findings are consistent with the response observed in 10 patients reported previously with Israeli genotypes that are highly homologous to American viruses and with cases reported outside of Israel. Eleven of the 12 patients reported here had genotypes homologous to the Europe/Africa viruses. Furthermore although none of the 5 new cases ventilated had complete recovery, there were 3 of 5 such patients reported previously with complete recovery. This is in contrast to the prolonged recuperation and recovery, and lack of complete recovery in 21 patients who did not receive IVIG reported in a review of the literature. The use of immunoglobulin for treatment West Nile virus illness is biologically plausible. Animal data indicate an important role for humoral immunity in controlling West Nile virus infection, and treatment with antibodies is still used in certain viral illnesses such as disseminated Vaccinia after small pox vaccination. Recent studies in mice have shown that antibodies present in Israeli plasma are effective in reducing morbidity in mice. We conclude that it is warranted to treat WNV neuroinvasive disease with IVIG because of the rapid response to treatment observed in some patients, and the favorable outcome in patients requiring respiratory support. Efforts should be made to initiate randomized control trials.

References

1. Lanciotti RS, Roehrig JT, Deubel V, et al. Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States. Science 1999;286:2333-7.
2. Chowers MY, Lang R, Nassar F, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. Emerg Infect Dis 2001;7:675-8.
3. Shimoni Z, Niven MJ, Ptíck S, Bulvík S. Treatment of West Nile virus encephalitis with intravenous immunoglobulin. Emerg Infect Dis 2001;7:759.
4. Saquib R, Randall H, Chandrakantan A, et al. High grade NHL. Loss of consciousness, paralysis, ventilated 4- No Died
5. F/37 None LOC, paralysis, ventilated 1- Awake/ Weakness Partial
6. M/74 Diabetes mellitus Stupor, paralysis, ventilated 5- Awake/ Weakness Partial
7. M/76 Diabetes mellitus Loss of consciousness, paralysis, ventilated 5- <20 Awake/ Tracheotomy Partial
8. F/65 High grade NHL Loss of consciousness, paralysis, ventilated 4- No Died
9. M/67 Thymoma Stupor, muscle weakness, tremor 1- No Died
10. F/41 None Paralysis 5- Weakness/ Ataxia Partial
11. F/45 Lung transplant- IPF Stupor, muscle weakness, ventilated 3- None Died
12. F/87 Dementia Stupor, weakness 3- <20 Complete Complete

Rx, treatment; CLL, chronic lymphocytic leukemia; NHL, Non-Hodgkin’s lymphoma; LOC, loss of consciousness; weakness means objective muscle weakness.

References

1. Lanciotti RS, Roehrig JT, Deubel V, et al. Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States. Science 1999;286:2333-7.
2. Chowers MY, Lang R, Nassar F, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. Emerg Infect Dis 2001;7:675-8.
3. Shimoni Z, Niven MJ, Ptíck S, Bulvík S. Treatment of West Nile virus encephalitis with intravenous immunoglobulin. Emerg Infect Dis 2001;7:759.
4. Saquib R, Randall H, Chandrakantan A, et al. West Nile virus encephalitis in a renal transplant recipient: the role of intravenous immunoglobulin. Am J Kidney Dis 2008;52:e19-21.
5. Kramer LD, Li J, Shi PY. West Nile virus. Lancet Neurol 2007;6:171-81.
6. Debiasi RL, Tyler KL. West Nile virus meningoencephalitis. Nat Clin Pract Neurol 2006;2:264-75.
7. Martin DA, Muth DA, Brown T, et al. Standardization of immunoglobulin M capture enzyme-linked immunosorbent assays for routine diagnosis of arboviral infections. J Clin Microbiol 2000;38:1823-6.
8. Bin HZ, Grossman S, Pokamunski M, et al. West Nile fever in Israel 1999-2000: From geese to humans. In: White D, Morse D, eds. West Nile virus: Detection, Surveillance, and Control. New York: New York Academy of Sciences (NYAS); 2002. p. 951.
9. Lanciotti RS, Ebel GD, Deubel V, et al. Complete genome sequences and phylogenetic analysis of West Nile virus strains isolated from the United States, Europe, and the Middle East. Virology 2002;298:96-105.
10. Savage HM, Ceanu C, Nicolescu G, et al. Entomologic and avian investigations of an epidemic of West Nile fever in Romania in 1996, with serologic and molecular characterization of a virus isolate from mosquitoes. Am J Trop Med Hyg 1999;61:600-11.
11. Shi PY, Kauffman EB, Ren P, et al. High-throughput detection of West Nile virus RNA. J Clin Microbiol 2001;39:1264-71.
12. Makhoul B, Braun E, Hershkovitz M, et al. Hyperimmune gammaglobulin for the treatment of West Nile virus encephalitis. Isr Med Assoc J 2009;11:151-3.
13. Agrawal AG, Peterson LR. Human immunoglobulin as a treatment for West Nile virus infection. J Infect Dis 2003;188:160-2.
14. Hales L, Retter AS, Fowler D, et al. The role for intravenous immunoglobulin in the treatment of West Nile virus encephalitis. Clin Infect Dis 2003;37:e88-90.
15. Saad M, Youssef S, Kirschke D, et al. Acute flaccid paralysis: the spectrum of a newly recognized complication of West Nile virus infection. J Infect Dis 2005;192:120-7.
16. Gea-Banacloche J, Johnson RT, Bagic A, et al. West Nile virus: pathogenesis and therapeutic options. Ann Intern Med 2004;140: 545-53.
17. Ben-Nathan D, Gershoni-Yahalom O, Samina I, et al. Using high titer West Nile intravenous immunoglobulin from selected Israeli donors for treatment of West Nile virus infection. BMC Infect Dis 2009;9:18.