

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).³ Since then, case studies have continued to suggest that IVIG therapy can be effective in some patients including immunosuppressed post-transplant patients.^{4,5} Recent reviews have called for randomized controlled trials⁶ and a multicenter randomized, placebo-controlled trial sponsored by the National Institute of Health is in progress.⁷ 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.

Serologic 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

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(≥ 2 fold).^{8,9} 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.⁹

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.¹⁰ Virus isolates were identified by standard RT-PCR methods,¹¹ amplified, sequenced,¹² 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-

Table 1. Clinical characteristics, treatment and outcome.

Case	Gender /age	Significant past history	Presentation	Days of Rx	Days to response	Response/residual disease	Recovery
1	F/72	Dementia-meningioma	Stupor, seizures, weakness	2	-	No	Died
2	F/86	Dementia	Seizures, paralysis, loss of consciousness	2	2	Complete	Complete
3	F/37	None	LOC, paralysis, ventilated	1	3	Awake/Weakness	Partial
4	M/74	Diabetes mellitus	Stupor, paralysis, ventilated	5	<5	Awake/Weakness	Partial
5	M/76	Diabetes mellitus	Loss of consciousness, paralysis, ventilated	5	<20	Awake/Tracheotomy	Partial
6	F/65	High grade NHL	Loss of consciousness, paralysis, ventilated	4	-	No	Died
7	F/83	Toxic Goiter	Stupor, weakness	1	1	Complete	Complete
8	M/40	Alcoholic	Stupor, muscle weakness	1	2	Complete	Complete
9	F/41	None	Paralysis	5	1	Weakness/Ataxia	Partial
10	M/67	Thymoma	Stupor, muscle weakness, tremor	1	<3	Awake/weakness	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.

ease. Our findings are consistent with the response observed in 10 patients reported previously with Israeli genotypes that are highly homologous to American viruses^{3,5,13} and with cases reported outside of Israeli.^{4,14,15} 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,¹⁶ and lack of complete recovery in 21 patients who did not receive IVIG reported in a review of the literature.¹⁷ 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.^{15,18} Recent studies in mice have shown that antibodies present in Israeli plasma are effective in reducing morbidity in mice.¹⁹ 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.

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