Hyperimmune Gammaglobulin for the Treatment of West Nile Virus Encephalitis

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ABSTRACT: **Background:** West Nile virus, the etiologic agent of West Nile fever, is an emerging mosquito-borne disease. WNV was recognized as a cause of severe human meningo-encephalitis in elderly patients during outbreaks in various parts of the world.

Objectives: To analyze WNV encephalitis therapy and its outcome after prescribing hyperimmune gammaglobulin therapy.

Methods: Eight subjects with WNV encephalitis were treated with supportive therapy and 5 days of IVIG 0.4 g/kg/day containing high WNV antibodies obtained from healthy blood donors.

Results: Patients who were treated with IVIG as soon as possible exhibited an improvement in their symptoms. All subjects presented with high fever, progressive confusion and headaches, nausea and vomiting. The Glasgow Coma Screen for six patients ranged between 8 and 13 and all were discharged with a score of 15. The remaining two subjects died during their hospitalization.

Conclusions: In severe WNV infection, where the disease affects the central and/or peripheral nervous system, early intervention with IVIG together with supportive treatment is recommended. *IMAJ* 2009;11:151–153

KEY WORDS: West Nile encephalitis, intravenous immune gammaglobulin

West Nile virus, the etiological agent of West Nile fever, is an emerging mosquito-borne disease [1]. WNV circulates in natural transmission cycles involving primarily Culex and other mosquito species and birds [2]. WNV is most commonly found in Africa, West Asia, and the Middle East where up to 40% of the human population have circulating antibodies [3].

Most human infections are mild and are characterized by a self-limiting acute febrile illness, accompanied by headaches, myalgia, polyarthropathy, rash and lymphadenopathy [4,5]. WNV was recognized as a cause of severe human meningo-encephalitis in elderly patients during outbreaks in Israel (in the 1950s and 2000) [6,7], France (in 1962), South Africa (in 1974), India (1980–1981), and Romania (1996) [4,8]. Since entering North America in 1999, WNV has been found in the northern United States in mosquitoes, birds, horses and other animals [1,9]. In 1999–2000, WNV was responsible for epidemics in southern Russia [10]. During the 2002 WNV epidemic in the U.S., 3800 cases of WNV infection evidenced by laboratory tests were reported, including more than 200 fatalities by the end of the same year [11,12].

There is no specific therapy for WNV infection and supportive treatment should be given. Ben-Nathan et al. [13] demonstrated that adding WNV antibodies *in vitro* plays a major role in protection and recovery from WNV infection, and that intravenous hyperimmune gammaglobulin can be used as first-line therapy in WNV encephalitis.

Immunoglobulin for intravenous infusion is a preparation obtained from pooled human normal serum containing all the immunoglobulin G. IVIG was originally used for the treatment of agammaglobulinemia. The drug preparation is known to have an immunomodulatory effect in a large number of conditions, such as immune thrombocytopenia, Guillain-Barre syndrome, myasthenia gravis, and viral infections such as the parvovirus B19 infection [14].

During the summer of 2007, eight patients were admitted to our hospital presenting with high fever, progressive confusion and headaches, nausea and vomiting. All the patients were treated with IVIG from healthy Israeli donors after confirmation of encephalitis-causing WNV infection.

PATIENT DESCRIPTIONS

From 1 September to 30 November 2007, eight adults were admitted to Rambam Health Care Campus for the diagnosis and therapy of fever. Five patients suffered from progressive headaches, confusion, nausea and vomiting; one presented with leg monoparesis, and two presented with fever and extreme weakness without focal symptoms. Demographic

WNV = West Nile virus
IVIG = intravenous hyperimmune gammaglobulin

Table 1. Demographic characteristics and presenting features of the study population

Year of birth	Patient	Gender	Presenting symptom on admission	Presenting symptom	Fever on admission (^{0}C)	Mechanical ventilation	MRI	Length of stay (days)	Outcome
1940	1	Male	24 hrs	Convulsions, confusion	36.9	None	Multiple lesions	9	Recovered
1963	2	Female	14 days	Confusion, nausea, vomiting	37.5	None	ND	7	Recovered
1951	3	Male	48 hrs	Dizziness, confusion	39.0	Non-invasive ventilation (CPAP)	ND	18	Recovered
1933	4	Male	4 days	Confusion, aggressive personality, vomiting	38.4	Ventilated	ND	9	Died
1929	5	Female	24 hrs	Confusion, headaches	38.0	None	ND	9	Recovered
1948	6	Male	48 hrs	Diplopia, fever, confusion, vomiting	39.5	Ventilated	No conclusive lesions	39	Recovered
1938	7	Male	10 days	Muscle pain	36.4	Ventilated	No conclusive lesions	25	Died
1941	8	Female	5 days	Muscle pain, monoparesis	36.8	None	ND	13	Recovered

CPAP = continuous positive airway pressure, MRI = magnetic resonance imaging, ND = not done

Table 2. Cerebrospinal fluid features and therapy

Patient	CSF protein (mg/L)	CSF glucose (mg/L)	CSF cells (mm3)	Starting IVIG (days after admission)	IVIG dose/total dose (g)	Glasgow Scale on admission	Glasgow Scale on discharge
1	90	52	3	3	40/200	13	15
2	78	64	400	1	30/150	13	15
3	64	65	31	4	30/150	13	15
4	110	52	30	6	30/150	12	Died
5	167	63	343	1	25/125	9	15
6	34	138	20	6	30/150	11	15
7	243	85	12	19	30/95	8	Died
8	50	69	22	6	30/150	13	15

descriptions, clinical and laboratory features are depicted in Tables 1 and 2. The cerebrospinal fluid of all patients was negative for bacteria as well as for enteroviruses and herpes virus by polymerase chain reaction testing.

Patient 8 was admitted for the investigation of right leg weakness due to lumbar radiculopathy or anterior myelitis. In all patients, a confirmatory positive WNV IgM test in serum was obtained for the diagnosis of WNV infection. A positive test was mandatory before starting IVIG therapy. The single exception was a critically ill patient (# 6) who received IVIG 24 hours before laboratory confirmation of WNV disease.

The prescribed IVIG was Omrix®, produced from healthy Israeli volunteer blood donations. The WNV antibody measured by others in the prescribed IVIG was 1:1600 (enzyme-linked immunosorbent assay kit for WNV) [15]. The prescribed dose for each subject was 0.4 g/kg/dose for 5 days, for a total dose of 2 g/kg. The dose and frequency of administration were arbitrarily chosen and proved to be efficacious in many previous studies [16]. In a consensus article, WNV encephalitis was not included in the list of indications requiring IVIG [17].

The average length of stay in hospital ranged between 8 and 15 days, except for one patient (# 7) who was immunocompromised and was hospitalized for almost a month.

It was noted that the earlier IVIG treatment was started, the better and faster was the improvement in the patient's neurological symptoms. The Glascow Coma Screen for six patients ranged between 8 and 13 and all were discharged after 5 days of IVIG treatment with a Glascow score of 15 [Table 2]. The remaining two patients, who were much older, died during hospitalization.

DISCUSSION

West Nile virus is an endemic viral disease in the Middle East. The overwhelming majority of infections are mild and asymptomatic, but there have been periodic symptomatic outbreaks [18]. An outbreak of West Nile virus occurred in Israel with 260 confirmed cases and 20 deaths by the end of September 2000. The only treatment given during the outbreak was supportive, with no proven *in vivo* specific therapy, although ribavirin has shown promise in *in vitro* studies [19].

Eight patients were treated with IVIG obtained from healthy blood donors. Two of the eight (25%) died during hospitalization, one of them (# 7) was a kidney-transplanted patient under immunosuppressive therapy. Three patients received supportive therapy and invasive respiratory support, and one patient received non-invasive respiratory interven-

tion (continuous positive airway pressure). Armali and co-authors [20] described the outcome of one WNV encephalitis patient who received supportive and immunosuppressive therapy for his kidney transplantation.

Five of our WNV encephalitis victims suffered mainly from fever, headaches, confusion, nausea and vomiting. Convulsions, aggressive behavior and monoparesis with radiculopathy were found in individual subjects. None had organomegaly, leukocytosis or liver function impairment.

WNV disease including neurological involvement has high (5–14%) mortality [21]. It is suggested that the only instrument that can positively or negatively confirm the WNV diagnosis is the presence or absence of IgM antibodies in serum and/or cerebrospinal fluid. The presence of IgG antibodies is compatible with the presence of a WNV post-infection.

It has been postulated that the disease in its encephalitic form can cause neuronal destruction, including lesions in the hypothalamus and cerebellum, such as poliomyelitis [22]. Considering the existence of *in vitro* evidence [13], the use of IVIG containing high WNV antibodies produced from healthy blood donors at a dose of 0.4 g/kg/dose for 5 days (2 g/total dose) is recommended for the treatment of WNV encephalitis to prevent possible neuronal destruction and future disabilities [23].

The timing of the administration of IVIG may be particularly important, as we found that starting treatment early led to a better outcome. Animal studies involving flaviviral encephalitis (St. Louis encephalitis) suggest that viral brain invasion may occur as early as 3 days after infection and that the window for successful application of antibody administration to prevent encephalitis closes 4–6 days after the infection [24]. In our group of patients, two who received IVIG 6 and 19 days after admission died, while those for whom therapy was prescribed between day 1 and day 6 from admission showed improvement of their symptoms. The main pitfall of the present report is that a comparison group for efficacy and safety of the suggested therapy was not included.

This is a descriptive presentation of eight patients who suffered from WNV encephalitis. All were treated with supportive therapy and high doses of IVIG (2 g total dose) containing WNV antibodies [25] obtained from healthy blood donors. In severe WNV infection, where the central and/or peripheral nervous system is affected by the disease, early intervention with IVIG together with supportive treatment is recommended.

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