A brief report of West Nile Virus neuroinvasive disease in the summer of 2012 in Hamilton, Ontario

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West Nile neuroinvasive disease is a severe infectious disease that is associated with a high mortality rate, especially in immunocompromised hosts. Physicians who are aware of its clinical presentations may be able to order diagnostic tests more appropriately and avoid inappropriate treatment. In the present series, the cases of seven patients admitted to Hamilton Health Sciences (Hamilton, Ontario) in the summer of 2012 with a diagnosis of West Nile neuroinvasive disease were retrospectively reviewed based on available medical records. According to the clinical and laboratory criteria published by the Centers for Disease Control and Prevention, five cases were diagnosed as encephalitis, one case as meningitis and one case as meningomyelitis. Patients were managed supportively. Forty-three percent (three of seven) presented with rash, 71% (five of seven) did not report headache despite exhibiting neurological symptoms, 43% (three of seven) did not have fever on presentation and 37.5% of cerebrospinal fluid samples exhibited a neutrophil predominance. The mortality rate in the present series was 14.3% (one of seven), and 57.1% (four of seven) of the patients had residual symptoms on discharge and at follow-up.

Key Words: *Cerebrospinal fluid; West Nile virus; West Nile virus neuroinvasive disease*

Bref rapport d'une maladie neuro-invasive du Nil occidental pendant l'été 2012 à Hamilton, en Ontario

La maladie neuro-invasive du Nil occidental est une grave maladie infectieuse associée à un taux de mortalité élevé, notamment chez les hôtes immunodéprimés. Les médecins qui en connaissent les présentations cliniques peuvent demander des tests diagnostiques plus pertinents et éviter un traitement inutile. Dans la présente série, le cas de sept patients hospitalisés au *Hamilton Health Sciences* de Hamilton, en Ontario, pendant l'été 2012 en raison d'un diagnostic de maladie neuro-invasive du Nil occidental a fait l'objet d'une analyse rétrospective d'après les dossiers médicaux disponibles. Selon les critères cliniques et de laboratoire publiés par les *Centers for Disease Control and Prevention*, cinq cas ont été diagnostiqués comme une encéphalite, un cas comme une méningite et un cas comme une méningomyélite. Les patients ont reçu une prise en charge de soutien. Quarante-trois pour cent d'entre eux (trois sur sept) ont eu une éruption, 71 % (cinq sur sept) n'ont pas déclaré de céphalée malgré les symptômes neurologiques, 43 % (trois sur sept) ne faisaient pas de fièvre à la présentation et 28 % (deux sur sept) avaient une prédominance de neutrophiles dans les prélèvements de liquide céphalorachidien. Le taux de mortalité observé s'élevait à 14,3 % (un cas sur sept), et 57,1 % des patients (quatre sur sept) présentaient des symptômes résiduels au congé et au suivi.

West Nile Virus (WNV) is a major vector-borne virus that poses an increasing threat to health care (1). Early diagnosis of neuroinvasive WNV is difficult because clinical presentations are nonspecific and may mimic other infections such as bacterial meningitis.

The virus has been endemic in Africa, Europe and Asia since it was first isolated from the blood of a febrile woman in the West Nile area of Uganda in 1937. WNV has quickly spread in North America since its introduction to the United States in 1999, and large outbreaks have been documented (1). A wide spectrum of symptoms may develop, depending on phenotypes of WNV and the status of host immunity. The majority of infected individuals are asymptomatic, while 20% may present with West Nile fever, with symptoms ranging from generalized malaise, mild fever, headache, arthralgia and nausea, to maculopapular rash (2). Less than 1% of infected individuals develop West Nile neuroinvasive disease (WNND), which is categorized as aseptic meningitis, encephalitis or acute flaccid paralysis (3).

As demonstrated in the surveillance statistics released by Hamilton Public Health (4), there was a dramatic increase in the rate of WNV infection in Hamilton, Ontario, in the summer of 2012, with 20 confirmed cases, a considerable increase from the average rates of zero to four cases per year over the past nine years. In the present article, seven patients with WNND admitted to Hamilton Health Sciences (Hamilton, Ontario) during this period are described. The clinical symptoms, radiological imaging, serological diagnosis, treatment and prognosis in this group of patients are summarized.

METHODS

According to the clinical and laboratory criteria published by the Centers for Disease Control and Prevention (Georgia, USA) (3), WNND was defined by the presence of acute neurological illness and laboratory evidence of WNV infection including WNV-specific immunoglobulin M (IgM) antibody detected by ELISA, and a confirmatory plaque reduction neutralization test in acute-phase cerebrospinal fluid (CSF) or serum samples. These criteria were followed, and positive laboratory results from the laboratory information system were identified. All tests were performed at the Toronto Public Health Laboratory (Toronto, Ontario). Seven patients with a diagnosis of WNND were recruited into the present case series, based on available medical records. The present study was reviewed and approved by the Research Ethics Board at Hamilton Health Sciences. In the present series, five patients were diagnosed with encephalitis, one patient with meningitis and one patient with meningomyelitis.

RESULTS

The patients were between 36 and 82 years of age. The ratio of men to women was 3:4. Comorbidities are outlined in Table 1; however, 42.9% (three of seven) had no preceding medical conditions. Nonspecific clinical features included fever (100%), nausea and vomiting (57.1%), diarrhea (42.9%), rash (42.9%) and headache (28.6%). In three of seven patients, rashes appeared on day 0 to day 10 post-onset of disease (POD), and lasted three to eight days.

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TABLE 1
Features of West Nile neuroinvasive disease cases

Cases	Case 1 Meningomyelitis	Case 2 Encephalitis	Case 3 Encephalitis	Case 4 Encephalitis	Case 5 Meningitis	Case 6 Encephalitis	Case 7 Encephalitis
Age, years/sex	38/female	76/male	82/male	81/male	36/female	73/female	69/female
Comorbidity	None	None	HTN, atrial fibrillation	DM, HTN, atrial fibrillation, bladder cancer resected, not immunocompromised	None	DM, HTN, osteoperosis	HTN, depression
Nonspecific symptom*							
Fever	D_0	D_{10}	D_0	D_0	D_6	D_6	D_0
Rash	No	D_{10} ×3 days	No	No	D_0 ×8 days	D_6 ×3 days	No
Neurological feature*							
Cranial nerve abnormality	Right facial droop D_4	No	No	No	No	No	No
Muscle weakness	Right arm, D_4 to D_{53}	Left adductor, D_{13} to D_{54}	No	No	Bilateral lower limbs, D_8	No	Right leg, D_{14}
Mental status changes	No change	LOC, D_{10} ×3 days	Prolonged coma since D_5	LOC, D_1 ×3 days	No change	LOC, D_7 ×5 days	No change
Accessory examinations*							
Cerebrospinal fluid	D_4	D_{11}	D_5 D_{16}	D_5	D_8	D_7	D_{28}
WBC, ×10^6/uL	334	38	563† 57	8	29	132	27
Neutrophils, %	10	3	85 0	20	69	83	0
Lymphocytes, %	86	97	6 89	63	27	14	96
Protein, g/L	1.16	1.44	1.59 1.05	0.8	normal	1.08	0.85
MRI	D_3 normal	D_{10} normal	D_{10}‡ D_{28}§	N/A	D_7¶	N/A	N/A
Electromyography	Anterior horn cells loss D_{53}	N/A	No sensorimotor conduction response	N/A	N/A	N/A	Right leg monoparesis, D_{28}
Cerebrospinal fluid IgM serology	D_4 positive	D_{11} positive	D_5 positive D_{16} N/A	D_5 positive	D_8 positive	D_7 positive	D_{28} positive
Treatment	Supportive	Supportive	Supportive + IVIG**	Supportive	Supportive	Supportive	Supportive

**All symptoms and accessory examinations are documented as the day (D) of appearance from the onset of disease if available from the medical records; †Traumatic tap, with red blood cell count of 1056 x10^6/L; ‡D_{10} Magnetic resonance imaging (MRI) showed hyperintensity in small posterior periventricular area; §D_{28} MRI showed hyperintensity at the bilateral thalami, midbrain and cerebellar peduncle; ¶D_7 MRI showed slight hyperintensity in bilateral sulci, possibly consistent with intracranial hypertension (HTN); **Supportive + Intravenous immunoglobulin (IVIG) D_{15} × 5 days. CSF Cerebrospinal fluid; DM Diabetes mellitus; IgM Immunoglobulin M; LOC Decreased level of consciousness; N/A Not available; WBC White blood cells*

The rashes were maculopapular, nonitchy and involved the chest, back and limbs in a nonspecific pattern. Four of seven patients (57%) experienced gastrointestinal symptoms preceding their neurological abnormality by one to 10 days. Less common and transient presentations, such as dizziness, psychiatric symptoms and eye complaints, were also reported in the present series. As presented in Table 1, neurological manifestations included: muscle weakness (57.1%); changes in mental status (57.1%); focal neurological deficiency (28.6%); and extrapyramidal symptoms (14.3%) such as noncogwheel rigidity, increased muscle tone and tremor. Mental status changes occurred as early as day 1 POD and improved over three to five days with supportive care, except in patient 3, who died after prolonged loss of consciousness/coma in the intensive care unit. Most patients denied neck stiffness (42.9%) and 33% of patients denied headaches. Neuromuscular weakness is a well-recognized feature of WNND. Five of seven patients (71.4%) complained of limb weakness. Patient 1 presented with right-sided weakness in the arm and leg from day 4 until day 53 POD.

CSF analysis revealed that 37.5% of the samples had elevated neutrophil counts. All samples had normal or elevated glucose levels, and 87.5% had elevated protein levels. Anti-WNV IgM was detected in all CSF samples from day 4 to day 28 POD. Notably, 71.1% of the patients were found to have normal peripheral white blood cell (WBC) counts on admission. All patients underwent computed tomography scans and four underwent magnetic resonance imaging (MRI). Neuroimaging abnormalities were only revealed in two patients on MRI. An MRI of patient 3 showed hyperintensity initially involving a small posterior periventricular area on day 10 POD, which subsequently spread to the bilateral thalami, midbrain and cerebellar peduncle on day 28 POD. MRI of patient 6 showed slight hyperintensity in bilateral sulci on day 7 POD, possibly due to intracranial hypertension. To evaluate disease etiology and prognosis, electromyography was performed in three of five patients with neuromuscular weakness, and only patient 1 was diagnosed with poliomyelitis with confirmed motor neuron damage in the anterior horn of the spinal cord, which suggested unfavourable strength recovery. Of note, patient 3 had symptoms similar to those observed in Guillain-Barré syndrome, with complete absence of motor and sensory nerve conduction on electromyography.

Patients were managed supportively, as shown in Table 1. Two patients (3 and 6) were admitted to the intensive care unit due to respiratory failure and/or decreased level of consciousness. The mortality rate in the present series was approximately 14.3%, and 57.1% of the patients had residual symptoms on discharge and on follow-up.

DISCUSSION

Clues to WNND on history

Multiple risk factors have been associated with the development of neuroinvasive diseases after WNV infection, such as advanced age, male sex, hypertension, diabetes mellitus, history of cardiovascular disease and immunosuppression (5). Major risk factors identified in the present study included hypertension, diabetes mellitus and advanced age. Consistent with previous case series (6) and outbreak reports (7), we found that the elderly were more susceptible to encephalitis,

while young patients were more likely to develop meningitis. The five patients with encephalitis in the present series were all older than 69 years of age, while the two patients with meningitis were 36 and 38 years of age. Only two of seven patients recalled receiving mosquito bites. No significant immune deficiency was identified in this group. Patient histories from our group indicative of WNND included outdoor activity during WNV season, living close to stagnant water, recollection of mosquito bite within the incubation period of WNV (three to 14 days), generalized nonitchy rash, eye pain, photophobia, sudden onset of muscular pain before neurological symptoms and acute asymmetric limb weakness with intact sensory function. The presence of gastrointestinal symptoms (such as nausea, vomiting and abdominal pain before neurological abnormality), lack of neck stiffness or headache with evidence of CNS infection may further increase clinical suspicion for WNND. This is consistent with previously reported rates of meningeal signs of 19% to 57% (8).

Physical examination findings to support a diagnosis of WNND

Helpful physical examination findings suggestive of WNND may include generalized maculopapular rash or, rarely, petechiae and nonblanchable rash. Neurological findings from our group of patients include cranial nerve palsy, often involving the seventh nerve, myoclonus and extrapyramidal symptoms such as tremor, noncogwheel rigidity, bradykinesia and postural imbalance. Asymmetric limb weakness with reduced muscle strength and reflex, and preserved sensory function, are indicative of acute flaccid paralysis.

Laboratory diagnosis of WNND

Typical CSF findings indicative of WNND include universal pleocytosis, elevated protein level and normal to elevated glucose level. CSF analysis provides physicians with evidence to differentiate between bacterial and viral etiology. The neutrophil predominance in CSF typically indicates bacterial meningitis; however, almost one-half of the patients in the present series exhibited a neutrophil predominance in their CSF. Similar findings have been reported in a study involving 250 patients with serologically confirmed WNND, of whom 41.1% had at least 50% neutrophils in their initial CSF specimen (9). In the present case series, 87.5% of patients exhibited increased CSF protein levels. Patient 5 (with meningitis) had a normal protein level, while all patients with encephalitis had elevated levels (>0.85 g/L). The finding that patients with encephalitis had higher CSF protein levels than those with meningitis has also been noted in other studies (6,9). However, only modest predictive value was identified for protein level and disease outcome according to multivariate analysis (9). Interestingly, 71.1% of our patients presented with normal peripheral WBC counts on admission, which may further prompt physicians to consider WNV infection in response to neutrophil-dominant CSF. Similar findings of 60% with normal WBC counts have been reported in a recent outbreak in Israel (10). One-half of MRIs performed were found to be normal, comparable with previously reported abnormality rates of 20% to 70% (3). Finally, anti-WNV IgM in CSF was detected in all of our patients, which is widely accepted as one of the diagnostic criteria for WNND due to the impermeability of the blood-brain barrier. However, it is critical for physicians to realize the limitations to this test such as cross-reaction with other members of the *Flavivirus* genus (11), antibody persistence in CSF for up to seven months postinfection (12) and the necessity of repeating serology during both acute and convalescent phases (two to three weeks later), if indicated (13).

Treatment

Supportive care is the mainstay of treatment for WNND infection, with no specific anti-WNV treatment currently approved by the Food and Drug Administration. Multiple promising interventions are currently under investigation (3,14,15).

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