Clinical Information on West Nile Virus (WNV) Infection

Introduction

In 1999, West Nile Virus (WNV), an Old World flavivirus, producing a spectrum of disease including severe meningoencephalitis, appeared in North America for the first time. It is one of several arboviral encephalitides found in North America. The initial outbreak led to 62 cases of meningoencephalitis (59 of them requiring hospitalisation) and 7 deaths. In the following four years the disease has spread across North America; in 2003 The same year, Canada had almost 500 cases in 2003 resulting in 10 deaths.

A recent risk assessment in the UK estimated the risk of indigenous WNV infection in the UK and Ireland to be low. Retrospective testing of human cases of encephalitis in 2003 to determine the burden of silent WNV disease including possible UK-acquired disease did not identify any cases. Similarly, testing of mosquitoes from selected wetland areas showed no evidence of WNV infection of vectors. Neutralising antibodies to WNV have, however, been identified in certain migrant and resident bird species in the UK.

Farther afield, in Europe, during 2003, there was one imported human WNV case in the Netherlands and two cases in France (acquired either locally or in Spain). There has been sporadic WNV activity in many countries bordering the Mediterranean and in Southeastern Europe over the last 25 years with occasional human cases being diagnosed.

Last season, there was widespread WNV activity over most of the continental United States; a total of 9862 human cases of WNV infection were reported, with 264 deaths. The peak season in the US for WNV cases was between mid July and early October. In 2003, Canada reported 1388 human cases, 14 of them fatal. So far this season (until 13/7/2004) there have been 61 cases of neuroinvasive WNV disease leading to three deaths in the US.

In response to the emergence of WNV in the US (and progressively warmer summers that have the potential to favour the expansion of WNV in Europe), recent UK guidance has been expanded, requesting that clinicians consider testing for WNV in patients with suggestive symptoms, including those without a history of recent travel in North America. The position adopted by the UK is a precautionary one. While recognising that the possibility of WNV arriving in the UK is low, authorities there reckon that the possibility cannot be ruled out.

Given that this possibility exists, in Ireland, we are requesting that clinicians be suspicious of suggestive illness in individuals over the age of 50 regardless of their travel history but to be

have a high index of suspicion of those with a history of recent travel to North America and to request diagnostic testing accordingly.

The following clinical information on the cardinal clinical features of WNV infection is adapted from material from the Centers of Disease Control and Prevention and is intended to provide information for clinicians who encounter a patient with suggestive symptoms who has recently returned from North America.

Clinical Features

1. Mild Infection

- About 80% of WNV infections are very mild and generally clinically unapparent.
- Few people infected will be able to recall any mosquito bite.
- Approximately 20% of those infected develop a mild illness (West Nile fever).
- **The incubation period is between 3 to 14 days.**
- Symptoms generally last 3 to 6 days.
- West Nile Fever is generally described as a febrile illness of sudden onset often accompanied by:
  - ✔ Malaise
  - ✔ Anorexia
  - ✔ Nausea
  - ✔ Vomiting
  - ✔ Eye pain
  - ✔ Headache
  - ✔ Myalgia
  - ✔ Rash
  - ✔ Lymphadenopathy

2. Severe Infection

- Approximately 1 in 150 infections will result in severe neurological disease.
- Case fatality rates during recent outbreaks have ranged from 4% in Romania (1996) to 12% in New York (1999) and 14% in Israel (2000).
- The most significant risk factor for developing severe neurological disease is advanced age (especially over 50; those over 80 are particularly vulnerable).
- Encephalitis is more commonly reported than meningitis.

- In recent outbreaks, symptoms occurring among patients hospitalised with severe disease include:
  - ✓ Fever
  - ✓ Headache
  - ✓ Weakness
  - ✓ Changes in mental status
  - ✓ Gastrointestinal symptoms
- Almost half of hospitalised cases in the US outbreaks had severe muscle weakness and this may provide a clue to severe WNV infection especially in conjunction with symptoms of encephalopathy.
- A minority of patients with severe disease developed a maculopapular or morbilliform rash involving the neck, trunk, arms, or legs.
- About 10% of patients demonstrated complete flaccid paralysis. Initially the first cases were though to be suffering from Guillain-Barré syndrome.
- Neurological presentations included:
  - ✓ Ataxia and extrapyramidal signs
  - ✓ Optic neuritis
  - ✓ Cranial nerve abnormalities
  - ✓ Polyradiculitis
  - ✓ Myelitis
  - ✓ Seizures
- Although not observed in recent outbreaks, myocarditis, pancreatitis, and fulminant hepatitis have been described.
- Encephalopathy along with severe muscle weakness, changes in level of consciousness and advanced age were the most powerful clinical predictors of death in those with severe disease.

Clinical Suspicion

- Diagnosis of WNV infection is based on a high index of clinical suspicion and obtaining specific laboratory tests.
- WNV should be strongly considered in adults >50 years who develop unexplained encephalitis or meningitis in summer or early autumn within 14 days of returning from areas where there is known WNV activity (but in particular US or Canada).
- It is important to bear in mind that severe neurological disease due to WNV infection has occurred in patients of all ages. It is however, much less likely in children. People over the age of 50 are about 10 times more likely than children and young people to develop severe symptoms; the risk for those over 80 years of age is almost 50-fold higher.
- Year-round transmission is possible in some parts of the US. Therefore, WNV should be considered in all persons returning from the US with unexplained encephalitis and meningitis.
- Any suspected cases should be reported to the Director of Public Health.

The following is a guide to undertaking testing for WNV:

A case of encephalitis or meningitis, especially in patients aged >50:

Encephalitis	
Any person with suspected viral encephalitis with **all** of the following criteria:	1. Fever over 38ºC **and**; 2. Altered mental state (altered level of consciousness, agitation, lethargy) and/or other evidence of cortical involvement (e.g., focal neurological findings, seizures) **and**; 3. Cerebrospinal fluid (CSF) pleocytosis with predominant lymphocytes and/or elevated protein with a negative Gram stain and culture **and**; 4. No alternative microbiological cause identified, e.g., herpes simplex virus.
Meningitis	
Any person with suspected viral (aseptic) meningitis with **all** of the following criteria:	1. Fever over 38º C **and**; 2. Headache, stiff neck and/or other meningeal signs **and**; 3. CSF pleocytosis with predominant lymphocytes and/or elevated protein and a negative Gram stain and culture **and**; 4. No alternative microbiological cause identified, e.g., enterovirus.

Diagnostic Testing

- WNV testing is available through the National Virus Reference Laboratory.
- The most efficient diagnostic method is detection of IgM antibody to WNV in serum collected within 8-14 days of illness onset or cerebrospinal fluid (CSF) collected within 8 days of illness onset using the IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA).
- Since IgM antibody does not cross the blood-brain barrier, IgM antibody in CSF strongly suggests central nervous system infection.
- Patients who have been recently vaccinated against or recently infected with related flaviviruses (e.g., yellow fever, Japanese encephalitis, dengue) may have positive WNV MAC-ELISA results.

Laboratory Findings

Among patients in recent outbreaks in the US:

- Total leukocyte counts in peripheral blood were mostly normal or elevated, with lymphocytopoenia and anaemia also occurring.
- Hyponatraemia was sometimes present, particularly among patients with encephalitis.

- Examination of the cerebrospinal fluid (CSF) showed pleocytosis, usually with a predominance of lymphocytes.
- CSF protein was universally elevated.
- CSF glucose was normal.
- CT scans of the brain mostly did not show evidence of acute disease, but in about 1/3 of patients, MRI showed enhancement of the leptomeninges, the periventricular areas, or both.

Treatment

- West Nile Fever is generally a self limiting illness, requiring simple measures only.
- Ina a small proportion of cases, severe infection CNS infection may develop. In such cases, treatment is supportive, often requiring hospitalisation, intravenous fluids, respiratory support, and prevention of secondary infections.
- Ribavirin in high doses and interferon α2b were found to have some activity against WNV in vitro, but no controlled studies have been completed on the use of these or other treatment options, including steroids, anti-epileptic agents or osmotic agents, in the management of WNV encephalitis.
- There are indications that a vaccine may be developed in the next year or two.

Further information

Further information can be found at:

- CDC Clinical Guidance: http://www.cdc.gov/ncidod/dvbid/westnile/clinical_guidance.htm
- A definitive paper, Petersen LR, Marfin AA. West Nile virus: a primer for the physician. *Ann Intern Med*, 2002; **137(3):**173-9, gives a broad overview of WNV and its clinical management and can be accessed at http://www.annals.org/cgi/content/full/137/3/173
- A list of Frequently Asked Questions on West Nile Virus can be found on the National Disease Surveillance Centre's website at http://www.ndsc.ie/DiseaseTopicsA-Z/WestNileVirusWNV/

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