ICU MANAGEMENT & PRACTICE

ICU Volume 12 - Issue 4 - Winter 2012/2013 - Cover Story: The Global ICU

West Nile Virus Encephalitis: Recognising and Diagnosing Infection

The increasing spread of West Nile virus (WNV) infection is worrying and requires that all intensivists be ready to recognise and diagnose the disease. Most individuals infected with WNV are asymptomatic, while one-fifth experience a flu-like illness and less than 1% develop neuroinvasive disease.

Introduction

West Nile virus, the most widely distributed arbovirus, belongs to the genus *Flavivirus*, within the family of *Flaviviridae*. WNV was firstly isolated in the West Nile province of Uganda in 1937 from the blood of a woman suffering a mild flu-like illness. The first cases of WNV in its encephalitic form were reported in Algeria in 1994, and the first large outbreak with a high number of neuroinvasive cases occurred in Bucharest, Romania, in 1996. WNV was introduced to New York City in 1999, where it was responsible for a huge epidemic (Hayes 2001). Within subsequent years, the WNV appeared ubiquitous in most states east of the Rocky Mountains, as well as in some Canadian provinces. The number of yearly reported cases in the US has increased from 1,021 in 2010, and 712 in 2011 (with 57 and 43 deaths, respectively) to 5,054 cases in 2012 by November 6, including 228 deaths. Of these 5,054 cases, 2,559 (51%) were classified as neuroinvasive disease and 2,495 (49%) as non neuroinvasive disease (Centers for Disease Control and Prevention, 2012).

The European Centre for Disease Prevention and Control monitored the WNV fever situation during the transmission season (June to November), and reported 130 probable and confirmed autochthonous cases in EU member states and 207 in neighbouring countries in 2011. As per figures on 8 November, 2012, 235 human cases of WNV fever have been reported in the EU and 587 cases in neighbouring countries so far this year (European Centre for Disease Prevention and Control, 2012). The spread of WNV has raised concerns regarding its presence in the Old World and the risks for epidemics of the neuroinvasive disease (Relter 2010). In light of this, all intensivists should know about WNV disease and be ready to recognise and diagnose it in their patients.

Virus and Transmission

WNV is a small spherical RNA virus, translated into a polyprotein, which is proteolytically processed to three structural and seven non-structural proteins. The latter hamper the host antiviral response, antagonising complement activation and inhibiting interferon-β promoter activation. It has recently been proposed that WNV can be grouped into seven lineages. Two major genetic lineages of WNV have been well described: lineage one is widespread and contains isolates from Europe, the USA, the Middle East, India, Africa and Australia (Barzon et al. 2012). Lineage two contains isolates from Southern Africa and Madagascar, and since 2004 from central and eastern Europe. In 2010 it caused outbreaks in Romania and Greece (De Filette et al. 2012). Interestingly, high and low neuroinvasive phenotypes exist in both lineages, but mutations responsible for increasing virulence in lineage two viruses have been described.

WNV lives in mosquitoes of genus Culex, which are considered the predominant vectors. Mosquitoes become infected with WNV after biting birds with highlevel viremia, and may transmit it when taking a blood meal from a host. Indeed, birds can also be infected via the oral route and by consumption of dead or dying infected birds. In birds, the incubation period is 10 to 14 days; the infection is associated with high mortality in Northern America but not in Europe (Relter, 2010). Humans and horses are "dead-end" hosts because the viremia is insufficient to infect a feeding naive mosquito. However, transmission in humans has been reported after blood transfusion, organ transplantation, or from a mother to her newborn via the intrauterine route or by breast milk (De Filette et al. 2012).

There is indirect evidence that WNV is transported to European temperate areas by migratory birds during spring migration. In addition, the transport technologies and increasing global trade of the last decades may have allowed infected mosquitoes to be transported by shipping, aeroplanes, and people travelling. Accordingly, at the county scale in eastern and western North America, human WNV incidences have increased with urbanisation and agriculture, respectively (Kilpatrick 2011).

Following inoculation from the bite of an infected mosquito, WNV replicates in the keratinocytes and then disseminates to the local lymph nodes causing a viremia. The WNV may pass into the central nervous system without disrupting the blood–brain barrier (BBB) (Rossi et al. 2010), but perivascular inflammation of lymphocytes and macrophages with glial cell upregulation has been found (Turtle et al. 2012).

Clinical Characteristics

Most of the individuals infected with WNV are asymptomatic. Approximately 20% of infected individuals develop an acute febrile flu-like illness after an incubation period of two to 14 days, with fever, malaise, myalgia, fatigue, skin rash, lymphadenopathy, vomiting and diarrhoea (Kramer et al. 2007; Rossi et al. 2010). Only approximately one in 150 infected individuals (Tyler 2010) and 5% of patients with symptomatic WNV infection (Rossi et al. 2010) develop neuroinvasive disease. The major categories of neuroinvasive disease include meningitis, encephalitis, and acute flaccid paralysis, with frequent overlap between these syndromes. Patients who develop encephalitis are typically older than those with meningitis or acute flaccid paralysis, and have a worse prognosis (Kramer et al. 2007). Additional risk factors for development of encephalitis

include immunosuppression, hypertension, diabetes mellitus, and liver disease (Tyler 2010).

WNV meningitis is clinically similar to other forms of “aseptic” meningitis and is characterised by fever, headache, stiff neck, and photophobia. Cranial nerve palsies, particularly of the facial nerve, occur in about 20% of cases. The cerebrospinal fluid (CSF) shows a pleocytosis with a mean of about 200 cells/mm3, an elevated protein level, and a normal glucose level. Almost half the patients have an initial polymorphonuclear pleocytosis rather than the lymphocytic pleocytosis generally characteristic of viral meningitis (Tyler 2010).

Patients with encephalitis have clinical or laboratory evidence of brain parenchymal involvement. Signs may include fever, headache, altered consciousness, disorientation, focal neurologic signs, dysarthria, seizures, tremor, ataxia, parkinsonism, and weakness. When present, magnetic resonance imaging (MRI) abnormalities typically consist of areas of increased signal on T2 and fluid attenuated inversion recovery sequences that occur in the thalamus, basal ganglia, and upper brainstem (Tyler 2010, Kramer et al. 2007).

Acute asymmetric flaccid paralysis is a poliomyelitis-like illness that occurs in 5% to 10% of patients with neuroinvasive disease. More than half the affected patients have associated encephalitis with concomitant findings of parkinsonism, myoclonus, or tremor. Approximately 90% have associated fever and headache. The flaccid paralysis is due to a selective lesion of spinal anterior horns by WNV. There is minimal or no sensory disturbance, and cranial nerves are usually normal, but bowel and bladder functions are disturbed in some patients. Most patients have substantial muscle ache in the lower back. Deep tendon reflex can be diminished in severely paralysed limbs, and muscular atrophy develops in the late phase of the illness (Kramer et al. 2007).

MRI scans may be normal or show focal abnormal signal intensity within the anterior horns of the spinal cord (Kramer et al. 2007). Electromyography and nerve conduction velocity studies show reduced or absent compound muscle action potentials with relatively preserved sensory neural action potentials. Electromyography abnormalities due to evidence of denervation develop after several weeks (Tyler 2010).

Diagnosis

CSF examination should be performed in order to differentiate WNV infection from stroke, meningitis-encephalitis due to bacteria or other viruses, myopathy, and Guillain-Barre syndrome (Rossi et al. 2010). Nevertheless, the diagnosis of WNV disease is based on specific serologic testing, so IgM and IgG ELISA should be used for testing serum and CSF. IgM serum antibodies develop within eight days and are still present at three months post-infection in almost all patients (De Filette et al. 2012; Kramer et al. 2007). The long persistence of WNV IgM after onset of infection could confound interpretation of serology results in patients subsequently presenting with clinical syndromes that resemble WNV infection (Diamond, 2009). Specimens submitted for arboviral serology should also be tested against other arboviruses that are known to be active or present in the given area. Detection of CSF WNV IgM antibodies is diagnostic of neuroinvasive WNV disease, as the presence of large size IgM molecules, which cross the BBB poorly, in CSF is generally indicative of intrathecal synthesis. However, WNV isolation attempts should be performed in CSF or postmortem brain tissue. Confirmation of virus isolate identity can be accomplished by indirect immunofluorescence assay using virus-specific monoclonal antibodies, nucleic acid detection, or virus neutralisation. Real timepolymerase chain reaction (RT-PCR) after amplification of the genetic material requires specialised equipment, and may not detect new emerging mutated WNV strains (Tyler 2010; De Filette et al. 2012).

Treatment and Prognosis

There is no specific treatment for WNV infection. The supportive care required by patients with neuroinvasive disease includes respiratory support, nutrition, analgesia and sedation, and prevention of secondary infections (Capuzzo et al, 2011). In fact, nearly half of the patients may have respiratory impairment requiring intubation or tracheostomy (Kramer et al. 2007). A mortality rate of approximately 12 to 15% for WNV encephalitis has been reported in the US (O'Leary et al. 2004; Sejvar 2007). Long-term complications like fatigue and weakness are common. Movement disorders, cognitive complaints and functional disability may occur after WNV neuroinvasive disease, and WNV paralysis in particular may result in limb weakness and ongoing morbidity (Sejvar 2007). Most adult patients admitted to a rehabilitation facility with WNV have required follow-up physical therapy after discharge from rehabilitation (Hoffman et al. 2012).

Conclusions

Intensivists should be aware of the possible risks for epidemics of the WNV neuroinvasive disease. The following factors are associated with the neuroinvasive WNV infection and may strike a chord, prompting physicians to consider WNV:

i) Seasonality, which varies according to bird migration in different geographic regions, and in temperate areas in late summer;

ii) Common flu-like symptoms before neurological impairment; and

iii)Presence of comorbidities, which are possibly responsible for immune system impairment, such as through the ensuing use of steroids.

Published on : Thu, 7 Mar 2013