Imported West Nile virus encephalitis in an Israeli tourist

Benjamin A Rogers, Linda Hueston and Irani Ratnam

West Nile virus is an arbovirus that has caused large outbreaks of febrile illness, meningitis and encephalitis in Europe, North America and the Middle East. We describe the first laboratory-confirmed human case of West Nile virus infection in Australia, in a 58-year-old tourist who was almost certainly infected in Israel. The case is a reminder of the need to consider exotic pathogens in travellers and of the risk of introducing new pathogens into Australia. ***(MJA 2009; 191: 232-234)***

Clinical record

A 58-year-old man presented to the emergency department of our hospital with chills, malaise, myalgia and epigastric pain. He was a tourist from Israel who had arrived in Australia with his family 3 days previously to visit relatives. The family flew directly from Tel Aviv to Melbourne, with a brief transit stop in Hong Kong airport.

The patient reported a 5-day history of low-grade fevers, malaise, headache and epigastric discomfort, which started before he left Israel. He was previously well with no significant past medical history. He resided on a large cooperative farm in the southern district of Israel but worked in administration, with minimal contact with farm animals. He was not taking any regular medications, consumed alcohol infrequently and was a non-smoker.

On examination, he had a temperature of 37.8°C and a diffuse erythematous macular rash. He was diagnosed with "viral illness", treated symptomatically and discharged from the emergency department.

On Day 7 of the illness, the patient re-presented to the emergency department increasingly unwell. Symptoms now included rigors, headache, dizziness and ear pain. On examination, he had a fever (temperature, 39.6°C), but no neck stiffness, photophobia or focal neurological deficit. After investigation and stabilisation in the emergency department, he was transferred to a ward for ongoing investigation by the infectious diseases team. Supportive care was instituted.

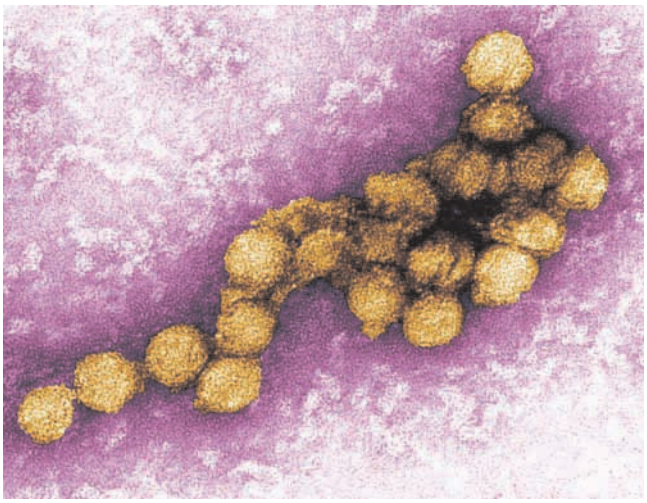
Over the next 24 hours, the patient's condition deteriorated with ongoing fevers and the onset of mild delirium and ataxia. A presumptive diagnosis of encephalitis was made, and diagnostic investigations were undertaken. Acyclovir was commenced empirically for herpes simplex encephalitis until this diagnosis was excluded.

The patient's fever began to resolve by Day 10 of the illness, and he was discharged after 18 days in hospital with mild ataxia. At outpatient review 2 weeks after discharge, he had persisting lethargy and mild ataxia. He returned to Israel with his family, where he underwent outpatient rehabilitation.

Investigations

Extensive investigations were undertaken to diagnose the aetiology of the encephalitis. Cerebrospinal fluid (CSF) sampled on Day 10 of the illness showed leukocytosis (polymorphs, 2×10^6/L; lymphocytes, 75×10^6/L; unidentified cells 12×10^6/L; and erythrocytes, 90×10^6/L), raised protein level (0.84 g/L; reference range [RR], 0.15–0.4 g/L), but a glucose level in the reference range (3.7 mmol/L; RR, 2.5–4.5 mmol/L). However, culture and polymerase chain reaction (PCR) tests for common viral and mycobacterial pathogens gave negative results. Serological testing of acute and convalescent blood samples for common viral and bacterial causes of encephalitis showed no acute infection. Appearance of the brain on magnetic resonance imaging (MRI) was unremarkable.

1 West Nile virus



Transmission electron micrograph of the West Nile virus (from another case). (Original image, Cynthia Goldsmith, Centers for Disease Control and Prevention, Atlanta, Ga, USA.) ◆

Diagnosis of West Nile virus

Paired sera from Day 9 and Day 31 of the illness were tested in parallel in a flavivirus group-reactive enzyme-linked immunosorbent assay (ELISA) for IgG and IgM. This showed a fourfold rise in IgG titre, and IgM seroconversion. The sera were then tested against a panel of flaviviruses for total antibody (by neutralisation) and for IgG and IgM (by immunofluorescence). The strongest reaction by immunofluorescence was against the New York 99 strain of West Nile virus (WNV; Box 1); seroconversion to this virus was confirmed by neutralisation ("gold standard") tests (Box 2).

A stored CSF sample tested positive for IgM against WNV by immunofluorescence. Flavivirus RNA was not detected in CSF or serum by PCR testing.

Discussion

This is the first report of a laboratory-confirmed human importation of WNV infection in Australia. The only previously diagnosed case of acute WNV infection in Australia was in a horse imported

2 Antibody titres against a range of flaviviruses* in the patient's acute (Day 9) and convalescent (Day 31) sera

Antibody assay	Day 9	Day 31
Enzyme-linked immunosorbent assay		
Flavivirus group		
IgG	100	400
IgM	< 100	800
Immunofluorescence test		
West Nile virus (New York 99)		
IgG	< 10	640
IgM	< 10	40
West Nile virus (Sarafend)		
IgG	< 10	20
IgM	< 10	< 10
Kunjin virus		
IgG	< 10	20
IgM	< 10	< 10
Murray Valley encephalitis virus		
IgG	< 10	< 10
IgM	< 10	< 10
Neutralisation test		
West Nile virus (New York 99)	< 10	2560
West Nile virus (Sarafend)	< 10	40
Kunjin virus	< 10	80

* Sera were tested against representatives of a range of West Nile virus groups: New York 99 (Lineage 1, Clade 1a); Kunjin (Lineage 1, Clade 1b), and Sarafend (Lineage 2). ◆

for the breeding season, which acquired the infection overseas but became symptomatic on arrival (unpublished data, Arbovirus Emerging Diseases Unit, CIDMLS, Westmead Hospital, Sydney, NSW). WNV transmission has not been recorded in Australia.

WNV is a single-stranded RNA flavivirus that was first isolated in 1937 from a patient with fever in the West Nile District of Uganda.[1] The virus exists in a bird–mosquito–bird cycle, with wild birds as the amplifying host and reservoir.[2] It has been isolated from 43 species of mosquito, mostly bird-feeding members of the *Culex* genus. Humans and other mammals are incidental hosts, when bitten by infected mosquitoes.

Since first described, WNV has spread widely, with an associated dramatic increase in disease severity.[3,4] It is found in Africa, Europe and the Middle East, with large outbreaks identified during the past decade in Romania, North America and Israel.[5-7]

About 80% of patients with WNV infection are asymptomatic. The incubation period for symptomatic disease is 2–14 days. "West Nile fever" is a non-specific febrile illness that includes headache, myalgia, and occasional gastrointestinal symptoms and usually resolves spontaneously in less than a week.[8] Acute neurological illness is uncommon, occurring in fewer than 1% of infections, and can present with meningitis, encephalitis or a poliomyelitis-like acute flaccid paralysis.[9]

Our patient was almost certainly infected in Israel, where WNV is endemic, with episodic outbreaks reported since the 1950s, most recently in 2000.[7] Israel is the likely origin of the WNV strain now circulating widely in North America.[6]

In Australia, WNV is not routinely considered in locally acquired encephalitis but was investigated in our patient because of the country where he acquired the illness. Close communication was needed with the testing laboratory to convey a more detailed history and clinical description than is usual on a standard request form.

The most frequent arboviral cause of encephalitis in Australia is Murray Valley encephalitis virus, which is endemic in northern Western Australia, the Northern Territory and northern Queensland, and has epidemic activity in southern Australia.[10] Less common arboviral causes of locally acquired encephalitis include Japanese encephalitis virus and Kunjin virus.[11] The latter shares 80% of its genome with WNV and has been classified as a subtype of WNV.[12] It is endemic in northern tropical regions of Australia,[13] and the usual presentation is as a febrile illness; it is a rare cause of encephalitis.[11] There have been no reports of locally acquired flavivirus in Melbourne, Victoria, where our patient resided while in Australia.

Infection with WNV was diagnosed retrospectively in our patient based on serological testing of acute and convalescent sera. WNV IgM concentration was then measured in a stored CSF sample. The initial low-positive serological results for flavivirus group IgG suggested the patient had previously been infected with another member of the flavivirus family. The fourfold rise in IgG titre and new detection of IgM antibodies to WNV indicated this presentation was a new infection. The strongest reaction was to the New York 99 strain of WNV, which is closely related to strains isolated in Israel. Reactions to the Sarafend strain of WNV and the closely related Kunjin virus were significantly weaker. Negative PCR results are common in WNV infection because of the low-level transient viraemia of WNV.[8] Similarly, only about 30% of patients have abnormal MRI findings.[8]

Our patient's presentation illustrates the common clinical features of encephalitis. Fever, headache, personality change or delirium and altered conscious state are typical, and focal neurological deficits and seizures may also occur.[14] The onset can be gradual. In this case, encephalitis was diagnosed on Day 9 of the illness. Initially, headache and dizziness were attributed to systemic infection until further neurological symptoms became apparent. The CSF findings were also typical of encephalitis, with an elevated white cell count and protein concentration, and glucose concentration in the reference range.[14] The likelihood of WNV causing encephalitis rather than an isolated febrile illness or meningitis increases with advanced age.[9]

From a public health perspective, this case raises the question of whether WNV could be introduced into Australia. *Culex* mosquitoes are distributed widely throughout the country, and recent research has confirmed that Australian *Culex* mosquitoes can be infected with, and transmit, the North American strain of WNV.[15] However, because of the similarity between WNV and Kunjin virus, antibodies to the latter in vertebrate hosts may limit the infectivity and establishment of WNV in the Australian environment, depending on the geographic distribution of Kunjin virus.[16] The type of animal harbouring, and thus importing, WNV is also important. Some research shows humans are likely to be "dead end hosts", with a level of viraemia that is too low to transmit to an uninfected mosquito.[17] This suggests the risk of secondary cases from our patient was very low. The inadvertent or illegal importa-

tion of infected mosquitoes or birds would pose a far greater risk of introducing WNV into Australia.

This is the first human case of laboratory-confirmed WNV infection recorded in Australia. It highlights the importance of considering the geographic origin of illness in travellers and is a reminder of the various arboviral causes of encephalitis. It is also a reminder of the possibility of international travellers, human or otherwise, introducing new infective agents. Fortunately, spread of the virus beyond the index patient was unlikely in this case. We urge vigilance regarding the possible introduction of new pathogens to the Australian environment. Any concern should be reported promptly to the relevant state or territory authorities.

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Competing interests

None identified.

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