Case Report: West Nile Virus (Kunjin Subtype) Disease in the Northern Territory of Australia—A Case of Encephalitis and Review of All Reported Cases

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Abstract. West Nile virus Kunjin subtype (WNV/KUNV) is enzootic across the tropical north of Australia, with epizootic spread into other jurisdictions. The clinical spectrum of illness in humans is poorly described. We report a clinical case of WNV/KUNV encephalitis and performed a retrospective chart audit of all cases of WNV/KUNV notified in the Northern Territory from 1992 to 2010. Thirteen cases of WNV/KUNV disease were identified; case notes were available for 10 of these presentations. Six of these patients had confirmed infection and presented with neuroinvasive illness, whereas the other four suspect cases comprised three cases with arthralgia, myalgia, and/or rash and one case with fever alone. On the available evidence, WNV/KUNV is of lower virulence compared with the New York 1999 strain. Difficulties in serological diagnosis, especially when paired acute and convalescent sera are not available, may adversely impact the accuracy of the epidemiological and clinical understanding of this virus.

INTRODUCTION

West Nile virus Kunjin subtype (WNV/KUNV) is a flavivirus first isolated in 1960 from *Culex annulirostris* mosquitoes in Northern Queensland and is named after a local Aboriginal group.[1] The epidemiology and ecology of WNV/KUNV is extensively monitored throughout mainland Australia, particularly because of the overlap with the occurrence of Murray Valley encephalitis virus (MVEV), which more commonly causes human disease. These encephalitic viruses are enzootic across the top end of the Northern Territory (NT) and the Kimberly region of Western Australia and probably as far north as Queensland.[2] Water birds serve as primary reservoirs of the virus, which is maintained and amplified in mosquito–bird cycles, with epizootic spread of WNV/KUNV into central and southern areas of Australia with the movement of viremic water birds and increased mosquito numbers in the setting of above average rainfall.[3] WNV/KUNV was previously designated as a separate species, but recent molecular phylogeny has shown that it is a subtype of the WNV group.[4] WNV has caused large outbreaks of epidemic encephalitis in Europe and North America with 5–15% mortality.[5] Infection with WNV/KUNV is less severe than the WNV/New York 1999 (NY99) strain in both humans and animals.[2] Currently, there is limited information about the clinical spectrum of disease caused by WNV/KUNV because of both the rarity of clinical cases and difficulties with routine serological tests distinguishing WNV/KUNV infection from other flaviviruses endemic to the NT, such as MVEV, Kokobera virus, Alfuy virus, Edge Hill virus, and Stratford virus.[6] Of these viruses, only MVEV and WNV/KUNV have been shown to cause encephalitis in humans.[6] In returned travelers, infection caused by flaviviruses endemic to neighboring countries, such as dengue virus and Japanese encephalitis virus (JEV), must also be considered. Since 1992, doctors and laboratories have notified cases of suspected WNV/KUNV infection diagnosed within the NT jurisdiction. Since 2001, all jurisdictions of Australia have

reported WNV/KUNV cases. We present here a case of encephalitis caused by WNV/KUNV as well as a retrospective analysis of reported cases of WNV/KUNV acquired in the NT.

METHODS

Cases of WNV/KUNV infection were identified from the NT Notifiable Diseases Surveillance System. Additional cases were identified by review of records held by the Department of Health Medical Entomology Branch and literature review. Hospital medical records as well as medical entomology records were investigated for clinical data. The case definition for WNV/KUNV infection used in the NT and nationally has changed over time, with the most recent changes in July 2010.[7] The current case definition requires both clinical and laboratory evidence of infection. For both encephalitic and non-encephalitic cases, acceptable laboratory evidence is detection of virus by culture, detection of viral RNA, seroconversion or a fourfold rise in specific WNV/KUNV antibodies in serum, or WNV/KUNV immunoglobulin M (IgM) detection in the cerebral spinal fluid (CSF) in the absence of IgM to other possible infecting flaviviruses. For cases of encephalitis, detection of WNV/KUNV IgM in the serum in the absence of IgM to other possible infecting flaviviruses is also accepted. Serology results were accessed from original pathology reports from nationally accredited reporting laboratories. Total antibody (IgG and IgM) was detected by the hemagglutination inhibition assay (HI), and IgM was detected by indirect immunofluorescence assay (IFA); specific antibodies to MVEV and WNV/KUNV were detected by epitope-blocking enzyme immunoassay and/or neutralizing antibody assays.[8]

RESULTS

A total of 13 cases of WNV/KUNV disease were identified from 1992 to 2010 (Table 1). Eleven of these cases were notified to the NT, including the case presented below. An additional two cases of disease acquired in the NT but notified in other jurisdictions were identified by review of medical entomology records (case 11) and literature review (case 3).[9]

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TABLE 1
Epidemiological and clinical features of West Nile Virus (Kunjin subtype) cases reported in the NT jurisdiction from 1992 to 2010

Case	Age (years)	Sex	Indigenous status	Onset	Location of exposure	Presenting syndrome	Outcome	Fulfills case definition
1	80	M	N	June 2010	Rural Darwin	Encephalitis with fever, confusion, and movement disorder	Residual vertigo (mild)	Yes
2	38	F	N	May 2009	Borroloola	Fever, headache, photophobia, rash, and arthralgia	Full recovery	No
3	67	M	N	May 2001	Barkly and Darwin	Encephalitis with fever, confusion, headache, and lethargy	Full recovery	Yes
4	23	F	A	April 2001	Alice Springs	Meningitis with fever, headache, photophobia, and neck stiffness	Full recovery	Yes
5	11	M	N	March 2001	Alice Springs	Meningitis with fever, headache, photophobia, neck stiffness, and vomiting	Full recovery	Yes
6	3	M	A	April 2000	Hermannsburg (Alice Springs)	Encephalitis with fever, headache, vomiting, irritability, and drowsiness	Full recovery	Yes
7	31	M	N	March 2000	Darwin	NA		NA

Case 3 has previously been reported.[9] A = Aboriginal; F = female; M = male; N = non-Aboriginal; NA = not available.

The median age of the patients was 38 years, with a range from 3 to 80 years and male prevalence of 69% of cases. The 11 most recent cases presented at the transition into the dry season (March to June), with a broad geographical distribution through tropical and sub-tropical regions of the NT (Figure 1). Three of the patients notified within the NT had no inpatient records associated with their diagnosis. Of the 10 patients with case records available, 10 patients presented with fever, 3 patients presented with encephalitis, 3 patients presented with meningitis, 3 patients presented with arthralgia, myalgia, or rash, and 1 patient presented with fever alone. When the current national WNV/KUNV case definition is applied in retrospect to all reported cases in the NT, only six cases fulfilled the criteria for notification (Table 1), and all were meningoencephalitic cases, with none reporting rash, myalgia, or arthralgia. The four other patients not fulfilling the case definition were non-encephalitic cases that had been previously notified on the basis of detected serum IgM, but testing of acute and convalescent samples was either not performed or did not reveal a rising titer (Table 2).

2010 WNV/KUNV subtype encephalitis case. An 80-year-old non-Aboriginal man presented in June 2010 with a 3-day history of fever and worsening hip pain. He had undergone cardiac bypass surgery 4 months before in preparation for a planned elective hip replacement for severe osteoarthritis of his left hip. He had been seen in the pre-operative clinic of the hospital 8 days before his presentation and was well. He had hypertension, myelofibrosis, and peripheral neuropathy attributed to chronic alcohol excess. On presentation, he was febrile to 40°C, with blood pressure of 150/90 mm Hg and a pulse of 90 beats/minute. He was orientated to time and place but displayed mild confusion when recalling events of the previous 24 hours. Examination showed splenomegaly attributed to his myelofibrosis and a well-healed sternotomy wound. His left hip pain was severe with any passive movement of the joint. C-reactive protein was 13.1 mg/L (< 5 mg/L), and white cell count was 12.2×10^9, with a neutrophil count of 7.2×10^9/L. X-ray of the hip confirmed severe osteoarthritis, and chest X-ray was normal. The provisional diagnosis was septic arthritis; he underwent surgical washout of the left hip, and broad-spectrum antibiotics were commenced. Fever persisted, and the patient became mute and unable to follow commands. From day 2 of his admission, he developed a movement disorder with myoclonic jerks, hypertonia and cogwheel rigidity of all his limbs, and marked opsoclonus. Serial blood cultures as well as the operative hip specimens remained culture-negative.

Computed tomography (CT) scan of the brain on day 3 of his admission was normal, and magnetic resonance imaging
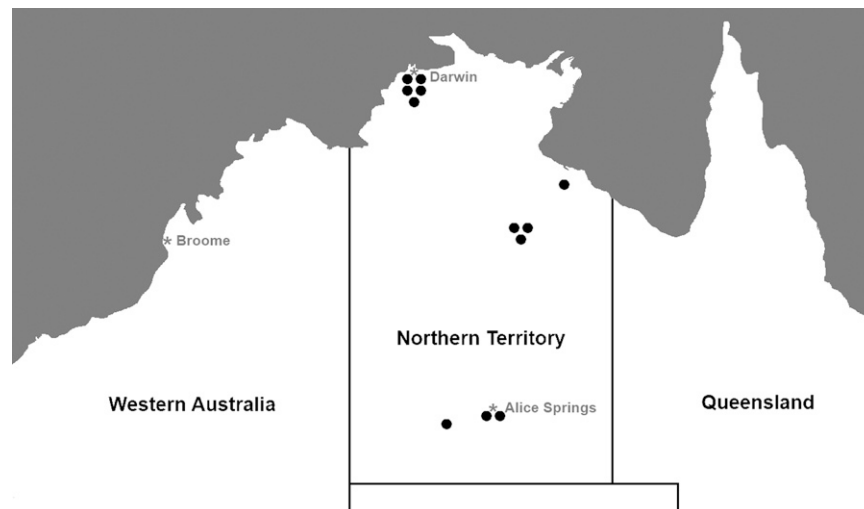

FIGURE 1. Regional map of Australia indicating the locations of WNV/KUNV strain infection acquired in the NT of Australia from 1992 to 2010.

TABLE 2
Investigation results of reported cases of West Nile Virus (Kunjin subtype) reported in the NT, Australia

| Case | Presenting peripheral WCC ($\times10^9$) | Serum serology | | CSF | | | | CT brain |
		KUN IgM-IFA	KUN HI (acute and convalescent)	Glucose (mmol/L)	Protein (g/L)	Neutrophils ($\times10^6$/L)	Lymphocytes ($\times10^6$/L)	
1	12.2	Detected	1:640 to 1:1,280	2.5	1.48	1	25	Normal
2	6.7	Detected	1:80 to 1:80	NP	NP	NP	NP	Normal
3	8.1	Not detected	< 1:10 to 1:40	6.3	0.55	196	36	Normal
4	5.8	Detected	1:80 to 1:160	2.5	0.42	35	6	Normal
5	8.8	Detected	< 1:10 to 1:320	3.5	0.32	8	8	Normal
6	20.3	Detected	1:10 to 1:160	NP	NP	110	75	NP
9	NA	Detected	< 1:10 to NP	NA	NA	NA	NA	Normal
10	6.5	Detected	1:160 to 1:160	NP	NP	NP	NP	NP
11	NA	Detected	1:80 to 1:80	NP	NP	NP	NP	NP

CSF protein normal range is 0.15–0.45g/L. CSF glucose normal range is 2.7–4.2 mmol/L. HI = hemagglutination inhibition test; IFA = indirect immunofluorescence antibody test; NA = not available; NP = not performed; WCC = white cell count.

(MRI) of his brain on day 7 revealed increased T2 signal in the cerebellum, brain stem, and particularly, the right thalamus. Lumbar puncture was performed on day 7, which revealed protein of 1.48 g/L (0.15–0.45 g/L) with glucose of 2.5 mmol/L (2.7–4.2 mmol/L) and a pleocytosis of 26×10^6/L leukocytes with 96% lymphocytes. Bone marrow biopsy excluded malignant transformation of myelofibrosis. Weak positive IgM to WNV/KUNV was detected in the CSF, with an equivocal result for MVEV IgM. Serum collected on the same day showed moderate positive IgM to KUNV/WNV and a negative IgM to MVEV. Paired serum samples collected on days 9 and 26 of illness showed a seroconversion to WNV/KUNV on the epitope-blocking enzyme immunoassay (EIA) from 0% to 44%, whereas the MVEV block remained at 0%; a rise in WNV/KUNV neutralizing antibodies using a 90% endpoint from 2,560 to 10,240 was noted. Neutralizing antibodies to other flaviviruses, including MVEV, dengue virus, and JEV, were undetectable. Attempts to detect WNV/KUNV in CSF and serum by cell culture and polymerase chain reaction (PCR) were unsuccessful.

Fever persisted for 14 days. The illness was complicated by hypertension to 240/120 mm Hg, acute gastrointestinal hemorrhage, and hospital-acquired pneumonia. After 4 weeks, memory, speech, and cognition began to improve, and he was transferred to a rehabilitation ward 7 weeks after his presentation. He was discharged from the inpatient rehabilitation service 18 weeks after the onset of his illness. He returned to his pre-morbid function (although formal neuropsychological testing was not performed) by 6 months. Mild residual vertigo persists but has slowly improved.

In the weeks before presentation, the patient reported multiple mosquito bites. The patient did not have insect screens on his rural Darwin residence and slept with the doors open. Sentinel chickens across the NT top-end flocks had seroconverted to WNV/KUNV regularly between January and July 2010, indicating widespread virus activity. Entomological investigation identified relatively high numbers of mosquitoes in traps set near and at the patient's residence, including the local vector of WNV/KUNV (*Cx. Annulirostris*).[10] Additional public health warnings focusing on mosquito avoidance were promoted after this case, and there were no additional notifications of flavivirus encephalitis in 2010.

DISCUSSION

WNV/KUNV encephalitis is a rare disease in humans, with only three cases acquired in the NT since 1992 (cases 1, 3, and 6).

There have been two other reported cases of WNV/KUNV encephalitis since the mixed outbreak of MVEV and WNV/KUNV in southeastern Australia in 1974,[2] one in Northern Victoria in 1985[11] and one in Broome, Western Australia, in 1978.[7] All of the patients with WNV/KUNV encephalitis have survived the illness. Morbidity is limited, with two of five patients having persisting mild neurological deficits, including vertigo in the current case and left facial weakness and unsteady gait in the 20-year-old woman in Broome.[12] Case fatality rates have been reported to be 5–15% for encephalitis from WNV/NY99 in the United States and 20–30% for encephalitis from MVEV in Australia, with neurological disability, often severe, in approximately 50% of encephalitis survivors for both of these flavivirus infections.[5,8,13,14] Although WNV/KUNV encephalitis is rare and case numbers are small, it seems that the clinical course of WNV/KUNV encephalitis may be less severe than encephalitis from the related WNV/NY99 and MVEV.[2,5,13] Of the six neuroinvasive cases in this series, three were meningitic, and three were encephalitic, which is in keeping with reported series of WNV/NY99 strain where 15–40% of neuroinvasive cases presented with meningitis and 60% presented with encephalitis.[5,14,15]

Several cases of non-encephalitis KUNV infection have been documented in the literature, most often presenting with fever, malaise, rash, and arthralgia.[2,8] Patients with these milder presentations may not be tested for WNV/KUNV infection but only for the more common alphavirus infections of Ross River virus and Barmah Forest virus. Even if tested, acute and convalescent serum samples are often unavailable, in which case they cannot meet the requirements of the national case definition. Nevertheless, it is unlikely that WNV/KUNV is a common cause of febrile polyartharlgic illness, even during periods of high activity. For example, no cases of WNV/KUNV illness, apart from the three neuroinvasive cases reported here, were notified during an extended and well-publicized outbreak of the illness in Central Australia in 2001.[16] This finding is in contrast with the WNV/NY99 strain, which causes West Nile fever, a symptomatic non-neuroinvasive disease, in 20% of exposed patients.[17]

Routine serological techniques for separating disease caused by WNV/KUNV from the disease of other flaviviruses remains problematic because of cross-reactions within the flavivirus group. Documenting a fourfold rise in neutralizing antibodies to WNV/KUNV in paired samples (in the absence of similar rise in other flavivirus antibodies) or increases in WNV/KUNV-specific antibodies using an epitope-blocking EIA or virus neutralization titers are the most specific serological methods,

but these techniques are limited to specialized laboratories. Isolation or detection of viral RNA from symptomatic patients is considered the gold standard, but it is rarely achieved.[18] In the current case, virus was not detected from any CSF or serum samples by culture or PCR. It is likely that the viremia of WNV/KUNV is short lived in humans, which is the case with other strains of WNV,[5] although transmission of WNV through blood and solid organ donation has been documented.[19,20]

Population serosurveys in Australia using specific serological assays for MVEV and WNV/KUNV have attempted to estimate the clinical to sub-clinical ratios after exposure. The largest study, using monoclonal antibody-blocking EIA, was performed in indigenous populations in three rural endemic areas across the top end of the NT in 1988 and 1989 and found an increasing WNV/KUNV seroprevalence with age, with overall level of approximately 30% in 834 individuals.[21] The rising seroprevalence with age for both MVEV and WNV/KUNV infections may partially explain the observation that presumed non-immune young indigenous and older non-indigenous individuals, often travelers, are more susceptible to disease with these viruses.[13] Although it is not possible to quantify, the available seroprevalence data are consistent with a high rate of asymptomatic disease in individuals exposed to WNV/KUNV. For other flaviviral infections, current estimates of the proportion of symptomatic infections to asymptomatic infections is approximately 1 in 700 to 1 in 1,200 for MVEV and 1 in 25 in non-immune adults compared with 1 in 1,000 for children living in endemic areas for JEV and 1 in 5 for the WNV/NY99 strain.[5,17,21,22]

The MRI changes showed in the current case are consistent with the inflammatory deep white matter changes typically found in the thalamus and brain stem in encephalitis caused by infection with other WN subtypes and the closely related flaviviruses, including MVEV and JEV.[13,23–25] The cerebellar, brainstem, and thalamic changes seen were consistent with the movement disorder in the presented case. Myoclonus, parkinsonism, and opsoclonus have been described in other flavivirus infections, including WNV/NY99, MVEV, and JEV.[5,13,26] As with encephalitis from MVEV and JEV, CT imaging of the brain is insensitive for WNV/KUNV meningoencephalitis, which was shown by normal CT imaging in all six cases that underwent this test.

This study has attempted to define the clinical manifestations of WNV/KUNV infection. A confirmed diagnosis of WNV/KUNV infection is often elusive, because of dependence on serological diagnostics; this dependence contributes to uncertainty when describing the epidemiological and clinical features of the disease. Clinicians are, therefore, encouraged to maintain diligence in completing convalescent serological tests in suspected cases. Although case numbers are limited, it seems likely that the proportion of WNV/KUNV infections that result in meningoencephalitic illness is substantially less than for MVEV, JEV, and WNV/NY99 infections; additionally, the clinical severity of the neurological disease is less, and the outcomes are better for those people who present with encephalitis. In summary, clinicians should consider WNV/KUNV infection in the differential diagnosis for meningoencephalitic illness in patients who have been exposed to mosquitoes in the flavivirus-endemic regions of Australia, particularly during the months of March to June when the majority of cases have historically occurred.

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