



DESCRIPTION OF WEST NILE VIRUS PEDIATRIC CASES LOS ANGELES COUNTY, 2004

BACKGROUND

West Nile virus (WNV, *Flavivirus*, *Flaviviridae*) has emerged as a major public health problem in the US. In 1999, New York City public health officials documented the first entry of WNV into the western hemisphere. During that first year, public health officials recorded 59 cases including seven fatalities from meningoencephalitis [1]. Since then, public health officials have documented the spread across North America from the Atlantic to the Pacific coasts [2] and from Canada [3] into Mexico [4]. In 2003, 9,862 human cases of WNV infections were reported nationwide to the CDC from 45 states and 46 states reported non-human WNV surveillance activity [5]. While one case of WNV infection was confirmed in a LAC resident in 2002, no environmental source was found. WNV was subsequently detected in California (CA) in July of 2003, when the virus was isolated from mosquito pools of *Culex tarsalis* near El Centro in Imperial County [6]. Subsequently, three human cases of WNV infection (two meningitis cases and one case of WNV fever) were confirmed in Southern CA [7]. In 2004, the state of CA reported the greatest number of WNV cases in the US with 828 confirmed WNV cases as of January 28, 2005; LAC reported 283 WNV symptomatic and 23 asymptomatic infections from blood donors, the greatest number of any CA jurisdiction [8].

Over the past four years, the clinical conditions associated with WNV infection have been well described: WNV fever (WNF) and neuroinvasive disease (NID), which includes encephalitis, meningitis, and acute flaccid paralysis (AFP) [9–11]. Despite the large number of adult cases reported, published information regarding the clinical presentation of WNV in children is limited [12, 13]. Generally, the clinical conditions associated with pediatric WNV infection are milder with most cases being WNV fever [12]. The CDC reported 150 (4%) and 763 (8%) pediatric cases nationwide in 2002 and 2003 respectively in children and adolescents under age 18 [14]. In this report, we describe a population based case series of 11 WNV-infected children reported during the LAC 2004 WNV season.

METHODS

Case Finding: In May of 2004, the LAC Public Health Department alerted all licensed physicians and infection control practitioners (ICP) to the risk of WNV infection in the coming months and the necessity and availability of free WNV serologic testing for suspected cases of WNV fever, viral meningitis, encephalitis, and AFP through the LAC Public Health Laboratory (PHL). In July of 2004, the LAC Health Officer made human cases of West Nile Virus infection reportable within one working day.

Case Definitions: WNV encephalitis was defined as fever ($>38^{\circ}\text{C}$), depressed or altered mental status, lethargy, or personality change lasting ≥ 24 hours and additional evidence of acute central nervous system inflammation, including cerebral spinal fluid (CSF) pleocytosis with ≥ 5 white blood cell (WBC)/ mm^3 and positive acute IgM WNV serological results in the CSF and/or serum; WNV meningitis cases had clinical signs of meningeal inflammation, including nuchal rigidity, Kernig or Brudzinski sign, or photophobia, and additional evidence of acute infection including fever, ($>38^{\circ}\text{C}$) headache without altered mental status, and CSF pleocytosis with ≥ 5 WBC/ mm^3 and positive acute WNV IgM serological results in the serum and/or CSF; WNV fever cases had two of three symptoms including fever ($>38^{\circ}\text{C}$), headaches, and rash and a positive acute serum WNV IgM.

Laboratory Testing: All commercial positive WNV serologic results were confirmed at either the LAC PHL or the CA Department of Health Services Viral and Rickettsial Disease Laboratory (VRDL). All confirmed cases had WNV positive serum and/or CSF IgM for WNV by two different serologic methodologies: IgM by antibody capture enzyme-linked immunosorbent assay (ELISA) (PANBIO; Windsor, Australia) and immuno-fluorescent antibody (IFA) slide test kit (PANBIO; Windsor, Australia). Plaque reduction neutralization tests (PRNT) were completed on selected pediatric cases by VRDL. LAC public health staff



administered a standardized WNV case report form (including patient demographics, clinical information, and WNV prevention practices) by telephone interview with the parent or legal guardian of the case. Additionally, hospital and emergency room medical records were reviewed. In cases where there was missing information, a physician contacted the patient's primary physician by telephone.

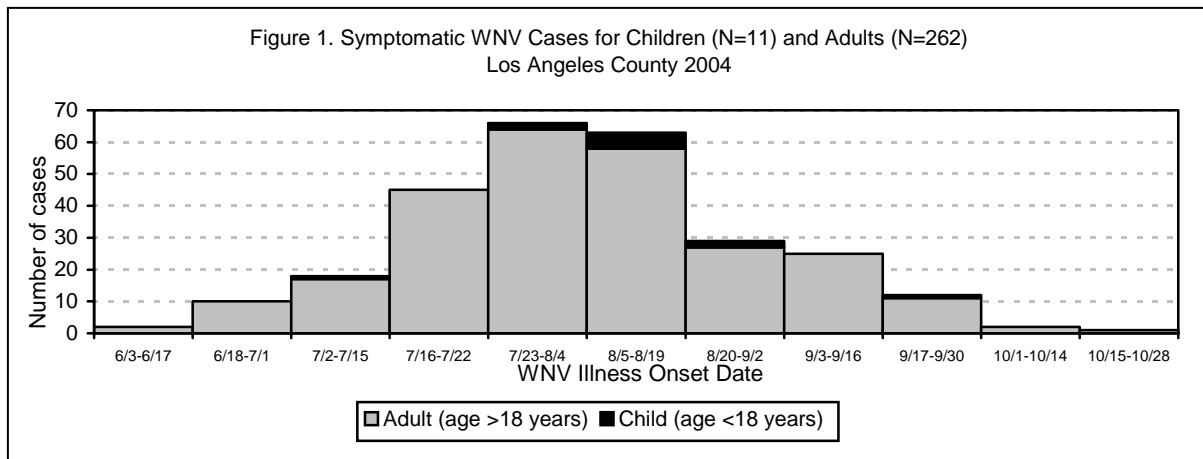
RESULTS

Of 283 reported and laboratory-confirmed symptomatic cases of WNV in LAC in 2004, 11 (3.9%) were pediatric cases under age 18 years (Table 1). The 11 pediatric cases included: eight with WNV fever (73%), two meningitis cases (18%), and one encephalitis case (9%). The median age was 10 years (range: 5-14 years). Ten were males; nine cases were Hispanic, one was White, and one was Asian. The symptom onset dates ranged from July 5 through September 27, 2004 (Figure.1). Complete medical and epidemiologic information was available for all 11 cases and is described in the case series.

Table 1. Characteristics of children with West Nile virus infection in Los Angeles County, 2004

Case	Age in years	Sex	Diagnosis	SO to C ¹	Duration of Illness	Fever	Headache	MW ²	Rash	GI ³	WBC ⁴	PRNT ⁵	ME ⁶
1	14	M	Fever	2 days	7 days	Yes	Yes	Yes	Yes	Yes	15.4	Yes	ER ⁷
2	6	M	Fever	3 days	2 days	Yes	No	No	Yes	No	3.6	Yes	OP ⁸
3	9	M	Fever	7 days	8 days	Yes	No	No	Yes	Yes	4.2	Yes	ER ⁷
4	10	M	Fever	5 days	3 days	Yes	Yes	No	Yes	Yes	4.0	No	ER ⁷
5	11	M	Fever	2 days	21 days	Yes	Yes	No	Yes	Yes	12.6	No	IP ⁹
6	14	M	Fever	2 days	7 days	Yes	Yes	Yes	Yes	Yes	12.6	Yes	ER ⁷
7	12	M	Fever	8 days	14 days	Yes	Yes	Yes	Yes	No	n/d ¹⁰	Yes	OP ⁸
8	14	F	Fever	3 days	3 days	Yes	Yes	Yes	No	Yes	14.3	Yes	IP ⁹
9	8	M	Meningitis	19 days	21 days	Yes	Yes	Yes	Yes	Yes	6.7	No	ER ⁷
10	5	M	Meningitis	3 days	7 days	Yes	Yes	Yes	Yes	Yes	13.3	No	IP ⁹
11	6	M	Encephalitis	4 days	5 days	Yes	Yes	Yes	No	Yes	20.9	No	IP ⁹

1. Number of days from symptom onset to collection of specimens.
2. Muscle weakness.
3. Gastrointestinal symptoms.
4. White blood cell count (WBC x ³/mm³).
5. Plaque reduction neutralization test.
6. Location of medical evaluation.
7. Emergency room.
8. Outpatient.
9. Inpatient.
10. Not done.





Clinical Features—WNV Fever: There were eight confirmed cases of WNF with a median age of 11 years (range: 6-14 years). The most common presenting symptoms included: fever (n=8, 100%), macular-papular rash (n=7, 88%), headache (n=6, 75%), nausea and vomiting (n=6, 75%), and muscle pain and weakness (n=4, 50%). The median duration of illness was 7 days (range: 2-21 days). All eight cases had positive acute serum IgM WNV capture-ELISA and IFA tests; additionally six cases had confirmatory PRNT completed (Table 1). The median duration between symptom onset and acute serum collection was three days (range: 2-8 days). Six of the eight WNV fever cases had additional laboratory tests which were within normal range, including serum chemistries and urine analyses, and negative blood and urine cultures. Of the seven WNF cases with peripheral white blood cell counts (WBC), three had a low total peripheral WBC, two were elevated, and three were within normal limits.

Case 1. This healthy 14 year-old Hispanic male presented to the emergency room (ER) with a 2-day history of anorexia, fever (39.5⁰C), headache, malaise, and a macular-papular rash on his extremities lasting one day. The patient stated that mosquitoes bit him 3-4 days prior to seeking medical care. The patient received intravenous fluids, acetaminophen, and ibuprofen in and was started on ceftriaxone 1gm IV every 12 hours for presumptive bacterial sepsis. His initial peripheral WBC was 15,400/mm³ with mostly neutrophils; electrolytes were normal. His clinical status improved and he was discharged home from the ER without subsequent sequelae. At follow-up, the acute serum WNV IgM was positive.

Case 2. This healthy 6 year-old Hispanic male presented to his primary medical doctor (PMD) with an acute onset of a diffuse macular-papular rash distributed on his arms, leg, face and trunk followed by 2 days fever without headache. A few days prior to development of the rash, the patient was swimming at a cattle ranch in Riverside, CA where there was free standing water, however, he did not recall getting bitten by mosquitoes. Given the recent media attention surrounding WNV, the parents were concerned and took their child to their PMD for WNV testing. This patient had a borderline-low WBC of 3,600/mm³ and normal hematocrit and platelet count. He was seen as an outpatient and at 2-week follow-up his rash and all WNV-associated symptoms had resolved and serum WNV IgM was positive.

Case 3. This 9 year-old Hispanic male was seen by his PMD for abrupt onset of fever to 39.4⁰ C and an erythematous macular-papular rash on his extremities. The patient had been playing outside 5 days before the onset of the rash but did not recall getting bitten by mosquitoes. He was sent by his PMD in the ER for further work-up. At the ER, the physician recommended a lumbar puncture but his mother was concerned about the risks and took the child home against medical advice. Peripheral WBC was 4,200/mm³, electrolytes and urine-analysis were normal. Follow-up with his PMD nine days later revealed that he was completely asymptomatic and serum WNV IgM was positive from the ER visit.

Case 4. This healthy 10 year-old Asian male presented to the ER with a 5-day history of fever and a 3-day history of vomiting and rash on his arms and face. At the ER, the patient was febrile to 39.3⁰C and CBC was borderline-low with 4,000/mm³ with normal hemoglobin and platelets, urine analysis, chest x-ray and abdominal x-ray were normal. The patient was given acetaminophen and discharged home from the ER. At follow-up his symptoms had resolved and serum WNV IgM was positive drawn during his ER evaluation.

Case 5. This 11 year-old Hispanic male presented to the ER with acute onset of abdominal pain, chills, vomiting, headache and fever. He was given supportive care and discharged home from the ER with a diagnosis of viral gastroenteritis. At home the patient continued to have 3 days of abdominal pain, chills, vomiting, and headache with intermittent fever, so his mother brought him to a local hospital for evaluation. At this ER visit, the patient was febrile to 38.3⁰C with chills, rigors, vomiting, diarrhea and presented with an erythematous macular-papular rash over his abdomen. His peripheral WBC was 12,600/mm³. According to the parents, the patient had recent close contact with their dog that had died of a probable viral infection. The patient was admitted with a diagnosis of viral gastroenteritis. A computer tomogram (CT) scan of the abdomen was negative but the patient was admitted to rule out appendicitis. The patient was started on Ceftriaxone, which was switched to cefotaxime during his 3-day hospital admission. Urine-analysis, blood and stool cultures were negative. The patient improved clinically and was discharged on hospital day 3. A WNV serologic test was ordered after discharge and was subsequently positive.



Case 6. This 14 year-old Hispanic male presented to the ER with a 7-day history of nausea, vomiting, muscle weakness, fever and erythematous macular-papular rash on his upper and lower extremities. Laboratories including WBC, serum chemistries, and urine analysis were normal, and discharged home for follow-up with his PMD. His PMD obtained WNV serology the following day, which was subsequently positive.

Case 7. A 12 year-old Hispanic male who presented to his PMD with a 1-day history of rash, fever, headache, body aches. The boy recalled mosquito bites 2 weeks prior to symptom onset. A WNV serologic test was obtained with no other additional laboratory testing. The patient's symptoms resolved within 7 days.

Case 8. This 14 year-old Hispanic female reported 3 days of fever, headache, body aches and muscle weakness to her PMD. The PMD obtained a WNV serologic test that was subsequently positive and CBC was elevated at 14,300/mm³.

West Nile Virus Meningitis: There were two cases of viral meningitis in an 8-year and a 5 year-old boy. Presenting symptoms included: headache, rash, vomiting, and fever. Both cases had CSF findings showing pleocytosis, acute serum WNV IgM positive, and normal peripheral WBC count. One case was evaluated in an ER and discharged home and one case was hospitalized for 3 days. The duration of illness was 21 and 7 days respectively for a full recovery.

Case 9. This 8 year-old white male had a 9-day history of headache with intermittent fevers, rash and limited vomiting, he was seen at a community hospital ER. The patient's WBC was 6,700/mm³, and a chest x-ray and CT of the head were both normal. A lumbar puncture revealed CSF that was consistent with viral meningitis WBC of 150 cells/mm³ with lymphocytic predominance; CSF glucose and total protein were within normal range. The patient was discharged from the ER to home and an acute serum WNV IgM titer was positive.

Case 10. This 5 year-old Hispanic boy presented to the ER with acute onset of a diffuse erythematous macular-papular rash over most of his body, abdominal pain, neck pain and fever. At the ER, the patient was confused and was febrile to 39.3°C. A CBC revealed a WBC count of 13,300/mm³ and the patient was given ceftriaxone while further studies pended. A CT of the head was negative and a lumbar puncture was consistent with viral meningitis: WBC of 200 cells/mm³ with a normal CSF total protein and glucose. An acute serum WNV IgM titer was positive. The patient was transferred to another facility for higher level of care. At the receiving facility he was found to be febrile with a headache and noted to have petechiae. His blood cultures and CSF cultures were negative and the patient was discharged home after 2 days without sequelae.

West Nile Virus Encephalitis:

Case 11. This is a previously healthy 6 year-old Hispanic male who presented to the ER with a 3-day history of headache, fever, lethargy and vomiting. On ER evaluation, the patient had a violent shaking episode but did not lose consciousness. At the ER, the admitting physical on the patient noted a fever of 39.9°C, did not note a rash present, and reported a normal neurological examination with laboratories showing a WBC of 10,700/mm³ and normal serum chemistries. Chest x-ray and CT of the head were both normal. A lumbar puncture revealed CSF that was consistent with viral meningitis (WBC = 460 cells/mm³ with a lymphocytic predominance) and normal CSF protein and glucose levels. The patient was started on cefotaxime. On the second day of admission the patient was described by clinical staff as being lethargic with ataxia and dysmetria on neurologic exam. Neurology was consulted; magnetic resonance imaging (MRI) of his brain and electroencephalography (EEG) were performed and were both interpreted as normal. The lumbar puncture revealed CSF that was IgM positive for WNV and the cefotaxime was discontinued. Physical therapy was consulted to help with the ataxia, which eventually resolved during the hospital course. By hospital day 5, the patient's temperature normalized, his mental status and ability to ambulate returned to baseline and he was discharged home.



DISCUSSION

Our case series of 11 laboratory-confirmed WNV cases documents that WNV in children and adolescents is generally a mild acute infection. The relatively few documented cases in children and adolescents within LAC, approximately 4% of all symptomatic WNV cases, is a smaller percentage that was reported nationwide by the CDC of approximately 8% in 2003 for children and adolescents [14]. The overall median age of our pediatric WNV cases was 10 years of age, notably the youngest age in our series was 5 years old. Most of our pediatric cases had WNF (n=8, 73%) and only three cases (37%) had evidence of NID. Of the NID cases, only one had encephalitis. It is notable that all of our cases were healthy children without history of underlying chronic illness or immunocompromising conditions. All cases had an excellent recovery with no neurologic sequelae. Although few pediatric cases were documented, it is highly likely many more children were infected with the WNV. Such children were either asymptomatic or experienced mild symptoms and were not tested for WNV infection.

Distinguishing characteristics of the pediatric cases compared to the adults cases (ages ≥ 18) reported to LAC in 2004 include: the high frequency of an erythematous macular-papular rash on the extremities (n=9, 82%), compared to just 35% of symptomatic adult cases. In addition, children tend to exhibit a high frequency of gastrointestinal symptoms; specifically, vomiting was also noted in 8 of 11 cases. Recent clinical descriptions of WNV fever from WNV outbreaks in Illinois in 2002 and Israel in 2000 reported rash and vomiting present in 57% and 22% and vomiting present in 28% and 31% in each of their respective WNF outbreak case series reviews [15–17]. In both previously noted case series, WNF cases were mainly adults with only 4 cases noted to be less than 25 years of age in the Illinois series and the Israeli case series had a median age to be 65 years. In our series, rash pruritis was not queried in our standardized case report. However, chart review did not reveal this in our 11 cases and also did not show that any of the children were on antibiotics prior to rash onset. It has been recently suggested that rash may be linked to overall favorable clinical outcome [18]. This would be consistent with our finding of a high percentage of rash observed in our pediatric WNV cases (9 of 11 cases) which had generally uncomplicated illnesses. In contrast to our pediatric cases, 18% of LAC adults with WNV NID and 48% of WNF cases presented with rash, which had more complicated and prolonged illnesses overall compared to children. Fever was common in both adults and children with 100% of our pediatric cases reporting fever and 90% of our adult symptomatic cases reporting fever. Altered level of consciousness was rare in our series, with only one of 11 pediatric cases reporting compared to the high frequency of 42% in our symptomatic adults ≥ 18 . In contrast to a recent WNF follow-up study involving adults from Illinois, which noted prolonged symptoms (e.g., fatigue, muscle weakness, difficulty concentrating, and fever noting median durations of 36, 28, 14, and 10 days respectively) [15], our total median duration of overall illness was only 7 days (range: 3-21). We did not query the specific symptoms and their duration in our case series.

Most of our pediatric cases were male (n=10, 91%) and Hispanic (n=9, 82%) which was a larger proportion of the population compared to our adult symptomatic cases with 61% of symptomatic male cases and 35% Hispanic. The symptom onset of our cases was noted to range from July 29 to September 27, 2004 and area of likely WNV acquisition was also consistent with the adult case data for LAC (Figure 1).

It is also notable that of our 11 pediatric cases, only three were diagnosed at their primary medical office visit, and eight were seen in an ER with three subsequently admitted to the hospital. The high rate of ER evaluation may speak to the fever and rash presentation that made these cases appear very ill. It was also interesting that in four cases WNV testing was performed upon strong parental urging.

The diagnosis of WNV infection was based on clinical symptoms consistent with WNV fever, meningitis, and encephalitis and accepted WNV laboratory testing. The most common method for diagnosis of WNV infection utilized the serum IgM capture ELISA. The WNV ELISA is Food and Drug Administration approved with demonstrated sensitivities of 90% to 100% demonstrated, whereas specificity has been reported at 92% due to cross-reactivity among flaviviruses and enteroviruses [13]. It is notable that only acute serologies were obtained for our cases and convalescents specimens were not obtained which is a



weakness in this case series. However, in six of the cases, PRNT was carried out as the accepted gold standard of WNV testing [10].

Although a massive public information campaign was cooperatively put in place by the LAC Public Health Department, the State of CA Department of Health Services, and the local mosquito abatement districts, upon questioning the parents of these cases, none of them admitted to mosquito repellent usage or encouraging their children to wear long sleeved clothing. It's possible the message about using DEET-based repellents did not reach these parents.

Public Health Implications: In July of 2004, WNV was added to the list of reportable diseases to the LAC Department of Health Services. In LAC reporting of dead birds, mosquito breeding sites and areas with water accumulation are strongly encouraged. The LAC Public Health Department has established a hotline to encourage the public to report dead bird sightings directly to the LAC Veterinary Public Health Section. In addition, local mosquito and vector control programs in LAC collect mosquitoes for speciation and WNV and other arboviral disease infection. Through these measures, it may be possible to improve WNV surveillance. It is predicted that WNV will remain endemic in most areas of the US, thus it is important that all clinicians become aware of the clinical presentation of WNV infection in children so that accurate diagnoses can be made and appropriate reporting can be done.

REFEFENCES

1. Nash D, Mostashari F, Fine A, et al. The outbreak of West Nile virus infection in the New York City area in 1999. *N Engl J Med* 2001; 344(24):1807-14.
2. Petersen LR, Marfin AA, Gubler DJ, West Nile virus. *JAMA* 2003; 290(4):524-8.
3. Buck PA, Sockett P, Barker IK, et al. West Nile virus: surveillance activities in Canada. *Annals of Epidemiology* 2003; 13:582.
4. Estada-Franco JG, Navarro-Lopez R, Beasley DE, et. al. West Nile virus in Mexico: evidence of widespread circulation since July 2002. *Emerg Infect Dis* 2003; 9:1604-8.
5. Statistics, Surveillance, and Control: 2003 West Nile virus activity in the United States. Available at: www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount03_detailed.htm.
6. Reisen W, Lothrop H, Chiles R, et. al. West Nile virus in California. *Emerg Infect Dis* 2004; 8:1369-78.
7. CA West Nile Virus. West Nile Virus 2003 human cases as of October 15, 2003 [CA West Nile Virus web site. Available at: www.westnile.ca.gov. Accessed December 21, 2004.
8. CA West Nile Virus. West Nile virus 2004 human cases as of December 20, 2004 [CA West Nile Virus web site. Available at: www.westnile.ca.gov. Accessed December 21, 2004.
9. Sampathkumar P, West Nile virus: epidemiology, clinical presentation, diagnosis, and prevention. *Mayo Clin Proc* 2003; 78(9):1137-43.
10. Campbell GL, Marfin AA, Lanciotti RS, Gubler DJ, West Nile virus. *Lancet Infect Dis* 2002 Sep;2(9):519-29.
11. CDC. Acute flaccid paralysis syndrome associated with West Nile virus infection—Mississippi and Louisiana, 2002. *MMWR* 2002; 51:825-828.
12. Hayes EB, O'Leary DR, West Nile virus infection: A pediatric perspective. *Pediatrics* 2004; 113(5):1375-81.
13. Yim R, Posfay-Barbe K, Nolt D, et al. Spectrum of clinical manifestations of West Nile virus infection in children. *Pediatrics* 2004; 114 (6):1673-1675.
14. Dan O'Leary, CDC, personal communication.
15. Watson JT, Pertel PE, Jones RC, et al. Clinical characteristics and functional outcomes of West Nile fever. *Ann intern Med* 2004; 141:360-365.
16. Weinberger MD, Pitlik SK, Gandacu D, et al. West Nile fever outbreak, Israel, 2000: Epidemiologic aspects. *Emerg Infect Dis* 2001; 7:686-691.
17. Chowars MY, Lang R, Nassar F, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. *Emerg Infect Dis* 2001; 7:675-678.
18. D. Ferguson. Rash caused by West Nile virus. 2005 National conference on West Nile virus in the United States February 8-9, 2005. San Jose, California: American Society for Microbiology, 1998.