
Use of an Enhanced Surveillance System for Encephalitis and Aseptic Meningitis for the Detection of Neurologic Manifestations of Dengue in Puerto Rico, 2003

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Dengue infection has been implicated as a cause of neurologic manifestations since the beginning of the 20th century. An enhanced surveillance system for encephalitis and aseptic meningitis developed by the Puerto Rico Department of Health in collaboration with the Dengue Branch, Centers for Disease Control and Prevention, identified eleven laboratory positive dengue patients presenting with neurologic manifestations in 2003. Anti-dengue IgM antibody was detected in serum of eight patients and in cerebrospinal fluid of one patient. DENV-2 and DENV-3 were isolated from the serum of one patient each. All patients were negative for serologic markers of West Nile Virus and St. Louis encephalitis. Nine

(82%) of the 11 patients had symptoms compatible with encephalitis. Their median age was 46 years (range: 9 months - 82 years) and five were males. Symptoms included severe headache, seizures, altered mental status, confusion, and coma. A motor disorder (upper extremities weakness and Guillain Barré Syndrome, respectively) occurred in two additional patients. Most patients recovered but there were two fatalities. Neurologic manifestations of dengue were rarely reported in Puerto Rico until the institution of enhanced surveillance, which resulted in the recognition of severe and fatal cases.

Keywords: Dengue, Neurologic manifestations of dengue, Dengue encephalitis, Puerto Rico

Although dengue fever (DF) (fever, myalgia, arthralgia, retro-orbital pain, and rash) and dengue hemorrhagic fever (DHF) (fever, hemorrhage, thrombocytopenia, and excessive vascular permeability) are well-known presentations of an acute dengue infection, the clinical manifestations of dengue may also include neurologic complications, which are infrequently reported (1). Although rare, these neurologic complications have been recognized since the beginning of the twentieth century and reported in almost every country in Asia and in many countries in the Americas (2).

At least three types of neurologic manifestations have been reported with DF or with DHF: non-specific symptoms such as headache, dizziness, delirium, drowsiness, sleeplessness, and restlessness; specific severe syndromes such as depressed sensorium, lethargy, confusion, seizures, meningismus, paresis, or coma; and

delayed syndromes such as paralysis of lower or upper extremities or larynx, seizures, tremors, amnesia, loss of sensation, manic psychosis, depression, dementia, and Guillain Barré. These symptoms are also produced by other viral encephalitides. Most patients with neurologic complications associated with dengue recover without any neurologic sequelae and while any virus serotype may be involved, DENV-2 and DENV-3 have most often been reported (3).

The frequency with which acute dengue infection presents as a neurologic illness is still undefined. In Indonesia, 70% of 30 virologically confirmed fatal dengue infections presented with one or more neurologic signs, and 7% were admitted for viral encephalitis, which was listed as the cause of death (4). In Vietnam, a study showed that 5% of patients admitted to a neurology ward with suspected central nervous system infections from 1994 to 1998 were in fact infected with dengue virus (5), while in Thailand, 18% of children admitted to a hospital with encephalitis-like illness between 1996 and 1998 were confirmed cases of dengue infection (6).

In Puerto Rico, few descriptions of cases with neurologic manifestations of dengue infection have been published (7-10). King in a description of a dengue epidemic in 1915 reported that he suffered from paresthesia of the upper extremities, which lasted several months after onset of an acute dengue infection, and described another

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The authors have no conflict of interest to disclose.

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patient who developed sensory and motor symptoms in some branches of the brachial plexus (7). In the dengue epidemic of 1977, two patients with aseptic meningitis and one patient with convulsions were documented (8). In 1982, a patient with altered mental status, seizures, progressive spastic paraparesis, and coma, and a patient with acute polyneuritis were described (9-11) Another patient with encephalopathy, cranial nerve palsy, and hepatitis occurring during a secondary dengue infection was described in 1985 (10).

In this article we discuss the clinical manifestations and outcome of eleven patients with a laboratory diagnosis of dengue infection presenting with neurologic manifestations, identified during 2003, after the implementation of an enhanced surveillance system for encephalitis and aseptic meningitis in Puerto Rico.

Methods

Enhanced surveillance system for encephalitis and aseptic meningitis

In late 2002, in preparation for the possible introduction of West Nile Virus (WNV) to Puerto Rico, an enhanced surveillance system for encephalitis and aseptic meningitis was implemented by the Puerto Rico Department of Health (PRDH) and the Dengue Branch, Centers for Disease Control and Prevention (CDC). This enhancement of the passive surveillance system for encephalitis and aseptic meningitis consisted of two main activities: increasing clinical awareness and laboratory capacity for WNV testing.

A total of 429 physicians and health care officials in the eight health regions of Puerto Rico were trained on the implementation of the improved surveillance system for encephalitis and aseptic meningitis through voluntary attendance at special training lectures. Educational materials (fact sheets and press releases) prepared in Spanish by PRDH and CDC staff included a brief overview of the diagnostic criteria, case management, and updated disease reporting procedures for encephalitis and aseptic meningitis. Physicians from private and public hospitals throughout the island were requested to submit serum and CSF specimens of all patients with encephalitis-like syndromes, aseptic meningitis (in patients aged 17 years or more), acute flaccid paralysis and/or other suspected infections of CNS without an etiology. These specimens were accompanied by a WNV encephalitis human case surveillance form in which demographic and clinical data of suspected patients were collected. To complete the report, the submitting physician also submitted to the PRDH the standard case reporting form for diseases of mandatory notification. Specimens submitted were tested

for anti-WNV IgM antibodies (12) and to the usual battery of dengue diagnostic tests (see below).

Clinical case definitions

Reported cases were classified, based on the physician's reported diagnosis or symptoms, into three clinical syndromes based on the National Surveillance Case Definitions for Arboviral Encephalitis/Meningitis (11). No laboratory confirmation or laboratory tests were required for this case classification.

1. Encephalitis-like syndrome: a person reported to the PRDH by a health care professional because of an illness diagnosed as encephalitis, or patients with reported fever, headache, and altered mental status ranging from confusion to coma, with or without additional signs of brain dysfunction (e.g., paresis, cranial nerve palsies, sensory deficits, abnormal reflexes, seizures or focal neurologic deficit). Since no laboratory results are part of this clinical case definition, patients with either encephalopathy or encephalitis could be classified as encephalitis-like syndrome.
2. Aseptic meningitis: a person reported to the PRDH by a health care professional because of an illness diagnosed as aseptic meningitis, or patients with reported fever, headache, and neck stiffness without alteration in the level of consciousness.
3. Motor disorder: a person reported to the PRDH by a health care professional because of an illness diagnosed as a motor disorder or patients with reported fever and acute paralysis or severe muscular weakness without an altered level of consciousness (e.g., acute flaccid paralysis, Guillain-Barré Syndrome).

Laboratory diagnosis of dengue or WNV encephalitis or aseptic meningitis

A laboratory positive case of WNV or dengue with neurologic manifestations was defined as a clinical case of encephalitis-like syndrome, aseptic meningitis or motor disorder submitted to the Dengue Branch for laboratory testing with positive virologic or serologic tests on serum or CSF as described below.

1. Virus-positive cases were defined as patients with dengue virus isolation from serum, CSF or autopsy tissue samples (WNV isolation was not then available at the Dengue Branch) (13).
2. Antibody-positive cases were defined as patients with IgM seroconversion from negative to positive in paired serum samples or a single serum or CSF sample positive for anti-WNV or anti-dengue IgM (14).
3. Single specimens negative for dengue virus or for anti-dengue or anti-WNV IgM antibody, if collected

5 or fewer days from the onset of symptoms, were considered non-diagnostic, and the case was categorized as indeterminate.

IgM positive dengue patients with neurologic manifestations were tested for anti-flavivirus IgG ELISA to evaluate for primary or secondary infection. Plaque reduction neutralization tests against the four dengue virus serotypes, WNV, and St. Louis encephalitis (SLE) were carried out to evaluate the possibility of cross-reactivity between antibodies against the different flaviviruses (15).

Hospital record review

The hospital records of laboratory positive dengue patients were reviewed (author EGR), as part of the surveillance system's procedures regarding unusual manifestations of dengue infection. The infection control nurses of hospitals with laboratory positive patients were contacted and a request to review the medical record of these patients was submitted in accordance with the confidentiality rules of each hospital. The information obtained from the medical records included medical history, the presence of concomitant diseases, detailed medication use, disease progression, in hospital complications, and standard clinical and laboratory test results.

Results

During 2003, the first year of enhanced surveillance for encephalitis and aseptic meningitis in Puerto Rico, diagnostic samples from 86 patients with suspected acute neurologic infection were submitted to the Dengue Branch for WNV and dengue testing. The median age was 37 years (range; one month to 90 years) and 47 (55%) were males. Specimens were submitted from 39 out of 78 municipalities in Puerto Rico, and from 31 (54%) hospitals throughout the island. Two patients were excluded from further analysis due to the absence of neurologic symptoms.

The reports (Table 1) included 34 patients with encephalitis-like syndrome, 25 patients with aseptic meningitis, and 11 patients with motor disorders. Fourteen patients had other diagnoses such as bacterial meningitis, myositis, or sepsis which could explain their neurologic symptoms. All patients were negative for serologic markers of an acute WNV infection but eleven showed evidence of acute dengue infection. Of these eleven, most (9, 82%) came from or near the metropolitan areas of San Juan, nine (82%) presented symptoms compatible with encephalitis, none with aseptic meningitis, and two (18%) had motor disorders. The nine patients with dengue and encephalitis-like illness represented 26% of all patients

reported with encephalitis-like syndrome, and the two patients with motor disorder represented 18% of all cases with motor disorders.

Table 1. Clinical classification and laboratory diagnosis of reported cases of encephalitis and aseptic meningitis, Puerto Rico, 2003

Clinical classification	Laboratory diagnosis			Totals
	Dengue	West Nile Virus	Indeterminate	
Encephalitis-like syndrome (%)	9 (26)	0	25 (74)	34
Aseptic meningitis (%)	0	0	25 (100)	25
Motor disorder (%)	2 (18)	0	9 (82)	11
Other diagnoses (%)	0	0	14 (100)	14
Totals	11	0	73 (87)	84

A summary of the demographic and clinical findings of the nine patients with encephalitis-like syndrome is shown in Table 2. The median age was 46 years with range from 9 months to 82 years. Most (8/9, 89%) patients were adults and five (55%) were males. A dengue diagnosis was suspected in only 4 (2 dengue fever and 2 DHF) of the 9 patients. In four cases (44%) the onset of neurologic symptoms occurred with the onset of fever, and in the rest from one to seven days thereafter. Reported neurologic symptoms ranged from severe headache and seizures to altered mental status, confusion, and coma. Motor involvement, including lower extremity weakness, hemiparesis, and paraplegia, was also present in three cases with encephalitis-like syndrome. Although most patients recovered, there was one patient with residual weakness at least two months after onset, and two fatalities; one patient died from pneumonia related to prolonged hospitalization and another patient arrived in coma and died 4 days after being hospitalized.

Disorientation, decreased sensorium, and coma were present in one patient each among those with reported altered mental status or changes in consciousness. Non-febrile, generalized tonic-clonic seizures were reported in three patients. Cognitive disorders were also reported, including poor concentration, fluctuation of mental status, and incoherent speech. All of these symptoms occurred during the acute phase of the disease.

Clinical data from the two laboratory positive dengue patients reporting a motor disorder without any alteration of the level of consciousness are summarized in Table 3. Both patients were adult females. One patient was diagnosed with dengue fever and presented with weakness of upper extremities and paresthesia during the acute phase of the infection. The other patient developed left

Table 2. Demographic and clinical features of laboratory positive dengue patients with encephalitis-like syndrome, Puerto Rico, 2003

Patient	Age/ Sex	Initial Dengue Diagnosis	Onset of Neurologic Symptoms	Symptoms or Clinical Diagnosis	Imaging Studies Results (days‡)	Dengue Test Results		Outcome
						Serum	CSF	
1	37/F	DF	With fever	Severe headache	-	IgM +	N/A	Recovered
2	31/M	DHF	With fever	Severe headache	-	IgM +	N/A	Recovered
3	9mo/F	DHF/DSS	4 days after fever onset	Seizures	Normal* (1)	DENV-2	N/A	Recovered
4	19/M	DF	2 days after fever onset	Seizures	Normal* (1)	DENV-3	N/A	Recovered
5	78/M	None	With fever	Hypoactivity, disorientation, prominent bilateral plantar response, left side hemiparesis	Abnormal enhancement of right temporal and parieto-occipital lobes† (10)	IgM +	N/A	Residual weakness
6	46/F	None	With fever	Altered mental status confusion, seizures	-	IgM +	N/A	Recovered
7	82/M	None	One day after fever onset	Altered mental status, confusion	-	IgM +	N/A	Recovered
8	76/M	None	One day after fever onset	Altered mental status, paraplegia cognitive deficits	T3-T4 thoracic myelitis*, transverse myelitis (3); Normal*† (9)	N/A	IgM+	Prolonged hospitalization- Fatal
9	49/F	None	One week after fever onset	Coma (only responding to noxious stimuli), weakness of lower extremities	Normal*† (9)	IgM +	N/A	Fatal

‡= days elapsed after onset of symptoms; CSF = cerebrospinal fluid; F= female, M= male; DF= dengue fever, DHF = dengue hemorrhagic fever, DSS= dengue shock syndrome; "-" = not on record; N/A = not available; * = Computerized tomography scan; † = Magnetic resonance imaging

Table 3. Demographic characteristics and clinical manifestations of laboratory positive dengue patients with motor disorders, Puerto Rico, 2003

Patient	Age (years)	Sex	Dengue Diagnosis	Onset of Neurologic Symptoms	Symptoms or Clinical Diagnosis	Imaging Studies Results (days‡)	Dengue test result		Outcome
							Serum	CSF	
1	50	F	DF	2 days after onset of fever	Upper extremities weakness and paresthesias	N/A	IgM +	N/A	Recovered
2	47	F	None	Two weeks after viral symptoms	Left side facial paralysis, right side weakness, decreased sensation, paresthesia - Guillain- Barré Syndrome	Normal* (2)	IgM +	N/A	Rehabilitation

‡ = days elapsed after onset of symptoms; CSF = cerebrospinal fluid; F = female; DF = dengue fever; N/A = not available; * = Computerized tomography scan

facial paralysis two weeks after an unspecified viral illness and a week later developed a right lower extremity weakness with progression towards the left side and the upper body, which was clinically diagnosed as Guillain Barré Syndrome. Motor symptoms were therefore reported in two patients without altered mental status and in three patients with encephalitis-like syndrome. In all cases, symptoms started as an asymmetric paralysis with sensory involvement (including paresthesias and

decreased sensation). In two patients decreased reflexes were documented, including the patient with Guillain-Barré Syndrome.

Dengue diagnoses were established through positive serologic tests in serum of eight patients, positive anti-dengue IgM antibody in CSF in one case, and isolation of DENV-2 and DENV-3 in serum in two patients (the predominant viruses in circulation in Puerto Rico in 2003). There was no evidence of WNV or SLE infection in these

patients. There were four primary infections (1 DENV-1, 1 DENV-2, and 2 with unknown serotype), four secondary infections, and one recent dengue infection with equivocal immune (primary or secondary) response.

Hospital laboratory analysis of CSF was available in five patients (Table 4). Most patients presented with elevated protein (4/5), normal glucose (3/5) and mild pleocytosis (3/5). In the CSF sample submitted for dengue testing, anti-dengue IgM antibodies were found. Other laboratory data obtained from the hospital record review revealed that only two patients fulfilled the four clinical criteria for DHF diagnosis (fever, bleeding, thrombocytopenia, and hemoconcentration). Hyponatremia (128mEq/L) was documented in one these DHF patients. Liver function tests were available in six patients. Three patients showed mild to moderate elevations of aspartame aminotransferase (AST) (range: 54 – 225U/L) and alanine aminotransferase (ALT) (range: 118 – 354U/L).

syndrome. Besides the expected changes in the level of consciousness, motor disorders also occurred in these patients including hemiparesis, paraplegia, and transverse myelitis. Also, two other patients had isolated motor disorder including one patient with Guillain-Barré, a post infectious polyneuropathy which had previously been reported with dengue (16). As reported by Solomon, et al. (5) from their studies in Vietnam, and Kankirawatana, et al. (6) from Thailand, the characteristic features of dengue fever or DHF were absent in most (7/11) patients, including the more severe neurologic cases. In the absence of this surveillance system, dengue as a possible cause of neurologic symptoms would probably not have been considered, since most physicians' perception of severe dengue has focused on hemorrhage and shock.

In our case series, most of the laboratory-positive dengue patients were adults. Age has been implicated as a risk factor for severe manifestations of dengue (17),

Table 4. Cerebrospinal fluid test results of laboratory positive dengue patients, Puerto Rico, 2003

Clinical Disease	Cerebrospinal fluid				
	Protein (nl 15-45 mg/dL)	Glucose (nl 50-80 mg/100dL)	WBC (nl 0-5)	RBC (nl 0-5)	Dengue Test
Guillain-Barré Syndrome	192	85	5	1193	Not submitted
Cognitive deficit, Transverse myelitis	80	53	30	7	IgM +
Encephalopathy, Hemiparesis	45	122	10	94	Not submitted
Encephalitis	137	70	3	800	Not submitted
Encephalitis	73	60	10	5	Not submitted

nl = normal values; WBC = white blood cell count; RBC = red blood cell count

Discussion

Although neurologic manifestations of dengue have been documented from nearly every country in Asia, the Pacific Islands, and the Americas, in Puerto Rico only few cases were reported until the implementation of the enhanced surveillance system for encephalitis and aseptic meningitis. This system enabled the identification and study of the demographic characteristics, clinical course, and outcome of the first case series of laboratory-positive dengue patients with neurologic manifestations in Puerto Rico.

The clinical manifestations reported by the patients identified through this surveillance system were consistent with previous reports in the literature (1-11). Neurologic symptoms included central and peripheral nervous system involvement and varied in severity and outcomes. Of the 11 dengue patients identified in the first year of this surveillance system, nine patients had an encephalitis-like

but how age relates to the presence of neurologic manifestations during an acute dengue infection has not been extensively evaluated. In our case series, motor involvement was exclusively present in adults. However, children are probably underrepresented in our surveillance system, established in anticipation of the possible introduction of WNV to Puerto Rico. Since neurologic complications of WNV are most commonly seen in older adults, the submitting physicians could be more likely to submit blood and CSF specimens for testing in older adults than in children.

The clinical descriptions presented in this case series were limited by the source of data. We relied on the information collected by physicians in the medical records, some without a formal evaluation by a neurologist, variable use of clinical diagnostic tests, few imaging studies, and little evaluation for other etiologic agents. In addition autopsy was not performed on fatal cases. In this report, we used the term encephalitis-like syndrome to include those patients with clinical evidence of CNS involvement, without making a distinction between encephalitis and encephalopathy. Unfortunately, we have a small number of CSF results and specimens for analysis, limiting our capacity to reach such distinction. CSF was available for testing in only one patient who developed transverse

myelitis and other severe neurologic manifestations. In this patient anti-dengue IgM antibodies were detected in CSF. Although several reports have documented intrathecal anti-dengue antibody or isolation of dengue virus from CSF or CNS tissue, supporting the hypothesis of direct central nervous system invasion, (18-22) blood contamination instead of direct invasion of the CNS has been argued as a possible explanation of those findings. In our patient, the CSF cell count suggested that the lumbar puncture was not traumatic. There was mild pleocytosis and increased CSF protein, and no metabolic derangement reported upon admission, suggesting true encephalitis.

The frequency of dengue among patients with encephalitis-like syndromes (26%) was higher than the frequency reported in other studies (5 to 20%) (4-5). A coincidental finding, due to a high incidence of dengue transmission in Puerto Rico, might be argued as a plausible explanation for this, but confirmatory evidence was present in two patients in whom dengue virus was isolated, and anti-dengue IgM antibodies were detected in the CSF of another patient.

Antibody cross-reactivity with another flavivirus can also be proposed as an explanation for these findings. However, neutralization tests against WNV and SLE were negative, and at the time of this study there was no epidemiologic or laboratory evidence of the presence of other flavivirus in Puerto Rico. In addition, neutralizing antibodies present in primary infections identified DENV-1 and DENV-2 serotypes. Therefore, even when we only have presumptive evidence of dengue infection through serology in most cases, the consistency to previous documented neurologic symptoms among dengue patients is highly suggestive of dengue as the cause of these manifestations.

In summary, neurologic manifestations of dengue infection appear to be an event more frequent than what was previously recognized in Puerto Rico. Although these manifestations are still a rare complication of an acute dengue infection, dengue should be considered as part of the differential diagnosis of patients presenting with fever and neurologic symptoms in dengue-endemic areas, regardless of the presence of classical dengue symptoms, and physicians should be encouraged to submit serum and CSF specimens for dengue diagnosis in these cases.

Resumen

La infección por el virus de dengue ha estado implicada como causa de manifestaciones neurológicas desde los inicios del siglo XX. Un sistema de vigilancia epidemiológica intensificada para encefalitis y meningitis aséptica desarrollado por el Departamento de Salud

de Puerto Rico en colaboración con “Dengue Branch, Centers for Disease Control and Prevention” identificó 11 pacientes con diagnóstico microbiológico positivo para dengue que presentaron manifestaciones neurológicas en 2003. Se detectó IgM antidengue en suero en 8 de ellos y en líquido cerebroespinal en 1. Se aisló virus DENV-2 y DENV-3 del suero de un paciente cada uno. Las pruebas para marcadores serológicos de infección por virus West Nile y encefalitis de St. Louis fueron negativas en los 11. Nueve (82%) de los 11 pacientes manifestaron síntomas compatibles con encefalitis. Su edad mediana fue 46 años (rango: 9 meses-82 años) y 5 eran varones. Los síntomas incluyeron dolor de cabeza fuerte, convulsiones, cambio en el estado mental, confusión y coma. En otros 2 pacientes se documentó un problema estrictamente motor (debilidad de extremidades superiores y síndrome Guillain Barré, respectivamente). Dos fallecieron. Las manifestaciones neurológicas del dengue se notificaron con baja frecuencia en Puerto Rico hasta la instauración de vigilancia intensificada, que resultó en el reconocimiento de casos graves y fatales.

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