Dengue Infection in Patients Presenting with Neurological Manifestations in a Dengue Endemic Population

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ABSTRACT

The evaluation of the contribution of neurological dengue in suspected central nervous system (CNS) viral infections is essential to better understand the impact of neurological dengue on morbidity and mortality in dengue endemic regions such as Jamaica. For this study, 401 cases of suspected viral CNS infections were investigated for evidence of dengue infection. The frequency of neurological dengue among these CNS cases was found to be 13.5% (54/401). Fifty-three cases were confirmed serologically by haemagglutination inhibition assay (HI) and IgM antibody (ELISA) and the virus was isolated in one case only. Clinical manifestations among dengue positive CNS cases included encephalitis in 51.8% (28/54), meningitis in 33.3% (18/54), seizures in 11.1% (6/54) and acute flaccid paralysis/Guillain-Barré syndrome in 3.7% (2/54). The clinical diagnosis of dengue neurological infection corresponded with laboratory confirmation in 22.2% (12/54) of cases only. Deaths occurred in 3.7% (2/54) of cases and were associated with patients with dengue neurological infection. The high risk of dengue among patients with suspected viral CNS infections in this study supports the need for an increased index of suspicion of dengue in patients presenting with neurological manifestations in dengue endemic countries.

Infección de Dengue en Pacientes que se Presentan con Manifestaciones Neurológicas en una Población con Dengue Endémico

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RESUMEN

La evaluación de la contribución del dengue neurológico en las infecciones virales sospechadas del sistema nervioso central (SNC) resulta esencial para un mejor entendimiento del impacto del dengue neurológico en la morbilidad y mortalidad en regiones donde el dengue es endémico tales como Jamaica. Para este estudio 401 casos de infecciones virales sospechadas del SNC fueron investigados en busca de evidencia de infección por dengue. Se haló entonces que la frecuencia del dengue neurológico entre estos casos de SNC, fue de 13.5% (54/401). Cincuenta y tres casos fueron confirmados por serología mediante ensayos de inhibición de hemaglutinación (IH) y ELISA para la detección de anticuerpos IgM, siendo el virus aislado sólo en un caso. Las manifestaciones clínicas entre los casos que resultaron positivos al dengue, incluyeron encefalitis en 51.8 % (28/54), meningitis en 33.3% (18/54), convulsiones en 11.1% (6/54) y parálisis facial aguda/síndrome Barré Guillain en 3.7% (2/54). El diagnóstico clínico de infección neurológica por dengue estuvo en correspondencia con la confirmación del laboratorio sólo en el 22.2% (12/ 54) de los casos. Se produjeron muertes en el 3.7% (2/54) de los casos, las cuales estuvieron asociadas con pacientes con infección neurológica por dengue. El alto riesgo de dengue entre los pacientes con sospecha de infecciones virales de SNC en este estudio, apunta a la necesidad de aumentar el índice de sospecha de dengue en pacientes que se presentan con manifestaciones neurológicas en países donde el dengue es endémico.

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INTRODUCTION

The documentation of neurological manifestations of dengue virus infection seen in previously diagnosed patients has provided a valuable foundation for the understanding of this disease spectrum (1–9). The more difficult task of suspecting and identifying this infection in patients presenting initially with varying neurological manifestations will depend on the knowledge and understanding of the frequency and clinical manifestations of dengue related neurological syndromes. This study was conducted to evaluate the frequency of dengue infection in patients presenting with suspected viral central nervous system (CNS) infections and to review the accuracy of diagnosis of dengue infection in such patients in Jamaica, a country in which dengue is endemic and all 4 dengue serotypes have been known to occur (9–14).

SUBJECTS AND METHOD

This study was conducted at the Department of Microbiology, University of the West Indies (UWI)/University Hospital of the West Indies (UHWI) in the Faculty of Medical Sciences (FMS), Mona, with the approval of the UHWI/UWI/FMS Ethics Committee. Specimens and clinical data submitted from cases with suspected viral CNS infections between 1994 and 2004 were reviewed for evidence of dengue infection. Basic information was obtained from request forms and laboratory data whilst additional clinical information was obtained from the patient's records.

Neurological manifestations of suspected viral CNS cases included meningitis, encephalitis, seizures, transverse myelitis, acute flaccid paralysis/Guillain-Barré syndrome (AFP/GBS) and peripheral neuropathies.

Specimens included in the study were those submitted from all patients presenting with neurological manifestations and in whom the clinician had a high index of suspicion of viral CNS infection. Specimens excluded from the study were those submitted from patients presenting with neurological manifestations with intracranial lesions/masses and/or evidence of concurrent bacterial or fungal CNS infection.

Virus isolation was confirmed by culture using acute serum which was inoculated into C6/36 mosquito cell lines (9). Confirmation of the virus was done using an indirect immunofluoresence assay (9). Isolates were referred to a CDC reference laboratory in Puerto Rico for serotype identification and molecular characterization.

An acute serum was used to detect Dengue IgM antibody. Dengue infection was also confirmed by a four fold or greater seroconversion in the haemagglutination inhibition assay (HI). Seasonal variation was analysed using Krothman's method (15).

RESULTS

Specimens were submitted to the virology laboratory from Type A and B (major regional) hospitals throughout the island. The samples investigated included 401 (95% confidence) specimens which were randomly selected from specimens submitted in 1962 from suspected cases of viral CNS infection.

Clinical manifestations among the 401 cases of suspected viral CNS infection included: encephalitis 126 (31%), meningitis 174 (43%), seizures 1 (0.2%), transverse myelitis 51 (13%) and acute flaccid paralysis/Guillain-Barré syndrome (AFP/GBS) 31 (7.7%).

Laboratory evidence of dengue infection was confirmed in 54/401 (13.5%) cases of suspected viral CNS infection (Table 1). The cases were evenly distributed between

Table 1: Neurological manifestations in 54 dengue CNS cases

Manifestation	No. Cases (%)
Encephalitis	28 (52.8)
Meningitis	18 (33.9)
Seizures	6 (11.3)
AFP/GBS*	2 (3.7)
Encephalitis and seizure**	1 (1.8)
Seizure and paralysis**	1(1.8)

*AFP/GBS = Acute flaccid paralysis/Guillain-Barré syndrome

**Total > 54 as two cases indicated by ** had more than one manifestation

males and females with a mean age of 9.6 years [range 8 months – 49 years] (Fig. 1). Serological confirmation by HI

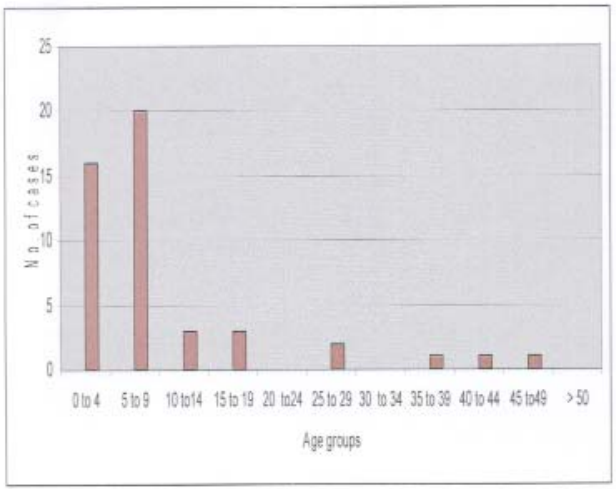

Fig. 1: Age distribution of suspected viral CNS cases with confirmed dengue virus infection (n = 54).

testing and IgM antibody detection was obtained in 53 cases and virus isolation from a patient's serum in one case only. This isolate was subsequently confirmed as Dengue serotype-2 by molecular typing.

There was no gender difference noted among confirmed positive cases. Clinical manifestations among these 54 dengue positive CNS cases included encephalitis 28 (51.8%), meningitis 18 (33.3%), seizures 6 [1 with encephalitis, 1 with paralysis] (11.1%), AFP/GBS 2 (3.7%).

The clinical diagnosis of dengue neurological infection was confirmed with laboratory evidence in 12/54 (22.2%)

cases and these cases had features of DHF in addition to the neurological presentations. There were 2/54 (3.7%) deaths associated with patients with dengue neurological infection. Both fatalities presented clinically with features of encephalitis and one case with hepatic involvement.

Cases of dengue neurological infection were detected throughout the year with an increased number of cases occurring in May and August. Seasonal variation was further analyzed using Krothman's online method (15). This method automatically generates a fitted frequency graph and estimates the time of peak using an adjusted monthly mean. Based on this analysis, the time of peak dengue neurological cases was August 22 (Tables 2 and 3, Fig 2).

Table 2: Monthly distribution of dengue neurological cases

Month	No. Positive CNS Cases* (%)**	Total Dengue Cases (n=401)
Jan	5 (14)	36
Feb	1 (4)	27
Mar	5 (15)	34
Apr	2 (7)	29
May	5 (26)	19
June	4 (10)	39
July	4 (13)	30
Aug	3 (20)	15
Sept	8 (28)	29
Oct	7 (27)	26
Nov	3 (8)	39
Dec	7 (9)	78
Total	**54**	**401**

*** n = 54 No. = Number**
**** of total monthly dengue cases**

Table 3: Seasonal analysis of dengue CNS cases at the UWI

Peak/Low Ratio = 1.942		
CI:	**Lower**	**Upper**
90%	1.000	3.931
95%	1.000	4.500
	Time of Peak	Aug 22 (232°)
	Hemi-amplitude	0.3201
	Adjusted monthly mean	4.500

DISCUSSION

The incidence of neurological manifestations in patients diagnosed with Dengue Haemorrhagic Fever (DHF) and severe Dengue has been documented to vary from 3% (24/858) in prospective DHF studies to 25% in retrospective studies (2, 4). Studies referring to the identification of dengue infection in patients presenting with neurological manifestations and suspected viral infection document the incidence of dengue neurological disease to vary from 18% (8/44) in patients presenting with encephalitis in dengue endemic regions to 4.2% of all cases of dengue infection (4).

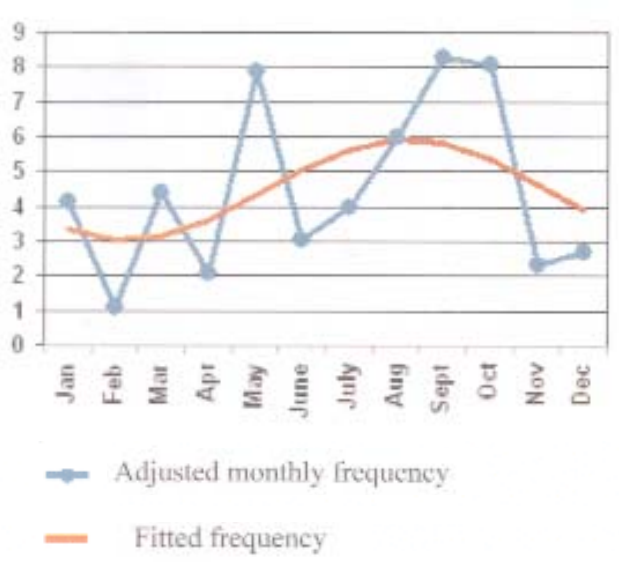

Fig. 2: Seasonal variation of dengue neurological cases documented at the Department of Microbiology, University of the West Indies.

Encephalitis is known to be one of the more frequent presenting manifestations of dengue neurological disease (4). The high frequency of occurrence of dengue infection in encephalitic patients (18%) in an endemic region or during an epidemic period is therefore possible and our finding of an incidence of 13.2% is higher than that of other comparable studies with an incidence of 4.2% (4). The finding of the higher incidence may be because this study investigated dengue infection among all suspected viral CNS manifestations. There are not many studies documenting meningitis as a feature of dengue neurological disease (4, 7). The incidence of meningitis among serologically confirmed dengue cases has been reported to vary from 24.4% to 30%. Clinical signs noted among such patients include drowsiness and nuchal rigidity as a feature of meningitis or meningoencephalitis (4, 7). In this study, meningitis occurred in 33% of patients with dengue neurological infection. Dengue neurological presentation was seen most frequently in the paediatric age group as with earlier studies (1).

Seizures and pyramidal tract signs have been documented to occur in 43–63.3% and 16.7–36.7% of dengue neurological disease respectively (4, 7). Seizures occurring in dengue-infected patients have been documented to be associated with intracerebral haemorrhages (3). Neurological dengue infections have also been shown to result in non-specific electroencephalography (EEG) slowing, however other conditions such as seizures, metabolic encephalopathy or structural brain lesion may also cause these changes (16).

The spinal cord is infrequently involved in dengue infection but AFP/GBS was seen in 3.7% of cases but no cases of acute transverse myelitis were seen. Seet *et al* postulated that flaccid paralysis may be associated with acute

parainfectious dengue infection and spastic weakness with postinfectious dengue infection (6).

Mortality rates reported in cases of neurological dengue and severe dengue infection ranged from 5% to 8.35% (2, 4, 7). Kamath *et al* also noted that most neurological events were unrelated to the perfusion status (shock or otherwise) of subjects studied and were found to be the commonest cause of death in complicated dengue infections (2). In this study, the fatality among dengue-infected patients with CNS manifestations was 6.6%.

Cases of dengue neurological infection were detected throughout the year in keeping with endemicity of the virus in Jamaica but most neurological dengue infections were detected in late August. This finding corresponds to the expected dengue seasonal trend (9, 10) and the stronger relation of dengue infection to temperature changes rather than rainfall (10).

Limitations of this study include the absence of routine molecular detection techniques for dengue virus in blood and CSF, the availability of which may have increased the detection of dengue virus in these specimens (17) and possible inconsistencies in the epidemiological surveillance for cases of dengue fever in the Caribbean (9). The high risk (13.5%) of dengue in patients with suspected viral CNS infection supports the need for an increased index of suspicion of dengue virus infection in patients presenting with neurological manifestations in dengue endemic countries (1, 9, 10).

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