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CENTRAL NERVOUS SYSTEM INVOLVEMENT IN DENGUE VIRAL INFECTION

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ABSTRACT

Neurological manifestations of dengue infection are rare. This review includes data regarding the epidemiology of the disease, neurological manifestations, pathogenesis, diagnosis and prognosis. It is based on 9 original articles and 10 case reports, adding up to 200 cases of dengue fever with neurological manifestations. Relevant cases have been reported from Asia, the Pacific rim, the Americas, the Mediterranean region, and Africa. A wide range of neurological manifestations has been reported. Altered consciousness and seizure are among the more common manifestations. The exact pathogenesis of this disease has not yet been established. However, recent studies hypothesize that the virus is neurotropic. Detection of IgM in CSF using ELISA has a high specificity. Most patients usually recover fully, but some develop neurological sequelae. Mortality ranges from 5-22% across the published literature. Dengue fever should be included in the differential diagnosis of a person presenting with fever and neurological symptoms. This becomes especially important in endemic areas or during epidemics in other areas.

Dengue is an arbovirus belonging to the flavivirus family. It has four serotypes. They all have the mosquito Aedes egypti as their principal vector. Incubation period of these viruses ranges from 2-7 days after which they cause a range of similar clinical syndromes.[1] One hundred million cases of dengue fever (DF) are reported yearly by the World Health Organization (WHO), making it one of the most important viral diseases in the world. WHO has developed a set of criteria that are useful for the diagnosis and grading of dengue infection (Table 1).

Dengue fever is also one of the leading causes of hospitalization and death among children.[2,3] Epidemics of dengue are being seen in almost all countries located within the tropical belt.[4] The increasing incidence of flavivirus infection has been linked to resurgence of the vector A. egypti, as well as to overcrowding and increasing travel.[4]

The relationship between hemorrhagic dengue fever and neurological manifestations was first described in 1976. Since then there have been various case reports and original articles published on this subject. In 1983, Gubler and others recorded neurological disorders associated with dengue from 25 different countries across Asia, the Pacific rim, the Americas, Mediterranean regions, and Africa.[5] In dengue-endemic areas, this infectious agent must be kept in mind when exploring causes of encephalitis and encephalopathy. For the purposes of this article, we reviewed 9 original articles and 10 case reports adding to a cumulative total of 200 cases of dengue fever with CNS manifestations.

EPIDEMIOLOGY

Neurological disorders associated with DF have been reported from 25 different countries representing Asia-Pacific, the Americas, the Mediterranean and Africa. All ages and both sexes are affected by the neurological complications. Cases have been reported among ages ranging from 3 months to 60 years.[6] However, there is a greater incidence among children.

The incidence of neurological symptoms among dengue patients varied from 1% to 25% of all dengue admissions.[4,6,7] In Indonesia, 70% of virologically confirmed fatal dengue infections (n=30) presented with one or more neurological signs, and 7% of those admitted for viral encephalitis turned out to be dengue-infected.[8] In another study, 4.2% of patients with neurological symptoms tested positive for dengue.[4]

TABLE.1
WHO criteria for making a diagnosis of DHF

It is a febrile illness with a platelet count of 100,000x 10e6/l or less and a hematocrit raised 20% or more above the norm.
Grade 1: Positive tourniquet test is the only manifestation
Grade2: Spontaneous bleeding occurs
Grade 3 and 4 are referred to as dengue shock syndromes
Grade 3: narrowing of pulse pressure, circulatory failure and a rapid weak pulse
Grade 4: profound shock and no detectable pulse

TABLE. 2
Manifestations of Dengue infection

Name Of Journal & Year	SEAJ Trop Med 1996(6)	Lancet 2000(4)	Am J Trop Med Hyg2001(11)	SEAJ Trop Med 1999(13)	SEAJ Trop Med(10)
Sample population	42 patients with DHF	383 patients with suspected CNS infection	5400 patients with DHF	30 serologically confirmed dengue patients with CNS manifestations	1493 serologically confirmed dengue patients
Age	4yrs-60yrs	3 months-40yrs	8 months-15yrs	3 months-14yrs	3 months-14yrs
Number with CNS	20 21	27	30	a80	
Neurological manifestations (%)	Altered sensorium (50) Convulsion(70) Decerebration Neck rigidity. Altered consciousness (30)	Reduced consciousness (85.7) Convulsions (43) Spastic paraparesis meningismus	Agitation Generalized seizures (77.8) Coma (96.3) hemiplegia	Altered consciousness (76.7) Seizures (63.3) Pyramidal tract signs(36.7) Meningeal signs(30) Headache(26.7)	Altered consciousness (44) Seizures (67.5)

PATHOGENESIS

Encephalopathy is the most common neurological manifestation. It may result from hypotension, cerebral edema, microvascular and frank hemorrhage, hyponatremia, and fulminant hepatic failure which may be part of Reye's Syndrome.[4,9] These metabolic factors are held responsible for neurological manifestations when the virus or its serological evidence cannot be found in the CSF. Two studies conducted in 2001 on neurological manifestations of dengue came to two different conclusions about the pathogenesis. One was a retrospective study in which all the collected CSF samples came out to be negative for IgM and PCR of dengue.[10] This report suggested that the neurological symptoms were due to metabolic changes rather than neuro-virulence on the part of the etiological agent. Another prospective[11] case-control study found IgM antibodies to dengue in 14 of 22 samples. This study suggests that dengue virus itself has neuro-virulent properties. Clinical studies have therefore established the neuro-virulent properties of DEN-2 subtype dengue infection and DEN-3 subtype dengue infection.[4,8,12,13]

Many cases of true dengue encephalitis have been reported.[12,16] Animal studies have shown a virus-mediated breakdown of the blood-brain barrier.[4,11] In the previous study, negative CSF results may be explained on the basis that the encephalopathy resulted from metabolic abnormalities. Also, titers are lower and shorter-lived in

Immuno-histochemical studies in one case showed infiltration of CD68+ macrophages after breakdown of the blood brain barrier, suggesting that virus-infected macrophages may be one of the pathways by which virus enters the brain.[14] More sensitive diagnostic measures are needed for detecting presence of dengue infection in CSF.

In 1993, two cases were reported in Thailand and New Caledonia. One patient developed focal subarachnoid hemorrhage, while the second patient showed peripheral facial palsy one week after fever onset. In neither case was viral presence or serological evidence of infection detected in CSF. It was suggested this may have been due to immuno-pathological consequences secondary to dengue.[18]

Encephalitis can only be said to have occurred when a histological diagnosis is available.[4,10] Several studies, however, have based diagnosis of encephalitis on indirect evidence, including absence of other explanations for encephalopathy, isolation of virus in CSF or its serological evidence, CSF pleocytosis, or focal neurological signs.[4] Den3 serotype is especially thought to have neurovirulent properties.[6,7,9] However, in various studies different serotypes have been isolated - Den1 serotype in a series from Rio de Janeiro[11] and Den2 serotype in cortical grey matter by immuno-histochemistry.[9,12] It is difficult to explain the presence of dengue viruse and IgM antibody other than by viral invasion across the blood brain barrier.[11]

In some studies, post mortem examination of brain tissue has revealed the presence of dengue virus.[13,14] Given lack of evidence supporting viral invasion of the CNS, the term encephalopathy instead of encephalitis has been used. Other members of the Flaviviridae family include neurotropic viruses causing Japanese encephalitis, Murray Valley encephalitis, West Nile encephalitis, St. Louis encephalitis, and yellow fever. In recent years, evidence has been gathered to show that dengue viruses can cause infection of the CNS;[12,17] Den2 and 3, especially, can cause dengue encephalitis in the form of both primary and secondary infections.[12]

CLINICAL MANIFESTATIONS

Some dengue patients manifesting neurological symptoms may not show any characteristic features of dengue fever on admission.[4] Diverse manifestations are reported in the literature, including depressed sensorium, convulsions, behavioral disorder, nuchal rigidity[12], positive Kerning's sign and Brudzinski reflex, focal neurological deficits[9,10, 12], flaccid paraparesis[19], transverse myelitis[4], peripheral facial paralysis[19], hemifacial spasm[20], a Guilllain-Barre syndrome-like illness[12,18,21], tremors, manic psychosis, depression, dementia[8], pyramidal tract signs, amnesia[22], short-term memory loss[23], decerebration[24], and coma.

Acute hepatic failure has been reported as part of dengue viral syndrome. Eighteen cases of dengue with liver failure and hepatic encephalopathy were observed among 334 patients admitted to a hospital in Thailand[25]; survival rate was 72%. In India, headache was reported in 34 and drowsiness in 28 in a prospective study based on a total of 59 children sero-positive for dengue[26]. Most manifestations were observed during the febrile stage, and few have been reported afterwards. In 5 studies reporting a total of 355 Southeast Asian cases of DF associated with symptoms of encephalitis (see Table 2), 47% were drowsy and 21% had seizures.[15,9,10,21,22,23]

LABORATORY FINDINGS

Laboratory findings seen in dengue with CNS involvement are provided in Table 3. Other laboratory observations include high CSF opening pressure, CSF protein above 45mg/dL, peripheral leukocytosis, leucopenia[11], and increased prothrombin time.[11,21]

DIAGNOSIS

Antibodies to dengue virus can be detected in the serum one day after onset of symptoms.[17] Titer of antibodies in serum usually persists for 30-90 days, although it has been reported to be detectable as long as 252 days after onset.[17] Thus it is possible that a dengue infection recognized as recent on the basis of IgM sero-diagnosis may in fact be 8 months old. Anitbodies in the CSF, however, usually disappear within a month after onset of illness[17], and are undetectable even with hemagglutination-inhibition testing.[17] ELISA appears to be more sensitive for detecting antibodies in the CSF.[13]

PROGNOSIS

Mortality rates vary from 5%[10] to 22%.[11] Causes of death include multi-organ failure[12], hemorrhagic complications, and circulatory collapse[19]. Most patients completely recover by the time of hospital discharge.[8,10,12,13,24] Neurological sequelae include spastic paresis, static myelopathy following transverse myelitis, residual spasticity, prolonged drowsiness, residual paralysis[12] and Parkinsonian syndrome.[14] Abnormal affect, altered

TABLE. 3

Laboratory findings in patients with dengue

Name Of Journal & Year	SEAJ Trop Med 1996	Lancet 2000	Am J Trop Med Hyg2001	SEAJ Trop Med 1999	SEAJ Trop Med 2001
CSF findings	**2** IgM Dengue +ve	**2** virus isolated **3** PCR +ve **3** IgM Dengue +ve	**1** PCR +ve **14** IgM Dengue +ve	**2** IgM Dengue +ve	PCR -ve no virus isolated
CSF Pleocytosis		**3**	Not present	**6**	**7**
Liver transaminases		More than 10 times above normal in 5	significantly elevated in all 27 of the patients in the study group		AST > 50 in 19 patients ALT >50 in 17 patients
Hyponatremia		6	27		54

TABLE. 4

Prognosis of dengue patients

Name Of Journal & Year	SEAJ Trop Med 1996	Lancet 2000	Am J Trop Med Hyg2001	SEAJ Trop Med 1999	SEAJ Trop Med 2001
Outcome	**1** expired **4** recovered data about others missing	**15** fully recovered between 2-20 days **6** neurological sequelae at discharge	**6** expired **21** fully recovered within a maximum of 7 days	**2** expired rest had uneventful recovery	**4** expired **1** long term neurological sequelae

CONCLUSION

Dengue viral infection is emerging as an important cause of CNS symptoms. It may cause encephalopathy or encephalitis. Studies suggest that dengue infection should be considered in cases of encephalitis in tropical countries, especially where the disease is endemic.[14] Due to diverse and protean manifestations, a low threshold for diagnostic suspicion is required.

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