

REVIEW

Dengue infections with central nervous system manifestations

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Abstract

Dengue is the most important mosquito-borne virus disease in the world and its prevention and control is a priority health programme of the World Health Organization. In its most severe form, it manifests itself clinically as dengue haemorrhagic fever and dengue shock syndrome. In recent years, an increasing number of such cases present with unusual clinical manifestations, including signs and symptoms involving the central nervous system. The neurological features include headache, seizures, neck stiffness, depressed sensorium, behavioural disorders, delirium, paralysis and cranial nerve palsies. Such neurological conditions were attributed to plasma leakage into serous spaces, haemorrhage, shock and metabolic disturbances in severe dengue infections. Using more sensitive laboratory diagnostic techniques, it has been possible to demonstrate the invasion of the central nervous system by the virus. The detection of dengue IgM and the isolation of dengue viruses from the cerebrospinal fluid of patients with neurologic disorders indicate the neurovirulence of dengue viruses and their capability of causing encephalitis.

Key words: Dengue, CNS manifestations, laboratory evidence.

Dengue is an acute viral infection characterized by abrupt onset of fever, severe headache, pain behind the eyes, muscle and joint pains, and rash. The disease is reported in over 100 countries, with approximately two billion people at risk. Annually there are millions of infections with tens of thousands of deaths, making it the most important mosquito-borne virus disease in the world. Due to the dramatic global increase of dengue, the World Health Organization passed a resolution in 1993 to make the prevention and control of dengue among its priority health programmes.

Infection by dengue virus may be asymptomatic or may lead to undifferentiated fever, dengue fever or dengue haemorrhagic fever¹. In infants and young children the disease may present as an undifferentiated febrile disease with a maculopapular rash. In older children and adults, the more classical disease is seen. The more severe form of dengue, known as dengue haemorrhagic fever (DHF), is manifested with high fever, haemorrhagic phenomena, hepatomegaly and often circulatory failure. This can lead to dengue shock syndrome (DSS) where the patient's condition suddenly deteriorates with signs of circulatory failure. In recent years, an increasing number of DHF/DSS with unusual clinical manifestations have been reported,

including signs and symptoms involving the central nervous system (CNS).

One of the earliest reports of CNS manifestations associated with dengue infections was by Rush during the 1780 epidemic in Philadelphia². Postinfectious neurologic disorders have also been reported in several early dengue outbreaks. The outbreak in Greece is particularly worth noting because of its severity. During this 1928 outbreak, there were thousands of severe dengue cases with 1,600 fatalities, due mainly to haemorrhagic disease. Some of the deaths were in cases with encephalitis-like disease as well as a variety of neurologic disorders. Halstead and Papaevangeloe believed that this outbreak was due to dengue 1³. During another dengue 1 outbreak in the Central Pacific in 1924, over 1,400 cases of dengue were reported in a period of 40 days⁴. Thirteen cases of palsy were documented which included Bell's palsy, long thoracic nerve palsy and neuronal nerve palsy. All the cases followed a classical dengue illness of 1 to 3 weeks duration.

There have been more recent reports of dengue infections associated with CNS involvement. Patients in Jamaica and Cuba have been reported to develop conditions compatible with Reye's syndrome and Guillain-Barre syndrome

respectively ^{5,6}. Interestingly, the virus responsible was thought to be dengue 1. Other reports arising from this region included an anecdotal case of a 51 year-old man with secondary dengue infection who presented with clinical evidence of severe hepatitis, encephalopathy, cranial nerve palsy and micro-angiopathic coagulopathy ⁷. Chimelli et al. reported 5 fatal cases of dengue shock syndrome in Rio de Janeiro which manifested neuropathologic features due probably to general circulatory disturbances ⁸.

In Asia, CNS manifestations associated with dengue infection are not uncommon. During the Second World War, the Japanese described many cases in Taiwan, Okinawa and Japan. In the Taiwan outbreak between 1942 and 1944, there were cases with neurologic disorders associated with presumed dengue infection. Common disorders reported were paralysis with loss of sensation, delirium, manic psychosis, depression and dementia ⁹. Neurologic complications as a result of dengue have been reported in Indonesia. From 1975 to 1983, Sumarmo et al. studied 1,452 serologically confirmed cases of DHF in Jakarta, Indonesia ¹⁰. Forty-two of the 142 virologically confirmed dengue infections had one or more encephalitic signs, the most common signs being coma and convulsions. Dengue 3 was found in 31 of the 42 cases with encephalopathy. Kho et al. reported 41 cases of DHF in Jakarta, confirmed by virus isolation, which were accompanied by neurological signs compatible to the diagnosis of acute encephalopathy ¹¹. Two of the cases in children showed typical signs and symptoms of Reye's syndrome. Hendarto and Hadinegoro cited a retrospective study in Jakarta where 152 out of 2,441 DHF cases had encephalopathy ¹². The most pronounced symptoms were hyperpyrexia, alteration of consciousness and convulsions. In 10 of these cases, neurologic abnormalities detected were hemiparesis and tetraparesis of the extremities, and second nerve atrophy.

In India, Srivastava et al. documented 24 cases of DHF/DSS syndrome ¹³. The majority of these cases were boys aged 6-10 years. Classical symptoms of dengue fever occurred in all the patients. Three patients who presented with encephalopathy died. Sharma et al. reported a sudden increase in numbers of births of newborns with neural tube defects from June to September 1989 ¹⁴. Out of a total of 4,785 deliveries whose records were collected, there were 87 newborns with neural tube defects with an incidence which was three times higher than the preceding 4

years. The cluster of neural tube defects was attributed to dengue virus infection and pointed to a potential relationship between dengue fever and neural tube defects in India.

In Malaysia, George et al. reported two dengue cases which presented with fulminant hepatitis and encephalopathy, one in a 7 month-old Chinese male and the other a 6 year-old Chinese female ¹⁵. Both cases were serologically confirmed as dengue. In another report from Malaysia, Lum et al. reviewed 20 critically ill dengue paediatric patients seen in the University Hospital over a two-year period ¹⁶. All the patients had symptoms and signs of dengue infection and all were serologically positive for dengue IgM. Twelve patients had mild encephalopathy with features of headache, photophobia, lethargy and mild to moderate drowsiness. In addition, a two year-old boy had generalized weakness of the upper motor neuron type after two weeks of unspecified fever. Eight patients had severe encephalopathic features such as deteriorating conscious levels, seizures and coma. Japanese encephalitis was excluded serologically in those cases presenting with encephalopathy symptoms. Dengue viruses were isolated from the acute blood of three patients. Patients who had severe encephalopathy and liver dysfunction was difficult to distinguish from Reye's syndrome.

CNS manifestations classically associated with dengue infection are headache, dizziness, sleeplessness, somnolence, restlessness, mental irritability, depression; altered sensorium such as lethargy, confusion, and coma. Seizures, neck stiffness and paresis are less common. These CNS manifestations are most commonly seen in Asian children and can be confused with other viral encephalitis. CNS manifestations may develop before or after haemorrhagic manifestations.

Many factors may be considered to be directly or indirectly associated with CNS signs and symptoms in DHF, the main pathology being leakage of plasma into serous spaces and abnormal hemostasis leading to hypovolemic shock and haemorrhage in many organs of the body. Acute liver failure is considered to be another factor causing CNS manifestation. Nimmannitya et al. in a retrospective study on 18 cases of DHF reported DHF cases with jaundice and neurological signs ¹⁷. They suggested that the causes of these unusual manifestations were multifactorial but most were commonly found to be associated with prolonged shock, metabolic acidosis and severe disseminated intravascular coagulopathy which

could result in both hepatic and brain dysfunction. Hepatic dysfunction may also contribute to the encephalopathy. In their study, there was no pathological evidence of encephalitis.

It is not known whether these signs and symptoms are the result of a true encephalitis due to the invasion of the CNS by the virus or the result of other pathologic mechanisms. In earlier studies, microscopic pathology of the brain of confirmed and presumed dengue cases suggests dengue viruses do not cross the blood-brain barrier. Attempts to isolate virus from nervous tissues have been generally negative. Comparative virus isolation results on several cases showed dengue viruses isolated from the serum of each case but all isolation from the brain and CSF were negative^{4,18}. Many pathologic reports of DHF did not discuss CNS involvement because the brain was frequently not examined. Nelson, in a study in Thailand, reported over 45% of 69 patients suffered from drowsiness and 35% had convulsions¹⁹. The brains of fatal cases were not examined. Findings which appear to be consistent in all studies have been cerebral or meningeal edema and focal haemorrhage. Although this type of pathology cannot explain all of the neurologic disorders reported, it certainly might be responsible for some.

Recent reports using more sensitive laboratory diagnostic techniques have indicated that dengue viruses can cross the blood-brain barrier and set up infection in the central nervous system. Such techniques include the isolation of dengue viruses in mosquitoes and mosquito cell cultures, dengue IgM capture immunoassay and polymerase chain reaction. During an outbreak of dengue between 1987 to 1989 in Taiwan, Chen et al. tested 6 specimens of CSF and sera by IgM detection from 4 virologically confirmed dengue patients who had neurologic symptoms²⁰. IgM was detected from both CSF and sera of all four dengue patients.

A recent report of dengue encephalitis in Malaysia contained convincing data of dengue neurovirulence²¹. In this paper, 6 serologically confirmed dengue cases presented with encephalitis in whom there was evidence of dengue virus invasion into the CNS. The clinical features of encephalitis included changes in sensorium, convulsions, abnormal behaviour, nuchal rigidity, Kernig's sign and focal neurological signs. Dengue 3 virus was isolated in the CSF of 4 patients, in one of whom the presence of the virus was confirmed by polymerase chain reaction. In the 5th patient,

although no virus was isolated, PCR detected dengue 2 virus in both the CSF and acute blood of the patient. In the 6th patient, dengue IgM was detected in both serum and CSF.

The evidence accumulated to date indicates that CNS manifestation in dengue infections is a fairly common phenomenon, resulting from the leakage of plasma into serous spaces, haemorrhage, shock and metabolic disturbances. However, recent findings has indicated that the virus is able to invade the CNS directly leading to viral encephalitis.

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