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Review article

Neurological manifestations of dengue infection: A review

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ABSTRACT

Dengue is a common arboviral infection in tropical and sub-tropical areas of the world transmitted by *Aedes* mosquitoes and caused by infection with one of the 4 serotypes of dengue virus. Neurologic manifestations are increasingly recognised but the exact incidence is unknown. Dengue infection has a wide spectrum of neurological complications such as encephalitis, myositis, myelitis, Guillain–Barré syndrome (GBS) and mononeuropathies. Encephalopathy is the most common reported complication. In endemic regions, dengue infection should be considered as one of the aetiologies of encephalitis. Even for other neurological syndromes like myelitis, myositis, GBS *etc.*, dengue infection should be kept in differential diagnosis and should be ruled out especially so in endemic countries during dengue outbreaks and in cases where the aetiology is uncertain. A high degree of suspicion in endemic areas can help in picking up more cases thereby helping in understanding the true extent of neurological complications in dengue fever. Also knowledge regarding the various neurological complications helps in looking for the warning signs and early diagnosis thereby improving patient outcome.

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Contents

1. Introduction

Dengue is caused by an infection with one of the 4 serotypes of dengue virus, family Flaviviridae, genus *Flavivirus* (single-stranded

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nonsegmented RNA viruses). Annually, there are millions of infections and thousands of deaths related to dengue infection and global incidence is increasing [1]. Dengue is transmitted by mosquitoes of the genus *Aedes*. Clinical manifestations range from an asymptomatic state to severe dengue with plasma leakage, bleeding or organ impairment.

Classical dengue fever is characterised by a rapid onset of fever, headache, retro-orbital pain with severe myalgia and arthralgia. Dengue fever can have more severe forms termed dengue haemorrhagic fever (DHF) and dengue shock syndrome [DSS]. The World Health Organization (WHO) has given new guidelines of case definitions consisting of dengue fever, dengue fever with warning signs and severe dengue. Hence, the terminology of dengue haemorrhagic fever and dengue shock syndrome is better avoided as they are no longer preferred and used.

Apart from the common manifestations of dengue fever, various neurological manifestations including encephalitis, myelitis, Guillain–Barré syndrome (GBS) and myositis have been well reported in dengue infection. Neurological complications were thought to result from the multisystem derangement leading to encephalopathy [2–4]. Although dengue virus initially was considered a non-neurotropic virus [5], neuroinvasion has been demonstrated by detection of dengue virus antigen in the brain by immunohistochemistry in fatal cases of dengue encephalopathy [6] and also by PCR (polymerase chain reaction) and IgM antibody tests in CSF (cerebrospinal fluid) in patients with dengue encephalitis [7,8]. Despite the recent increase in reporting of neurological complications the exact extent of these complications are lacking. Also clinical research has not been conclusive and pathogenesis of neurological manifestations is still controversial regarding various clinical syndromes. Better knowledge both in endemic and nonendemic countries regarding neurological involvement can go a long way in early diagnosis, treatment and referral of these cases to specialised centres leading to a better treatment outcome. So a detailed review of various neurological manifestations that are reported in literature is necessary. This helps in understanding the different neurological syndromes that are being attributed to dengue infection. Also the review can help in making way for further research and clinical study to better understand the various links between dengue fever and neurological manifestation. The literature was searched through Pubmed and Google scholar for various case reports, series and observation studies on neurological manifestations of dengue. These data was then classified based on type of clinical syndromes and then analysed individually.

2. Epidemiology

The first record of a case of probable dengue fever is in a Chinese medical encyclopaedia from the Jin Dynasty (265–420 AD) where it was referred as “water poison” associated with flying insects. The earliest report of neurological involvement was probably by Benjamin Rush, who published an account of a probable dengue fever epidemic that had occurred in Philadelphia in 1780 [9]. Population explosion, uncontrolled urbanisation in tropical and subtropical countries with poor sanitation, proliferation of breeding sites for *Aedes* mosquitoes and the lack of effective mosquito control are potential reasons for the global resurgence and spread of dengue fever [10]. The rapid evolution of dengue viruses with more virulent genotypes of the virus replacing the less virulent ones may also be contributing to the rapid spread of infection [11]. Dengue is now the most rapidly spreading mosquito-borne viral disease in the world [12]. The disease is now endemic in more than 100 countries in Africa, America, Eastern Mediterranean, South-east Asia and the Western Pacific and approximately 2.5 billion people are at risk (two fifths of the world's population). The World Health Organization (WHO) estimates that 50 to 100 million infections occur annually [12]. An estimated 500,000 people with severe dengue require hospitalisation each year, a very large proportion of whom are children. About 2.5% of those affected die [12]. Not only is the number of cases increasing as the disease is spreading to new areas, but explosive outbreaks are also occurring. The estimated global mortality rate is 25,000 patients annually [13].

A change in the serotypes of prevalent dengue viruses results in major dengue epidemics [14]. In Asian regions, the predominant dengue serotype of DEN-2 has been replaced with DEN-3 [15]. In 1998, a new DEN-3 virus subtype (subtype III) emerged and expanded from the Indian subcontinent, resulting in a major pandemic of dengue viral infections affecting more than fifty countries [16].

3. Epidemiological trends in India

In India, dengue has been endemic for over two centuries. Recently, there is an increasing frequency of outbreaks. Since the first epidemic in Kolkata during 1963–64, dengue has emerged as a major public health problem [17]. The first major outbreak of dengue in India was reported in 1991 and one of the largest outbreaks in North India occurred in Delhi in the year 1996. It was mainly due to the dengue-2 virus [18]. In the year 2003, another outbreak occurred in Delhi and all four dengue virus serotypes were found to be co-circulating [19]. In the year 2006 also, an epidemic of dengue infection occurred in northern India and more than three thousand confirmed cases are reported from Delhi only. Dengue infection is prevalent as an endemic infection since 2006 in India. Most cases were reported in the post-monsoon season and young adults (21–30 years) were predominantly affected.

4. Dengue transmission

Dengue viruses are transmitted to humans through the bites of infective female *Aedes* mosquitoes. Mosquitoes generally acquire the virus while feeding on the blood of an infected person [12]. *Aedes* mosquitoes namely, *Aedes aegypti*, *Aedes albopictus*, *Aedes scutellaris* and *Aedes polynesiensis* are known to act as vectors in the transmission of dengue infection. It is important to note that each vector has a particular ecology, behaviour and geographical distribution. *A. aegypti*, the most important vector originated in Africa and spread to tropical and subtropical areas. *A. polynesiensis* and *A. scutellaris* are common in South Pacific regions. *A. albopictus* is native to the tropical and subtropical regions of Asia. But due to an increase in international travel and through transportation of goods this vector has spread all over the world thereby leading to a geographical expansion of the dengue endemic area. These vectors are mainly a container breeder and day biting mosquitos are active during dusk and dawn [20]. Although these vectors can breed and bite during any part of the year, significant increases in the mosquito larval populations are seen during and after the rainy season. This is because the eggs can survive months during the dry season and they turn into larvae when they are washed by rain water. This causes post-monsoon epidemics of dengue in the South and Southeast Asian countries [21]. Infected humans are the main carriers and multipliers of the virus (primary reservoirs), serving as a source of the virus for uninfected mosquitoes. Dengue virus can also pass vertically into eggs thus surviving the dry season inside eggs. Nonvector-borne modes of dengue transmission are also identified such as vertical transmission from mother to foetus, transfusion-related transmission, transplantation-related transmission, and needle-stick-related transmission [22]. But these are very uncommon.

5. Clinical spectrum

Clinical manifestations range from an asymptomatic subclinical state to the most severe dengue fever with plasma leakage, bleeding manifestations and multisystem involvement.

6. Dengue fever and severe dengue

Dengue fever is a flu-like illness; it classically starts with an acute onset of high fever, which could be biphasic lasting 3 to 7 days [23]. A

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