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Dengue Encephalitis

Sandra Theresa Jackson, Justin Jang Hann Chu, Po-Ying Chia,
Owen St. Clair Morgan and Lee-Ching Ng
University of the West Indies
Jamaica

1. Introduction

Dengue encephalitis and other neurological manifestations of dengue infection have been documented with increased frequency since the early 1900's. Infections with the dengue virus present with a wide range of clinical manifestations which have been classified according to severity by the World Health Organization (WHO) as; non-specific febrile illness, classical dengue syndrome, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (WHO 1997). In 2009, WHO adjustments in the classification of the disease resulted in the recognition of two main presentations of dengue. These are referred to as Dengue Fever and Severe Dengue. Neurological dengue is classified as a form of Severe Dengue (WHO 1997, 2009).

A member of the Flavivirus genus of the family Flaviviridae, there are 4 genetically and antigenically distinct serotypes of dengue (DENV 1–4). Co-circulation of multiple serotypes (hyperendemnicity) (Gubler D. 2006), serotype virulence and hyperimmune responses have been identified as risk factors for Severe Dengue, an emerging and major public health concern in the Americas and the Pacific (Bennett, 2010). The incidence and prevalence of dengue encephalitis and other forms of neurological dengue will vary according to the degree of endemnicity and epidemic activity of dengue within geographic regions. Increased documentation of evidence based dengue encephalitis has accompanied the resurgence of dengue infections with the prevalence of dengue encephalitis ranging from 4.2 % to 13% of central nervous system infections (Solomon et al., 2000 & Jackson, 2008). The morbidity and sometimes fatal outcome of dengue encephalitis necessitates a better understanding of the disease, early diagnosis and appropriate management. This chapter reviews the epidemiology, pathogenesis, clinical features, laboratory diagnosis and evidence supporting dengue encephalitis.

2.Epidemiology

2.1 Vector and geographic distribution

Outbreaks of dengue have been documented in the Eastern Mediterranean Region since 1799 in Egypt. William Smart documented descriptions of neurological manifestations of dengue as early as 1827. An example of such documentation is demonstrated in the excerpt which follows (Smart, 1877).

"In children, the attack may be ushered in with convulsions, and the resolution may be attended by sensorial depression, approaching more or less to "dementia", which last

condition may attend the stage of resolution of the disease in elderly persons also" (Smart, 1877).

By then the disease had earned numerous names including that of "dandy fever" given to it by the West Indian negro slaves from the strange attitudes of the sufferers when it first appeared among them. It was translated as dengue in Spanish and altered into denguis for scientific classification (Smart, 1877, Thomas, 1880). J Thomas also described other names given to this disease of wide clinical presentations including: "break-bone fever," "el dengue," which means literally "affectation," denguis, aburunka-bah, which means "father of the knee," " scarlatinarheumatica," "eruptive articular fever," "eruptive rheumatic fever," "eruptive epidemic fever of India," " broken-wing fever," mudak-mariata, mudka meaning contraction or stiffness, and mariata, the name of an idol or Hindoo deity (Smart, 1877, Thomas, 1880).

Though sporadic prior to the World War II, the frequency of dengue outbreaks increased significantly after the war. It was accompanied by an increase in the incidence of complicated forms of dengue (DHF and DSS) in South East Asia (Halstead, 1966). Since then, there has been a worldwide surge in the number and severity of dengue cases. Currently, an estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries (WHO, 2009a). It is the most rapidly spreading mosquito-borne viral disease in the world and in the last 50 years its incidence has increased 30-fold with increasing geographic expansion to new countries. Besides making a comeback in places such as the Americas and Singapore, where dengue was previously successfully controlled for decades (Koh et al., 2008, Guzman and Kouri, 2003), it breached the subtropical temperate barrier and expanded from urban to rural settings extending its reach into places as far north as Nepal (Pandey et al., 2008), Ningbo China (Xu et al., 2007) and France (Gould et al., 2010); and as far south as Bueno Aires in Argentina (Natiello et al., 2008). The Pacific islands, with much lower population densities, have also not been spared, with increasing dengue outbreaks since the 1970s (Singh et al., 2005).

Incidences in South East Asia and the Western Pacific account for greater than 75% of the global burden of dengue. Within the Americas the burden of dengue accounts for 64.6% in the Southern Cone countries, 19% in the Andean contries, 12.5% in Central America and Mexico and 3.9% in the Caribbean (WHO 2009). In North America dengue is frequently seen in Texas and Hawaii (WHO 2009). Other regions in which dengue is endemic include the Eastern Mediterranean and the East and West African Regions (WHO, 2009).

The increased intensity of dengue transmission is effected by the rise in number and size of densely populated urban cities, which are conducive for the spread of the disease and the adaptation and proliferation of dengue vectors; and by international travel which results in the continuous importation and exchange of dengue serotypes and genotypes that become established at various levels (Lee et al., 2010, Ng et al., 2009, Lambrechts et al., 2009). Although the efficiency of dengue virus transmission is affected by a complex interplay of multiple factors, the displacement of one genotype by another more "virulent" or "fit" type has been documented (Rico-Hesse, 2003). The epidemiology of dengue encephalitis and neurological dengue will therefore vary according to the interplay of virus virulence, transmissibility, host susceptibility, endemnicity and/or epidemic activity within geographic locations (Salazar et al., 2010).

2.2 Incidence of dengue encephalitis

Neurologic involvement occurs in 4%-5% of confirmed dengue cases (Puccioni-Sohler et al., 2009). The incidence of dengue infection in patients with suspected central nervous system

(CNS) infection is noted to range from 4.2% in southern Vietnam (Solomon et al., 2000) to 13.5% in Jamaica (Jackson et al., 2008). The higher frequency of neurological dengue (13.5%) reported by Jackson et al.,may be attributed to the inclusion of both adults and children in the study. In this study the frequency of dengue encephalitis among 401 patients with suspected viral central nervous system infections was found to be 6.9% (Jackson et.al., 2008). The incidence of dengue among patients with clinical manifestations of encephalitis-like illness ranges from 18% (Kankirawatana et al., 2000) to 22% (Jackson et al., 2008). Among confirmed neurological dengue cases studies have documented encephalitis to be the presenting clinical manifestation in 52% (Jackson et al., 2008) to 56% (Solomon et al., 2000).. Other neurological manifestations of dengue noted in the Jamaican study include; meningits (34%), seizures (11%), acute flaccid paralysis and Guillain-Barré syndrome (4%).

2.3 Transmission

The transmission of DENV includes a sylvatic, enzootic cycle between nonhuman primates and arboreal mosquitoes of the genus Aedes, and an urban, endemic/epidemic cycle between human reservoir hosts and peridomestic *Aedes spp.*, particularly mosquitoes with larval development in peridomestic water containers. Though the sylvatic dengue strains are associated with illness in Africa and Asia, they do not lead to sustained urban transmission. The *Aedes (Stegomyia) aegypti* (Egyptian tiger mosquito), a day-biting mosquito that is widespread along the tropical and subtropical belt, is the primary vector of the urban cycle. The *Aedes (Stegomyia) albopictus,* also known as the Asian tiger mosquito or forest day mosquito, is a secondary vector of dengue in Asia (Moncayo et al., 2004). In places such as China (including Hong Kong), Hawaii and France (Xu et al., 2007, Gould et al., 2010, Effler et al., 2005), where *Ae. aegypti* is absent, the Asian Tiger mosquito has been shown to be the vector of dengue transmission.

Humans are the main amplifying host of the virus in the urban cycle. DENV circulating in the blood of viraemic humans is ingested by female mosquitoes during feeding. The virus then infects the mosquito mid-gut and subsequently spreads systemically, including the salivary glands, over a period of 8-12 days. After this extrinsic incubation period, the virus can be transmitted to immunologically naive humans during subsequent probing or feeding. The extrinsic incubation period is influenced in part by environmental conditions, especially ambient temperature and the genetic make up of the virus. Thereafter the mosquito remains infective for the rest of its life. *Ae. aegypti* is one of the most efficient vectors for arboviruses because it is highly anthropophilic, frequently bites several times before completing oogenesis, and thrives in close proximity to humans. The eggs can remain viable for many months in the absence of water. Vertical transmission (transovarial transmission) of DENV has been documented with infected eggs remaining viable for many months in the absence of water. Factors influencing virus transmission include environmental and climate factors related to vector distribution and proliferation, host-pathogen interactions and population immunological factors.

Evolution and virus adaptation have resulted in endemic DENV-2 strains being more efficient than sylvatic strains at infecting the peridomestic DENV vectors *Ae. aegypti* and *Ae. albopictus*. Evolutionary DENV emergence events (DENV 1–4) suggest that adaptation of DENV to new vectors and hosts occurred repeatedly from 300 to 1,500 years ago in Asia or Oceania. Continued emergence of endemic DENV from sylvatic progenitor strains occurs in conjunction with the peridomestication of *Aedes* mosquitoes and virus adaptation to these anthropophilic vectors (Moncayo et al., 2004).

3. Dengue virus

Dengue virus (DENV) belongs to the Flavivirus genus of the family Flaviviridae. There are 4 genetically and antigenically distinct serotypes,(DENV 1–4). Infection with one genotype confers life long immunity to the serotype, but only temporary immunity to the other three. The virus is non-enveloped, spherical with a diameter of 50nm containing multiple copies of three structural proteins, a host-derived membrane bilayer and a single copy of a positive-sense, single-stranded RNA genome. The genome is cleaved by host and viral proteases in three structural proteins (capsid, prM, the precursor of membrane protein and envelope protein) and seven nonstructural proteins (NS).

4. Clinical manifestations of Dengue

4.1 Classification of Dengue disease spectrum

The significant contribution of dengue virus (DENV) as an etiological agent of central nervous system infections is evidenced by studies documenting the prevalence of dengue encephalitis of 4.2 % to 13% in dengue endemic regions and during dengue epidemics respectively (Solomon et al., 2000; Jackson, 2008). The 1997 World Health Organization (WHO) classification of symptomatic DENV infections defined dengue as:
i) undifferentiated fever, ii) dengue fever (DF), and iii) dengue haemorrhagic fever (DHF). In this classification system, DHF is further classified into four severity grades, with grades III and IV being defined as dengue shock syndrome (DSS). Plasma leakage with or without

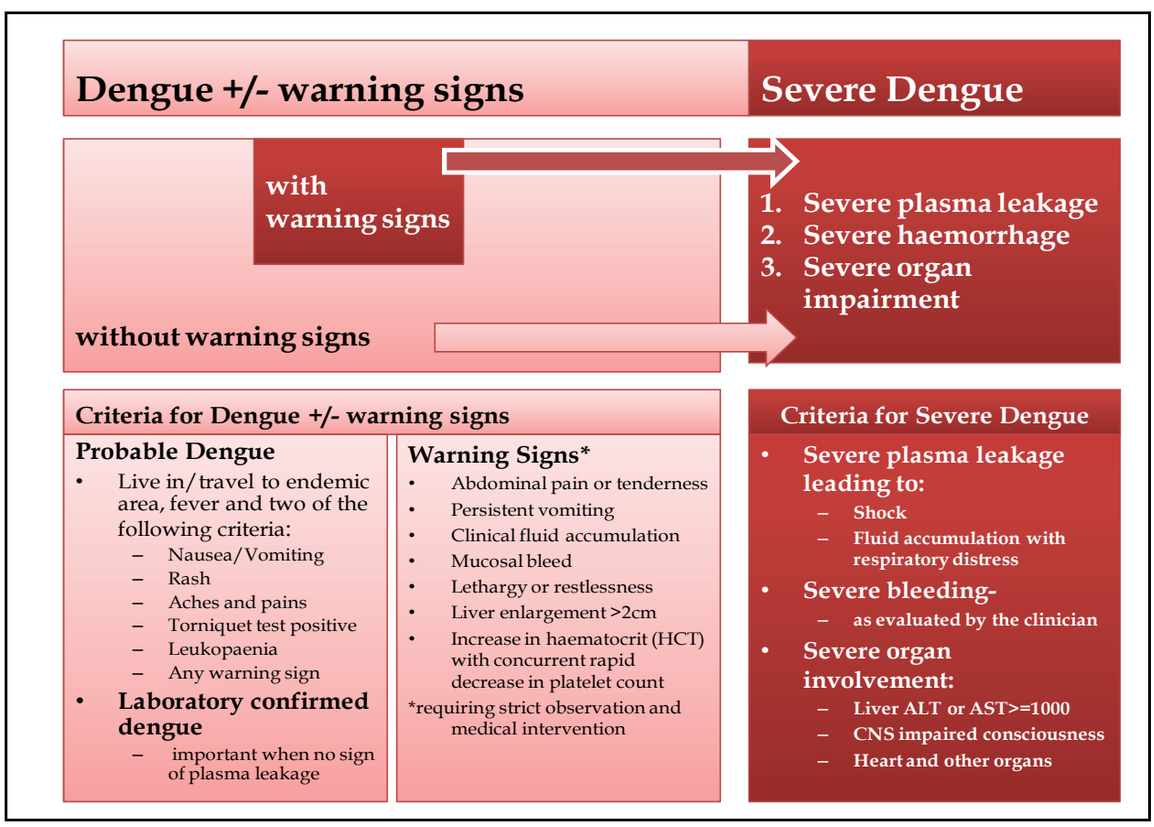

Fig. 1. WHO suggested dengue case classification and levels of severity, (WHO, 2009)

hemorrhage and thrombocytopenia (platelet count of less than 100,000mm^3) are important criteria of DHF/DSS (WHO, 1997) and assist in differentiating DHF/DSS from other arboviral encephalitides. Although this classification into DF/DHF/DSS continues to be widely used, changes in the epidemiology of dengue and difficulties in the use of the 1997 WHO classification (Deen et al., 2006), together with the increase in clinically severe dengue inclusive of neurological dengue resulted in the proposition of an adjusted case classification according to levels of severity by WHO in 2009 (WHO, 2009b).

The suggested classification system divides dengue infection into patients with severe dengue and those with non-severe dengue. Non-severe dengue is divided further into two subgroups -patients with warning signs and those without them (Figure 1). The challenge in classification and clinical diagnosis of dengue is indeed reflected by the statement made by the Expert Consensus Groups in Latin America (Havana, Cuba, 2007), South-East Asia (Kuala Lumpur, Malaysia, 2007), and at WHO headquarters in Geneva, Switzerland in 2008: "Dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome" (WHO, 2009b). Nevertheless, the proposed 2009 WHO classification acknowledges the evidence of research findings that dengue patients without warning signs may develop severe dengue and that central nervous system (CNS) impaired consciousness may be one of the presentations of severe dengue.

4.2 Clinical manifestations of Dengue encephalitis

Dengue encepahlitis is a severe form of dengue. Clinical manifestations of dengue encephalitis documented in early and present descriptions of the disease suggests that it is an infrequent but serious manifestation of dengue virus infection. It should be considered in the differential diagnosis of acute viral encephalitis in geographic regions in which dengue is known to occur. Patients with Dengue encephalitis may be at risk of developing complications of dengue haemorrhagic fever (Muzaffar et al., 2006) although some patients with encephalitis may not show any characteristic features of the disease (Solomon et al., 2000). It is possible that earlier descriptons of encephalitis may have been referred to as encephalomyelopathy because of failed attempts to demonstrate direct invasion of the central nervous system by the dengue virus (Muzaffar et al., 2006, Varatharaj, 2010).

Several forms of Dengue encephalitis have been described. These include focal-encephalitis, pan-encephalitis, acute disseminated encephalomyelitis and meningoencephalomyelitis. The onset of encephalitis is usually sudden with non-specific prodromal symptoms, which include myalgia, malaise, fever, vomiting and diarrhoea. Within a few days patients display headache, disorientation, depressed sensorium and seizures. Other features which have been identified include frontal release signs, abnormal posturing, facial nerve palsy and tetraparesis. Isolated case reports describe more esoteric features ranging from altered sensation to hippocampal encephalitis presenting as amnesia (Varatharaj, 2010, Newman Dorland, 2003).

5. Pathogenesis

5.1 Virus entry and replication

Though evidences for various mechanisms are emerging, there is no consensus on the pathogenesis of DENV. During the feeding of mosquitoes on humans, DENV is presumably injected into the bloodstream, with spillover in the epidermis and dermis, resulting in infection of keratinocytes and immature Langerhans cells (epidermal dendritic cells [DC]). Infected cells then migrate from site of infection to lymph nodes, where monocytes and macrophages are recruited, which become targets of infection (Martina et al., 2009).

The DENV envelope (E) glycoprotein is known to play a key role in the binding of the virions to cells, which is critical for infectivity (Anderson et al., 1992). The virus binds on the cell surface, via the E glycoprotein and viral receptors which may include heparan sulfate or the lectin Dendritic Cell-Specific Intercellular adhesion molecule-3- Grabbing Non-integrin (DC-SIGN) (Nielsen, 2009, Chen et al., 1997, Tassaneetrithep et al., 2003). The virus can also bind to cell surface immunoglobulin receptors in the presence of antibodies to the E glycoprotein or membrane precursor (pre-M) protein, (Morens, 1994). In mature dendritic cells, antibodies enhance dengue infection via Fc receptors.

Following fusion of viral and cell membranes in acidified endocytic vesicles, the viral RNA enters the cytoplasm. The viral proteins are then translated directly from the viral RNA as a single polyprotein, which is cleaved to yield three structural and seven nonstructural proteins (Henchal and Putnak, 1990). Cleavage of several of the viral proteins requires a functional viral protease encoded by the nonstructural protein NS3. The nonstructural protein NS5 is the viral RNA-dependent RNA polymerase, which assembles with several other viral proteins and several host proteins to form the replication complex. The complex transcribes the viral RNA to produce negative-strand viral RNA, which serves as the template for the production of the viral genomic RNA.

Viral protein and RNA synthesis occur predominantly in the cytoplasm of host cells. Replication begins within 15 hrs after infection. DENV replication does not significantly affect the metabolic function of the host cell as exemplified by normal levels of protein synthesis by the infected host cells (Noisakran and Perng, 2008). Replication of the virus results in amplification of infection and dissemination through the lymphatic system. As a result of this primary viremia, several cells of the mononuclear lineage, including blood-derived monocytes , myeloid DC and splenic and liver macrophages are infected (Martina et al., 2009). DENV's tropism for circulating mononuclear cells in blood and for cells residing in the spleen, lymph nodes, and bone marrow has been demonstrated in infected AG129 mice. Leukocytes also have been shown to be infected with DENV in experimentally infected nonhumans primates (Martina et al., 2009).

Downstream of dendritic cells, T-cells become activated and generate cytokines associated with vascular leakage and shock in addition to activating effector cells. Both the virus and the antibodies are involved in release of complement and anaphylatoxins which can cause or exacerbate DHF/DSS. These systems are inextricable and strongly associated with dengue pathogenesis (Nielsen, 2009). It should be noted that during secondary infections with heterologous DENV, high concentrations of DENV-specific immunoglobulin G (IgG) will complex newly produced virus that adheres to and is taken up by mononuclear cells. Following infection, mononuclear cells predominantly die by apoptosis , while abortively infected or bystander DC are stimulated to produce the bulk of mediators that are involved in inflammatory and hemostatic responses of the host. In this regard, factors that influence the amount of target cells infected, and consequently the levels of viremia, may determine the ratio of different proinflammatory and anti-inflammatory cytokines, chemokines, and other mediators, as well as the way in which the inflammatory response affects the hemostatic system (Martina et al., 2009).

5.2 Antibody response

At or a few days prior to the onset of illness, the virus can be detected in serum, plasma, circulating blood cells and other tissues for 4–5 days followed by the disappearance of DENV and antigens from the blood coincident with the appearance of specific antibodies.

The NS1 antigen may be detected in some patients for a few days after defervescence (WHO, 2009b, Pok et al., 2010). Antibody response to infection differs according to the past exposure of the host to dengue serotypes and/or other flaviviruses. Previously unexposed patients develop a primary response characterized by a slow increase of specific IgM antibodies between days 3 to 5 after the onset of illness. IgM levels peak about two weeks after the onset of symptoms and then decline generally to undetectable levels over 2–3 months. Anti-dengue serum IgG is generally detectable at low titres at the end of the first week of illness, increasing slowly and remains detectable after several months, and probably even for life. During a secondary dengue infection (a dengue infection in a host that has previously been infected by a dengue virus, or sometimes after non-dengue flavivirus vaccination or infection), IgG antibody titres rise rapidly to high levels, even in the acute phase and persists for periods lasting from 10 months to life. IgM levels at early convalescent stage are significantly lower in secondary infections than in primary ones and may be undetectable in some cases (WHO, 2009b).

5.3 Pathogenesis of severe Dengue

The pathogenesis of severe dengue is not completely understood but is likely to be multifactorial (Martina et al., 2009). Secondary infections are considered as one of the risk factors for severe dengue disease (DHF/DSS) (Thein et al., 1997, Guzman et al., 1991, Guzman et al., 1990) and form the basis of the antibody-mediated pathogenesis or antibody-dependent enhancement theory (Nielsen, 2009, Noisakran. & Perng, 2008, Martina et al., 2009). There have however been reports on the absence of association between secondary dengue or circulation of multiple serotypes and DHF/DSS (Harris et al., 2000, Morens et al., 1986). It is believed that antibody-mediated enhancement of infection either results in a high viral load or represents the link to type 2 cytokine responses (Martina et al., 2009).

Dengue cross-reactive T cells have been shown to lose their cytolytic activity (Martina et al.,2009) and once primed during primary infection with one of the dengue serotype or a member of the Flavivirus family respond vigorously (memory T-cell responses) upon exposure to a second infection releasing massive amounts of proinflammatory cytokines, which induce vascular endothelial cell activation and are the likely cause of the capillary leak syndrome and predispose to DHF and DSS (Noisakran and Perng, 2008). Involvements of the liver and endothelial cell lining of different organ systems are important factors in the pathogenesis of severe dengue. Vascular permeability is increased through mediators which promote the widening of adherens junctions. Disruption of vascular integrity and increase capillary fragility is also affected by; thrombocytopenia, platelet dysfunction and virus infection of the endothelial cells (Martine et al., 2009).

High levels of complement activation products C3a and C5a can be found in the plasma accompanied by accelerated consumption and a marked reduction of the complement components in DHF/DSS the time of defervescence and onset of plasma leakage. In severe dengue, complement can be directly activated by the NS1 dengue antigen or via the binding of heterotypic antibodies to NS1 expressed on infected cells. Production of the C5b-C9 complex subsequently triggers cellular reactions and stimulates the production of inflammatory cytokines that are associated with development of DHF/DSS. (Martina et al., 2009)

The virulence theory hypothesis states that certain dengue strains are responsible for more severe disease (Martina et al. 2009) with increased severity being associated with primary infection with DENV-1 followed by infection with DENV-2 or DENV-3. Intra-epidemic evolution of the virus has also been found to be responsible for increased severity of disease.

Hyperthermal factors, physical status of virus in viremic individuals, conditioning of neutralizing antibody assay in DENV infection, concept of vector transmission, serotype virulence, nutritional status and genetic attributes of the infected individual (Noisakran and Perng, 2008) are factors which have been associated with severe dengue (Martina et al. 2009).
The mechanism by which the dengue virus enters into the central nervous system in severe and non-severe dengue is not clearly understood. It is hypothesized that the increased capillary permeability and the effects of the "cytokine storm" play a role in the neuropathology of dengue. This is evidenced by the finding of cerebral edema even in cases of benign dengue, and which may explain the origin of severe headaches (Chaturvedi et al., 1991).

5.4 Pathogenesis of neurological Dengue

5.4.1 Primary and secondary infections

Several studies have refered to a pan-tropic nature of the dengue virus with increased documentation of its neurtopism in recent years. One pathogenesis theory of neurological dengue proposes secondary and systemic derangements as a cause. In such cases encephalopathy and not encephalitis is the primary manifestation. Although encephalopathy can exist in severe dengue as a result of multi-oragan involvement, there is a growing body of evidence in support of dengue neurotropism. This is evidenced by the documentation of neurological manifestations in both primary and secondary dengue infections (Cam et al., 2001, Hendarto and Hadinegoro, 1992, Solomon et al., 2000, Janssen et al., 1998, Thisyakorn et al., 1999). Several studies have also reported neurological manifestations as the presenting symptom of dengue infection (Pancharoen and Thisyakorn, 2001, Solomon et al., 2000, Soares et al., 2008, 2010).

5.4.2 Virus detection in the CNS

The early onset of neurological signs and symptoms in the viremic phase suggests direct CNS invasion by DENV (Lum et al., 1996, Soares st al. 2006). Studies with mice models have shown that with the intravenous inoculation of dengue Induced cytotoxic factor, there is transient compromise in the integrity of the blood brain barrier. This occurs in a dose-dependent manner, allowing leakage of protein and erythrocytes (Chaturvedi et al., 1991). Infiltration by DENV infected macrophages have also been proposed as one of the mechanisms of direct CNS invasion (Miagostovich et al., 1997).
There have been several reports of detection of dengue specific immunoglobulin IgM via enzyme linked immunoassay and dengue RNA via real-time polymerase chain reaction (RT-PCR) in the cerebrospinal fluid (Agarwal et al., 2009, Cam et al., 2001, Angibaud et al., 2001, Garcia-Rivera et al., 2009, Puccioni-Sohler et al., 2009, Thisyakorn et al., 1999). In addition studies have also supported the intrathecal synthesis of IgG (Puccioni-Sohler et al., 2009, Soares et al., 2006). Direct infection of the central nervous system (CNS) by dengue has been documented thorough virus antigen detection using immunoperoxidase stain in CNS biopsies in fatal encephalopathy cases with confirmed dengue infection (Miagostovich et al., 1997, Nogueira et al., 2002) and in CNS biopsies in fatal cases which presented with encephalitis (Pancharoen and Thisyakorn, 2001, Thisyakorn et al., 1999). Although the detection of viral antigens is not evidence of viral replication studies have identified dengue antigens in the neurons, astrocytes, microglia and Purkinje cells in autopsies and necropsies (Bhoopat et al., 1996, Ramos et al., 1998, Bordignon et al., 2008, Jessie et al., 2004). Encephalitis, apoptosis and CNS replication of dengue virus has also been observed in the neurons in the cortex and hippocampus following intracerebral inoculation of mice with

neuroadapted DENV1 viruses (Despres et al., 1998). Neuronal apoptosis has also been observed in fatal human DENV2 and DENV3 infections but the authors of the report attributed this to severe brain ischemia as dengue virus antigens were not detected via immunohistochemical staining in these cases (Limonta et al., 2007, Limonta et al., 2009).
Immunostaining for NS3 of all dengue serotypes has revealed the presence of dengue antigen in perivascular cells of the cerebrum in interferon-receptor deficient mouse models infected with dengue and in fatal cases of human dengue infection (Balsitis et al., 2009). However in the study by Balsitis et al., none of the fatal cases presented with signs of neurological involvement thus demonstrating that DENV-infected cells may be present in the central nervous system even in patients without neurological manifestations who present with classic DHF/DSS signs and symptoms (Balsitis et al., 2009).

5.4.3 Serotypes

Neurological manifestations have been documented to occur with all dengue serotypes (Kunishige et al., 2004, Ramos et al., 1998, Solomon et al., 2000), with more frequent identification of serotype 2 and 3 (Lum et al., 1996, Garcia-Rivera et al., 2009, Hendarto and Hadinegoro, 1992, Solomon et al., 2000) and less frequently with serotype 4 (Ramos et al., 1998). However in other serotype neurovirulence studies using parental and live attenuated DENV2 and DENVV3 in monkeys, specifically *Macacafascicularis* and *Macacamulatta*, lesions were less frequently observed in the central nervous system and clinical manifestations were not severe (Angsubhakorn et al., 1986, Angsubhakorn et al., 1987, Angsubhakorn et al., 1994).

5.4.4 Genetic diversity

It is important to note that most studies on clinical manifestations center on DENV serotypes as the main subdivision, with limited consideration to the genetic diversity among viruses within a serotype (Rico-Hesse, 1990, Lanciotti et al., 1994, Lanciotti et al., 1997). Animal studies using mice have shown that DENV3 genotype I , can cause neurological disease clinically and histologically if intracerebrally inoculated while genotype III (P1-64/2006) causes only asymptomatic disease with mild disease on histology (Ferreira et al., 2010). Infection with DENV3 genotype I is associated with decreased leukocytosis, the detection of viable virus concentrations in the brain and higher levels of interferon-gamma, interleukin-6 and monocyte chemoattractant protein 1 (Ferreira et al., 2010). The phenomenon that RNA viruses are known to be of low fidelity, forming numerous variants called quasispecies (Clyde et al., 2006), has been observed in acute dengue infections (Lauring and Andino, 2010).

5.4.5 Envelope protein

Substitution of aspartate-67 for asparagine-67 in DENV envelope sequences is associated with a greater electrostatically negative charge and this substitution has been identified in the sequences of viruses causing encephalitis (Barker et al., 2009). In contrast asparagine is found in the position corresponding to glycosylated asparagine-67 in DENV2, in all known flaviviruses causing hemorrhagic disease, and in 93% of sequences of viruses causing hemorrhagic fever . However, asparagine was only located in 33% (2/6) flaviviruses causing encephalitis and in 2.6% of the relevant encephalitic sequences (Barker et al., 2009).
Different amino acid substitutions have been described (Bordignon et al., 2007) and studies on the other DENV serotypes have shown an association of amino acid substitutions in E protein domain with neurovirulence (Bray et al., 1998, Kawano et al., 1993, Lee et al., 1997).

Amino acid substitution of glutamate to lysine at position 126 in E protein domain II, has been shown to contribute to DENV2 neurovirulence in mice (Hiramatsu et al., 1996, Gualano et al., 1998). Substitutions at position 62 and 203 of domain II of DENV2 E protein were also reported to alter neurovirulence (Zhao et al., 2003). Another amino acid substitution which occurs is in the alpha-helical region E400-412. This region participates in the conversion of E dimer to homotrimers and cellular attachment (Modis et al., 2004, Stiasny et al., 2005).
The position of isoleucine-209 on non-structural protein 3 (NS3) on domain 1 has been found in association with all viruses causing encephalitis (Xu et al., 2005). One such amino acid substitution observed in a study on mice neuroadapted DENV1, is valine-209 to isoleucine-209 (Bordignon et al., 2007). This coincides with the NTPase domain of DENV2 (Xu et al., 2005). A second significant neurovirulent amino acid substitution is observed in the NS3 domain II at position 435 (Bordignon et al., 2007, Despres et al., 1998) which corresponds to the beta-hairpin tip of the helicase domain (Duarte dos Santos et al., 2000).

5.4.6 Host factors

Reserch studies indicate that genetic factors are improtant and play a role in population susceptibility and disease severity (Martina et al., 2009). Host genetic predisposition has been proposed to be a risk factor in presentations such as monophasic neuromyelitis optica (NMO), a rare form of post-infectious acute disseminated encephalomyelitis (ADEM) (Miranda de Sousa et al., 2006). Non-HLA and HLA-associated genetic factors implied as predisposing factors for severe dengue include; Vitamin D receptor polymorphism, glucose-6-phosphate dehydrogenase (G6PD) deficiency, mannose-binding lectin (MBL)2, Fc_RIIa polymorphism, TNF-alpha (-308) A allele and IL-10 (-1082/-819/-592) ACC/ATA haplotype, CTLA- 4, transporters associated with antigen presentation and human platelet antigen, DC-SIGN polymorphism, HLA class I alleles A*01, A*0207, A*24, B*07, B*46, B*51 and HLA class II alleles DQ*1, DR*1, DR*4 (Martina et al., 2009). TNFalpha (-308) GG and TGFbeta1 (c25) GG genotypes have been shown to be associated with protection.

5.4.7 Ancillary studies

Ancillary investigations include lumbar puncture, neuroimaging and electroencephalogram (EEG). Lumbar puncture may be normal or may demonstrate pleocytosis with normal or mildly elevated protein and normal glucose (Muzaffar et al., 2006, Lum et al., 1996, Misra et al., 2006).
Cerebral edema has been the primary finding of neuroimaging studies using computed tomography and magnetic resonance imaging (MRI). In the prospective case control study by Cam and coworkers, MRI revealed cerebral edema (12/18) or no changes (4/18) in the majority of the patients with dengue encephalopathy, while only the minority (2/18) showed specifically scattered focal lesions (Cam et al., 2001,Muzaffar et al., 2006). EEG revealed slow background waves for the majority of the patients which resolves with clinical recovery (Angibaud et al., 2001, Arachchi et al., 2003, Lum et al., 1996, Misra et al., 2006, Wasay et al., 2008).

6. Laboratory diagnosis

Early laboratory confirmation of clinical diagnosis may be valuable as some patients progress from mild to severe disease and sometimes to death, within a short period of time. Early intervention may be life-saving. Several laboratory methodologies are available for

confirming acute DENV infection and may be used singly or in combination. These include detection of the virus, viral nucleic acid, antigens and/or antibodies (Table 1). The hallmark for the laboratory diagnosis of encephalitis is the demonstration of the DENV or antigen in the tissues of the central nervous system and or the cerebrospinal fluid.

Diagnostic Method	Specimen	Time of collection after onset of symptoms	Diagnosis of acute infection
Virus isolation Serotype confirmation	Whole blood, serum, Tissue	1 to 5 days	Confirmed
Nucleic acid detection	Whole blood, serum, plasma, Tissue	1 to 5 days	Confirmed
NS1 antigen detection	Serum Tissue	1 to 6 days	Confirmed
IgM ELISA -paired seroconversion	Serum, plasma, whole blood	Acute sera (1-5 days) Convalescent sera (>15 days)	Confirmed
IgM ELISA-Single sera	Serum, plasma, whole blood	>5 days	Probable
IgM rapid test	Serum, plasma, whole blood	>5 days	Probable
IgG single serum , HI titre>1280	Serum, plasma, whole blood	>5 days	Probable
IgG (paired sera) by ELISA, HI or Neutralization test (seroconversion or 4 fold rise)	Serum, plasma, whole blood	Acute sera (1-5 days) Convalescent sera (>15 days)	Confirmed

Table 1. Summary of laboratory methods used in the diagnosis of dengue infection

Adapted from summary of operating characteristics and comparative costs of dengue diagnostic methods, and interpretation of dengue diagnostic tests from Dengue and Control (DENCO) and other studies (WHO, 2009b, Pok et al., 2010). To distinguish primary and secondary dengue infections, IgM/IgG antibody ratios are now more commonly used than the haemagglutination-inhibition test (HI) (WHO 2009).

7. Prognosis

The reported morbidity and mortality due to dengue encephalitis itself is low with most survivors recovering fully (Cam et al., 2001, Angibaud et al., 2001, Pancharoen and Thisyakorn, 2001). Documented sequelae from encephalitis included weakness and spasticity (Pancharoen and Thisyakorn, 2001) and, spasms (Soares et al., 2006). Encephalitis accompanied by post-infectious neurological manifestations however may have a prolonged recovery. Residual weakness can occur in patients with nerve palsies (Chappuis et al., 2004). Post-infectious myelitis may complicate encephalomyelitis. Myletis patients can remain

symptomatic with urinary retention or spastic paraparesis (Puccioni-Sohler et al., 2009, Soares et al., 2006). Residual abnormalities in vision have been documented in cases of maculopathy, optic neuritis and neuropathy (Sanjay et al., 2008, Wen et al., 1989). The majority of deaths are associated with dengue hemorrhagic fever or dengue shock syndrome (DHF/DSS) and not with direct neurological involvement. Studies have documented an increase risk of developing DHF/DSS among patients with neurological dengue (Muzaffar et al., 2006 & Ramos et al., 1998). Infrequent causes of death have been attributed to tonsillar herniation secondary to cerebral edema (Wasay et al., 2008) and pontine hemorrhage with no underlying systemic derangement (Janssen et al., 1998).

8. Conclusion

The resurgence of dengue in the Americas and Pacific regions has been accompanied by a corresponding increase in frequency of documentation of dengue encephalitis. Dengue encephalopathy and dengue encephalitis are two distinct manifestations of neurological dengue. Although not a primary clinical manifestation, dengue encephalitis is a form of severe dengue which infrequently may occur without co-existing features of DHF and DSS. As the clinical presentation of dengue encephalitis is similar to that of other encephalitides, the diagnosis of this entity may be easily misdiagnosed. Identification of other criteria of severe and non-severe dengue will assist in greater accuracy of diagnosis of dengue encephalitis. Mortality associated with dengue encephalitis has been frequently associated with features of DHF and DSS. Although advances in unveiling the pathogenesis of dengue have been made, continued research is needed to fully elucidate the pathogenesis of the complex interplay of immunological responses, virus characteristics and host predisposing factors.

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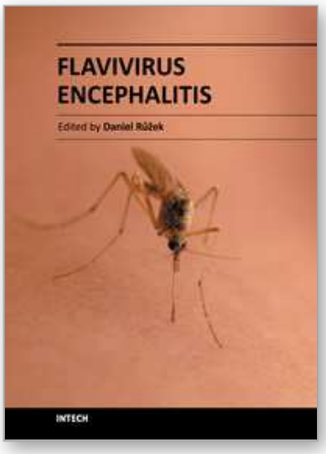

Flavivirus Encephalitis

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Encephalitis is an inflammation of the brain tissue associated with clinical evidence of brain dysfunction. The disease is of high public health importance worldwide due to its high morbidity and mortality. Flaviviruses, such as tick-borne encephalitis virus, Japanese encephalitis virus, Murray Valley encephalitis virus, or St. Louis encephalitis virus, represent important causative agents of encephalitis in humans in various parts of the world. The book Flavivirus Encephalitis provides the most recent information about selected aspects associated with encephalitic flaviviruses. The book contains chapters that cover a wide spectrum of subjects including flavivirus biology, virus-host interactions, role of vectors in disease epidemiology, neurological dengue, and West Nile encephalitis. Special attention is paid to tick-borne encephalitis and Japanese encephalitis viruses. The book uniquely combines up-to-date reviews with cutting-edge original research data, and provides a condensed source of information for clinicians, virologists, pathologists, immunologists, as well as for students of medicine or life sciences.

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InTech Europe
University Campus STeP Ri
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51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821