Neurological complications of dengue virus infection

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Dengue is the second most common mosquito-borne disease affecting human beings. In 2009, WHO endorsed new guidelines that, for the first time, consider neurological manifestations in the clinical case classification for severe dengue. Dengue can manifest with a wide range of neurological features, which have been noted—depending on the clinical setting—in 0·5–21% of patients with dengue admitted to hospital. Furthermore, dengue was identified in 4–47% of admissions with encephalitis-like illness in endemic areas. Neurological complications can be categorised into dengue encephalopathy (eg, caused by hepatic failure or metabolic disorders), encephalitis (caused by direct virus invasion), neuromuscular complications (eg, Guillain-Barré syndrome or transient muscle dysfunctions), and neuro-ophthalmic involvement. However, overlap of these categories is possible. In endemic countries and after travel to these regions, dengue should be considered in patients presenting with fever and acute neurological manifestations.

Introduction

Dengue is a mosquito-borne viral disease caused by one of four closely related dengue virus serotypes (DENV 1–4). It is the second most common mosquito-borne disease affecting human beings after malaria.[1] Around 4 billion people are at risk of the disease, with about 100 million cases of symptomatic dengue occurring annually.[2] Reported case-fatality rates of severe dengue range from less than 0·2% to 5%.[1] Population growth, urbanisation, deterioration of mosquito-control programmes, and an increase in air travel and trade have contributed to the emergence and geographical spread of the disease over past decades.[1,3]

In 2009, WHO released new dengue guidelines and a new case classification, which included CNS involvement in the definition of severe disease.[1] From the time dengue was recognised as a clinical entity, neurological manifestations of the disease have been described.[4,5] Factors that might contribute to neurological manifestations include prolonged shock, hyponatraemia, hepatic failure, or intracranial bleeding.[4,6] Therefore, the noted abnormal neurological signs in patients with dengue could be due to encephalopathy and not encephalitis.[4] Since the end of the 1990s, evidence of dengue virus neurotropism has increased and the number of reports on dengue patients with virus isolation from CSF or brain tissue has risen.[7–9]

We did a literature review of evidence for dengue virus neuroinvasion and the frequency either of neurological features in patients presenting with dengue or of dengue diagnosis in patients presenting with encephalitis-like illness, at hospitals in endemic areas. Here, we discuss the findings of our literature search and describe the epidemiology of dengue, its diagnosis, clinical manifestations, and treatment of the disease and its neurological features.

Epidemiology, virus, and vectors

Dengue viruses consist of single-stranded RNA and are members of the Flaviviridae family (genus *Flavivirus*). The RNA genome includes seven non-structural (NS) protein genes and three structural protein genes that encode the capsid, membrane, and envelope proteins.[10] Four antigenically distinct serotypes (DENV 1–4) circulate simultaneously in endemic countries,[11] and all can cause severe disease. Transmission occurs via aedes mosquitoes that feed during daytime, with *Aedes aegypti* and *Aedes albopictus* being the two main vectors.[1]

Dengue is endemic in almost all tropical and subtropical countries. The highest incidences are reported in Asia and in Central and South America, although reports are increasing from African countries.[1] In prospective cohort studies from Thailand and Cambodia, the incidence of symptomatic dengue virus infection was more than 20 cases per 1000 children a year, leading to around 2·6–4·6 admissions per 1000 children.[12] Among travellers, dengue is a common disease. In a cohort of 1207 short-term travellers from the Netherlands in 2006–07, the incidence of symptomatic dengue virus infection was four cases per 1000 adults.[13]

Clinical findings

Most dengue virus infections are asymptomatic.[14] Symptomatic infections were classified traditionally into undifferentiated fever, dengue fever, dengue haemorrhagic fever, and dengue shock syndrome.[15]

Fever, severe frontal and retro-ocular headache, muscle, bone and joint pain, abdominal pain, nausea, and vomiting are common during dengue fever. A mild transient skin rash can arise, and a maculopapular or scarlatiniform rash can be seen after the third or fourth day in half of infected people (figure 1). Dengue haemorrhagic fever is defined by the presence of four criteria: fever, haemorrhagic features (eg, ecchymosis, petechial haemorrhage, epistaxis, gum bleeding, vaginal or gastrointestinal bleeding), thrombocytopenia (<100 000 platelets per µL blood), and evidence of plasma leakage due to increased vascular permeability.[15] However, augmented vascular permeability and plasma leakage (rather than haemorrhagic manifestations) are the key features that differentiate dengue haemorrhagic fever from dengue fever. Dengue shock syndrome has the same characteristics as dengue haemorrhagic fever in addition to circulatory failure, hypotension, and shock.

The traditional case classification for dengue fever and dengue haemorrhagic fever has been used for several

decades and has supported decision making for the management of dengue. However, this classification is difficult to apply, and many cases of severe dengue have been missed in some studies.[16–18] The new dengue case classification, published by WHO in 2009, categorises the disease into dengue without warning signs, dengue with warning signs, and severe dengue (panel 1).[1] By comparison with the traditional case classification, the update had similar specificity (78·5% *vs* 75·5%) but better sensitivity (92·1% *vs* 39·0%) to capture severe dengue cases that needed treatment in an intensive-care unit in Nicaragua.[17] By contrast with the traditional system, the revised classification also includes severe organ manifestations such as liver failure, heart involvement, or CNS involvement. Nevertheless, neurological complications are not well described in the 2009 guidelines, and little is known about the frequency of these manifestations.

Why do most dengue virus infections lead to asymptomatic or mild self-limiting disease, and why do some infected people develop severe dengue? Subsequent (secondary or tertiary) infection with a heterologous dengue virus serotype has been postulated to be the main factor associated with severe disease, via antibody-dependent enhancement.[19,20] According to this hypothesis, non-neutralising antibodies from a previous dengue virus infection facilitate cell invasion, enhance viraemia, and initiate a self-amplifying cascade that can lead to release of cytokines and other pro-inflammatory mediators.[21] However, severe dengue cases have been described that are primary infections, and strains of dengue virus exist that cannot be enhanced, suggesting that additional viral and host factors have a role in the development of severe dengue.[3]

Neurological complications

Neurological complications of dengue virus infection can be categorised into dengue encephalopathy, encephalitis, immune-mediated syndromes, dengue muscle dysfunction, and neuro-ophthalmic disorders. However, in practice, classification can be difficult because these categories overlap and clinical data—eg, for CSF examinations—might be missing.

In our literature search, we identified 247 publications describing original studies or reports of dengue with neurological, neuromuscular, or neuro-ophthalmic complications (figure 2). In 55 of these, the number of patients with neurological manifestations of dengue was presented as a proportion either of total admissions for dengue or of all individuals with encephalitis-like illness (classified as context studies). Manifestations compatible with encephalitis were mentioned in 24 context studies and complications according with encephalopathy were noted in 20; in the remaining 11, either both terms were used or multiple neurological manifestations were described. However, these two terms have been used interchangeably. Furthermore, results from CSF testing for dengue were reported rarely, in only 13 of these 55 context studies. CSF testing was done in patients with neurological manifestations to check for CSF abnormalities and dengue diagnosis (eg, dengue virus RNA, NS1, or dengue virus-specific antibodies in CSF). 12 studies are summarised in tables 1 and 2 and one study of fatal dengue cases is presented in table 3 (additional study details are presented in the appendix, pp 1–6).[8,9,22–33]

See Online for appendix

Of all laboratory-confirmed cases of dengue presenting at hospital, the proportion with neurological manifestations ranged between 0·5% and 5·4% in four studies from southeast Asia and was 21% in a prospective study from Brazil (table 1).[8,9,22–25] Of those with encephalitis-like illness or suspected CNS infection, the proportion of patients with dengue ranged between 4·6% and 20% in five studies from Asia and was 47% in a study from Brazil and 26% in one from Puerto Rico (table 2).[8,26–32] CNS involvement has been described in all three categories of the traditional case classification: dengue fever, dengue haemorrhagic fever, and dengue shock syndrome.

98 case reports and series were identified by the literature search on dengue-associated encephalitis and encephalopathy, multiple neurological manifestations of dengue, and autopsy studies of patients with dengue who had neurological manifestations (figure 2). Of these, 67 were published between 2000 and 2013 and 31 were published between 1960 and 1999. 33 reports were of patients with dengue encephalitis and 41 were of cases with encephalopathy.

In total, eight autopsy studies were identified by our literature search that reported on fatal dengue virus infection with neurological manifestations (table 3).[4,33–40] In

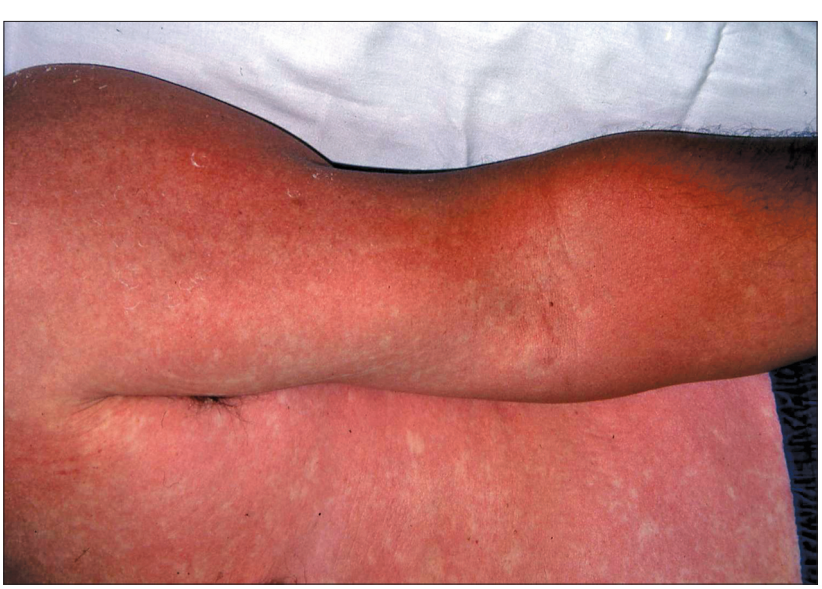

Figure 1: **Maculopapular rash in a 29-year-old man with dengue**

Panel 1: **2009 WHO clinical case classification for dengue[1]**

Criteria for dengue and warning signs

Probable dengue

- Fever

and two of either

- Nausea or vomiting
- Rash
- Aches and pain (headache, myalgia, arthralgia)
- Tourniquet test positive
- Leucopenia
- Any warning sign

Warning signs

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleeding
- Lethargy, restlessness
- Liver enlargement >2 cm
- Increase in packed-cell volume concurrent with rapid fall in platelet count

Criteria for severe dengue

Either

- Severe plasma leakage leading to
  - Shock (dengue shock syndrome)
  - Fluid accumulation with respiratory distress

Or

- Severe bleeding (assessed by clinician)

Or

- Severe organ involvement
  - Liver enzyme concentrations, aspartate aminotransferase or alanine aminotransferase ≥1000 U/L
  - CNS involvement, impaired consciousness
  - Heart or other organ involvement

these reports, dengue virus was identified by PCR or virus isolation in CSF (two studies used this method) or in brain tissue (four studies). Moreover, dengue virus antigen was identified by immunohistochemical methods in five studies. Autopsy findings showed cerebral congestion or oedema most typically, and histopathological evidence for encephalitis was provided rarely (table 3).

Dengue encephalopathy

Acute encephalopathy is the most commonly reported neurological disorder associated with dengue virus infection. Dengue encephalopathy involves a diminished level of consciousness that can be precipitated or caused by several factors, including prolonged shock, anoxia, cerebral oedema, metabolic disturbances (eg, hyponatraemia), systemic or cerebral haemorrhages, acute liver failure, or renal failure.[6,41] CSF analyses, including measurements of protein, glucose, and cell count, are usually normal.

In a retrospective assessment from Indonesia, 152 (6%) patients with dengue encephalopathy were identified from 2441 people admitted to hospital for dengue haemorrhagic fever.[6] 152 had normal CSF analyses, 146 had altered consciousness, and 123 had seizures. Of 98 cases classified by the traditional case definition, most (78%) had pending or profound shock. The diagnosis of dengue haemorrhagic fever was based on clinical criteria only; no examinations were done to detect dengue virus or antibodies in CSF or serum.[6] In Thailand, neurological manifestations were recorded in 80 (5%) of 1493 children with serologically confirmed dengue, and half presented with encephalopathy (table 1).[23] Laboratory findings included hyponatraemia, abnormal liver enzymes, and CSF pleocytosis. Dengue virus-specific IgM and dengue virus RNA in PCR were not recorded in 16 available CSF specimens; however, no information was provided on the tests used and the day of illness. One of the 80 children had evidence of encephalitis based on histopathological findings at autopsy (four children died; results from autopsy were provided for one).[23] In a retrospective review from Thailand of 18 people (including ten who died) with dengue haemorrhagic fever and neurological features, CSF was normal in all five patients who were tested.[4] Shock, jaundice, metabolic acidosis, and intracranial (subdural and pons) haemorrhage were noted. CSF or brain tissue analyses for dengue virus RNA or antigen were not done.[4] In a retrospective review from Thailand of patients with dengue (1995–99), encephalopathy was most usually seen in obese children (1·3% *vs* 0·5% in children of normal weight) and in babies (4·1% *vs* 0·6% in children aged 1 year or older).[42,43]

The outcome of individuals with dengue encephalopathy is variable and depends on causal factors. Without supportive treatment mortality can be high. In a case series of 15 patients with dengue encephalopathy from Sri Lanka (all dengue shock syndrome) seven cases were fatal.[44] Factors that contributed to encephalopathy included acute liver failure (11 cases), electrolyte imbalances (12), and shock (six).

Encephalitis

In the past decade, an expanded clinical spectrum has emerged of encephalitis due to CNS invasion and neurotropic effects of dengue virus. Five studies were identified by our literature search that provided results of CSF analysis of cell counts and detection of dengue virus or dengue virus antigen among patients admitted with dengue (table 1).[8,9,22–24] In a prospective study from Vietnam, 16 (1%) of 1691 patients admitted with suspected dengue virus infection had neurological presentations, and another five dengue-positive patients had CNS abnormalities.[8] Of these 21 individuals, dengue virus was isolated or detected by PCR in CSF in ten. Nine of these patients were classified as having dengue with encephalitis. In a study from Brazil, 11 of 18 patients with

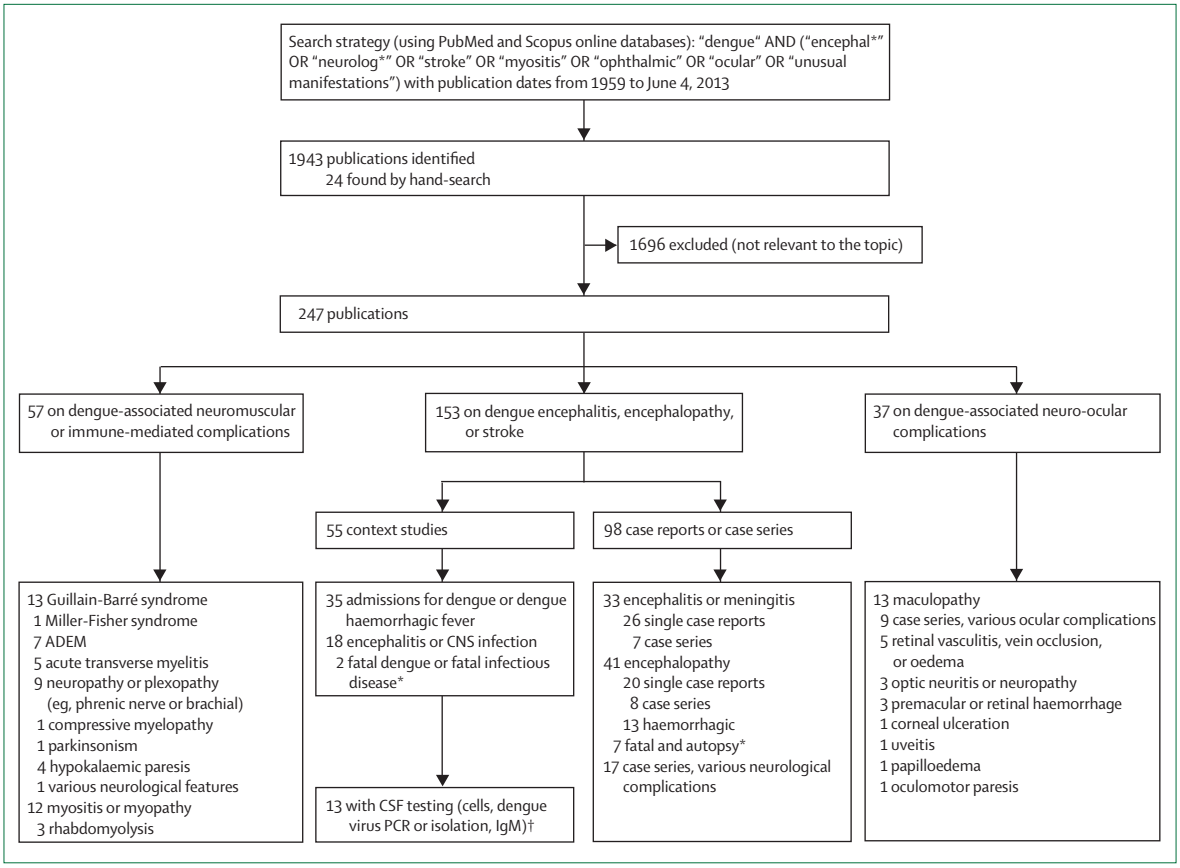

Figure 2: **Search strategy showing identification and inclusion of relevant studies**
Studies were classified into reports presenting cases with encephalitis or encephalopathy, according to the term used in the study. *For details see table 3. †For details see tables 1 and 2. ADEM=acute disseminated encephalomyelitis.

neurological features of dengue were classified as having encephalitis (table 1).[9]

Table 2 presents the proportion of dengue among admitted patients with encephalitis-like illness (n=6) or febrile encephalopathy (n=1).[26–32] In a hospital-based case series from Thailand, eight of 40 children admitted with encephalitis had dengue virus infection.[26] In India, dengue virus was the cause of acute febrile encephalopathy in 39 (15%) of 265 children.[29] In 21 of 29 CSF samples tested, the presence of dengue virus was shown by PCR, and in 16 of 36 CSF samples, the white-blood-cell count was raised (44% polymorphs on average).[29] In Brazil, findings of a hospital-based prospective case series showed that dengue not only was the leading cause of encephalitis (in eight of 17 cases) but also was detected in two of 20 patients with viral meningitis.[31] Pleocytosis was present in two of two patients clinically diagnosed with dengue meningitis and in two of eight patients with dengue encephalitis, and dengue virus was detected by PCR in CSF in both groups (table 2). However, because six of the eight patients with encephalitis had normal CSF cellularity and none of them had dengue virus-specific IgM, we are unsure whether these six patients represent true encephalitis (ie, caused by direct virus invasion) or encephalopathy cases.

Some case reports and case series were identified by our literature search in which patients were described with probable dengue encephalitis (figure 2); however, in only a few reports were data presented of CSF examinations for dengue virus or dengue virus antigen.[7,45–47] Other mechanisms apart from neuroinvasion—such as blood–brain barrier compromise—might lead to the presence of virus in the intrathecal space. Pleocytosis and high viral load in CSF without blood contamination indicate the neuroinvasive capacity of dengue virus. However, in most studies that presented CSF results (tables 1 and 2), a proportion of cases with dengue CNS involvement not only had no pleocytosis but also had no other underlying complications such as severe liver involvement, making definite categorisation into either encephalitis or encephalopathy difficult (panel 2).

Nine publications presented data from autopsy studies (table 3),[4,33–40] and additional fatal cases were reported within some context studies (appendix pp 1–2).[23,25] Evidence of dengue virus neurotropism from these studies is convincing. Of three fatal cases from Thailand, dengue

	Country	Study design; population	Proportion with neurological features	CSF diagnosis	Clinical manifestations
Cam et al (2001)[22]	Vietnam	Prospective case-control; 5400 children (age 0–15 years) admitted with dengue haemorrhagic fever	27 of 5400 (0·5%)	14 of 22 IgM-positive; one of 22 PCR-positive; 22 of 22 normal protein, glucose, cells	Coma (26 of 27), seizures (21 of 27), hemiplegia (1 of 27); 22% case fatality
Domingues et al (2008)[9]	Brazil	Prospective; 85 admissions (all ages) with laboratory-confirmed dengue	18 of 85 (21%)	Seven of 13 PCR-positive (copy number 265–417 per mL); three of seven PCR-positive in CSF but PCR-negative in serum; four of six PCR-negative in CSF but PCR-positive in serum	Encephalitis (11 of 18), encephalopathy (6 of 18), meningitis (1 of 18)
Pancharoen and Thisyakorn (2001)[23]	Thailand	Retrospective; 1493 children (age 0–15 years) admitted with laboratory-confirmed dengue	80 of 1493 (5·4%)	0 of 16 IgM-positive; 0 of 16 PCR-positive; seven of 31 pleocytosis in CSF	Encephalitis (42 of 80), seizures (35 of 80), miscellaneous (3 of 80); four (5%) of 80 died, one of 80 had long-term neurological sequelae
Solomon et al (2000)[8]	Vietnam	Prospective; 378 children and adults with suspected CNS infection in intensive-care unit, and 1691 admissions for dengue	16 of 1691 (1%) admissions for dengue; 16 of 378 (4%) with suspected CNS infection; five additional cases with CNS abnormalities studied subsequently	Eight of 16 IgM-positive; four of 16 PCR-positive or isolation-positive; three of four IgM-negative but PCR-positive or isolation-positive in CSF; three of 21 with pleocytosis; seven of 21 with protein >45 g/L	Encephalitis (9 of 21), encephalopathy (9 of 21), transverse myelitis (2 of 21), meningism (1 of 21)
Thisyakorn et al (1999)[25] (update from 1994)[24]	Thailand	Prospective; 2975 children (age 0–14 years) admitted with serologically confirmed dengue	30 of 2975 (1%)	Two of 19 IgM-positive; six of 28 pleocytosis	Altered consciousness (23 of 30 with CNS symptoms); seizures (19 of 30), pyramidal-tract signs (11 of 30), meningeal signs (9 of 30)

Further study details are presented in the appendix (pp 1–2).

Table 1: **Proportion of neurological features in patients admitted with dengue or dengue haemorrhagic fever**

	Country	Study design; population	Proportion with dengue diagnosis	CSF diagnosis	Clinical manifestations
Chokephaibulkit et al (2001)[26]	Thailand	Prospective; 40 children admitted with possible encephalitis or meningoencephalitis	Eight of 40 (20%)	One of eight PCR-positive; one of eight increased protein (69 g/L)	All eight had signs of encephalitis, one of eight had facial palsy (PCR-positive in CSF)
García-Rivera et al (2009)[27]	Puerto Rico	Prospective; 84 patients (all ages) with suspected acute neurological infection (enhanced hospital-based surveillance system), 34 encephalitis-like illness, 25 aseptic meningitis, 11 with motor disorder	Nine of 34 (26%) with encephalitis-like illness; two of 11 (18%) with motor disorders	One IgM-positive; three of five with mild pleocytosis; four of five increased protein	Encephalitis (9 of 11), motor disorder (2 of 11); two of 11 died
Kankirawatana et al (2000)[28]	Thailand	Prospective; 44 children (age 7–12 years) with acute viral encephalitis	Eight of 44 (18%)	One PCR-positive (cranial nerve palsy); none of eight tested for pleocytosis; one of eight mildly increased protein	Altered consciousness (8 of 8), cranial nerve palsy (1 of 8), meningism (2 of 8), papilloedema (1 of 8)
Kumar et al (2008)[29]	India	Prospective; 265 children (age 1–12 years) with acute febrile encephalopathy	39 of 265 (15%)	21 of 29 PCR-positive (copy number 35–68 718); 16 of 36 increased cell number	Seizures (31 of 39), meningeal signs (7 of 39), hyperventilation (13 of 39), cranial nerve palsies (4 of 39), neurological deficits (4 of 39); nine of 39 died
Le et al (2010)[30]	Vietnam	Prospective; 194 children (age <16 years) admitted with acute encephalitis (presumed viral)	Nine of 194 (5%)	Four of nine PCR-positive; six of nine virus isolation-positive; seven of nine IgM-positive; none of nine tested for pleocytosis	Limb weakness (2 of 9), neck stiffness (2 of 9), seizures (1 of 9); three of nine with Glasgow coma score ≤9, one of nine died
Soares et al (2011)[31]	Brazil	Prospective; 37 adolescents and adults with viral meningitis (20) or encephalitis (17)	Eight of 17 (47%) with encephalitis; two of 20 (10%) with viral meningitis	Of eight with encephalitis, one PCR-positive, one IgM-positive, and two with pleocytosis; of two with meningitis, one PCR-positive, two with pleocytosis	Seizures (7 of 8), mental confusion (4 of 8)
Srey et al (2002)[32]	Cambodia	Prospective; 99 patients (47 adults, 52 children) admitted with clinical encephalitis	Four of 52 (8%)	Three of four PCR-positive; one of four IgM-positive, but serum:CSF antibody titre ratio >40	All four had encephalitis

Further study details are presented in the appendix (pp 3–4).

Table 2: **Proportion of dengue diagnoses in patients admitted with encephalitis or encephalopathy**

	Country; study setting	Description of fatal dengue cases	CSF diagnosis	Dengue testing of brain tissue	Neuropathological autopsy results
Araújo et al (2012)[33]	Brazil; retrospective context study on fatal cases (age 0–86 years) with suspected infectious disease	84 dengue cases among 150 deaths, including 41 with neurological features (45 dengue fever, 20 dengue haemorrhagic fever, 19 dengue not suspected)	Seven of 41 PCR-positive; one of 41 isolation-positive; 22 of 41 NS1-antigen-positive; 27 of 41 IgM-positive	NA	Histopathological evidence for meningitis (9 of 75) and encephalitis (3 of 75); of 41 with neurological features of dengue, 13 had cerebral congestion, 23 oedema, one haemorrhage, two brain necrosis, two cerebellum oedema, two cerebellum congestion (multiple findings possible)
Bhoopat et al (1996)[34]	Thailand; Chiang Mai hospital	Three fatal cases (age 5–13 years) with neurological features (all dengue haemorrhagic fever)	NA	Dengue virus antigen in parenchymal cells (immunoperoxidase stain), including cerebral cortex neurons, Purkinje cells in cerebellum, microglia, and astrocytes	NA
Chimelli et al (1990)[35] and Miagostovich et al (1997, follow-up study)[36]	Brazil; outbreak in Rio de Janeiro	Five fatal cases (age 16–51 years) with neurological features (all dengue fever)	CSF not tested for dengue; one of two normal, one of two with 175 leucocytes per µL	Three of five were positive for dengue virus antigen (immunoperoxidase stain) in brain tissue	Brain oedema (3 of 5), focal haemorrhages (5 of 5), perivascular lymphocytes (5 of 5), perivenous demyelination (1 of 5)
Janssen et al (1998)[40]	Dutch traveller after returning from Thailand	One fatal case (age 25 years) with neurological features (dengue fever)	NA	PCR-positive (DENV 3); virus isolation-positive from brain tissue	Brain diffusely swollen, secondary haemorrhage in the pons; no infiltration of mononuclear cells; no signs of meningoencephalitis
Nimmannitya et al (1987)[4]	Thailand; retrospective review of autopsy reports and microscopic slides at Children's Hospital, Bangkok	Ten fatal cases (age 0–12 years) with unusual neurological manifestations (all dengue haemorrhagic fever)	CSF not tested for dengue; two of five normal, three of five with red blood cells	NA	Microscopic examination showed no pathological evidence of encephalitis; brain oedema (3 of 10), intracranial haemorrhage (6 of 10), unremarkable (1 of 10)
Nogueira et al (2002)[37]	Brazil; state of Rio Grande do Norte	One fatal case (age 67 years) with neurological features (dengue fever)	NA	Positive for dengue virus antigen (immunoperoxidase stain) in cerebral cortical grey matter; DENV 2 isolation-positive and PCR-positive	Brain oedema; no infiltration of mononuclear cells
Nogueira et al (2005)[38]	Brazil; outbreak in Rio de Janeiro	40 fatal cases (age 7–65 years); proportion with neurological features unknown	One of two PCR-positive; none of two isolation-positive; none of two IgM-positive	Three of three PCR-positive; none of three isolation-positive; two of seven positive immunohistochemistry	Oedema and congestion of brain; microhaemorrhagic foci; no striking inflammatory reactions noted; frequent meningeal congestion
Ramos et al (1998)[39]	Mexico; outbreak in Sinaloa	1 fatal case (age 17 years) with neurological features (dengue haemorrhagic fever)	NA	PCR-positive in tissue from inferior olivary nucleus of medulla and granular layer of cerebellum; positive immunohistochemistry	Slight meningeal opacity; vein congestion; generalised oedema with bilateral uncus herniation; no distinctive histopathological features of brain viral infection

NA=not available. Further study details are presented in the appendix (pp 5–6).

Table 3: **Neurological manifestations of fatal dengue**

virus antigen was detected in parenchymal cells of the brain using immunoperoxidase stain.[34] In a fatal case from Brazil, analysis of cerebral cortical grey matter showed dengue virus antigen and DENV 2 was detected by PCR in ground brain.[37] In a series of 40 laboratory-confirmed fatal cases of dengue from Brazil,[38] dengue virus was detected by PCR in three of three brain samples and dengue virus antigen was recorded in two of seven samples. However, despite the presence of dengue virus or dengue virus antigen in brain tissue, distinctive histopathological features of viral brain infection were not noted (table 3).

Patients with dengue encephalitis can present with diminished consciousness, headache, dizziness, disorientation, seizures, and behavioural symptoms.[9,48] Tetraparesis might be seen in severe cases.[41] Seizures seem more common in individuals with dengue encephalitis than in those with encephalopathy; in a study of 16 patients with dengue encephalitis, generalised seizures were noted in roughly half of them.[8] Epilepsia partialis continua has been described as a manifestation of dengue encephalitis in a case report.[49]

Because manifestations of dengue encephalitis and dengue encephalopathy are indistinguishable clinically, acute liver failure, hypovolaemic shock with metabolic deteriorations, and intracranial haemorrhage need to be ruled out, and CSF examinations should be done if safe and feasible. The outcome of dengue encephalitis is variable, with most patients recovering spontaneously in one case series whereas some deaths were noted in others.[27,30,41]

***Panel 2:* Proposed definitions for neurological features of dengue**

Dengue diagnostic test highly suggestive of or confirming acute dengue virus infection, as recommended by WHO*, AND one of the following clinical categories:

Dengue CNS involvement

At least one of the following: impaired consciousness (for children younger than 6 years, Blantyre coma score ≤4; for those older than 5 years, Glasgow coma score ≤14), neck stiffness, focal neurological signs, or seizure

Dengue encephalopathy

- Dengue CNS involvement, AND
- Presence of one of the following dengue-associated complications: hepatic failure, metabolic acidosis, severe hyponatraemia, prolonged shock, disseminated intravascular coagulation, or brain haemorrhage, AND
- Normal CSF (in brain haemorrhage, blood in CSF is possible)

Dengue encephalitis

- Dengue CNS involvement, AND
- Presence of dengue virus RNA, IgM, or NS1 antigen in CSF, AND
- CSF pleocytosis without other neuroinvasive pathogens

Immune-mediated dengue CNS involvement

Other or non-specified dengue CNS involvement

Dengue-associated neuromuscular complications

- Guillain-Barré syndrome
- Rhabdomyolysis
- Other or non-specified peripheral neuromuscular complications

Dengue-associated neuro-ophthalmic complications

- One of the following clinical symptoms: blurred vision, eye flashes, floaters, sudden decrease in vision, visual field defect, scotoma, eye redness, metamorphopsia, or micropsia, AND
- Eye examination with at least one of the following: optic neuropathy (optic disc swelling or hyperaemia), maculopathy (oedema or blot haemorrhages), retinal vasculitis, retinal haemorrhages, exudative retinal detachment, cotton wool spots, or signs of foveolitis or anterior uveitis

*Highly suggestive dengue is defined as: IgM-positive in one serum sample; or IgG-positive in one serum sample with haemagglutination inhibition titre of 1280 or greater. Confirmed dengue is defined by one of the following: PCR-positive; virus culture-positive; IgM seroconversion in paired serum samples; IgM seroconversion in paired serum samples or four-times IgG titre increase in paired serum samples.[1]

Post-dengue immune-mediated syndromes

Post-dengue immune-mediated neurological syndromes include acute transverse myelitis, acute disseminated encephalomyelitis, and Guillain-Barré syndrome (figure 2). Reports are rare of neuromyelitis optica,[50] Miller-Fisher syndrome,[51] and mononeuropathies such as phrenic neuropathy,[52–54] long thoracic neuropathy,[55] isolated Bell's palsy,[56] abducens nerve palsy,[57] and oculomotor palsy.[58] Usually, post-infectious disorders are only linked temporally to dengue virus infection, with a causal association merely inferred. Post-dengue syndromes generally resolve within weeks or a few months, as is typical with these disorders.[54,57,59,60]

Acute transverse myelitis

Spinal cord involvement can happen in patients with dengue both during and after infection. Direct virus invasion can take place in the parainfectious stage whereas immune-mediated factors are noted post-infection. Several cases of post-dengue acute transverse myelitis have been reported.[61–66] Here, acute weakness and numbness of the lower limbs and urinary retention are seen. Post-infectious immune-mediated myelitis usually arises 1–2 weeks after the onset of initial symptoms,[61] whereas parainfectious myelitis can take place within the first week of infection.[63,64]

Intrathecal synthesis of dengue virus-specific IgG antibodies has been detected in patients with dengue myelitis.[65] MRI of the spinal cord can either be normal or show areas of high signal on T2-weighted sequences.[61] In some patients, T2-weighted MRI shows a high-intensity signal from the lower cervical to upper lumbar regions in the spinal cord.[64]

Acute disseminated encephalomyelitis and neuromyelitis optica

Some cases of acute disseminated encephalomyelitis have been reported in the convalescence stage of dengue virus infection, in both classic dengue fever and dengue haemorrhagic fever.[50,65,67–76] CSF analysis might show a moderate rise in protein concentration and pleocytosis.[69,72] Brain MRI can show areas of high signal on T2-weighted images and gadolinium enhancement on T1-weighted images (figure 3).[69,72,77] In patients with neuromyelitis optica, many high-intensity lesions can be seen on T2-weighted images in the spinal cord, whereas MRI images of the brain show no abnormalities.[72]

Guillain-Barré syndrome

Dengue virus infection preceding Guillain-Barré syndrome has been described in case reports and case series of patients presenting with various neurological manifestations.[27,59,60,65,70,78–91] Acute onset of limb weakness and areflexia was noted a week after symptom onset.[59,70,78–81,83] The acute pure axonal motor-sensory variant of Guillain-Barré syndrome has also been described after dengue virus infection.[89] CSF analysis might show increased protein concentrations without pleocytosis (albumin-cytological dissociation). Guillain-Barré syndrome has also been described in patients with oligosymptomatic dengue virus infection.[84]

Cerebrovascular complications

Intracranial haemorrhages have been reported during the convalescence stage of dengue.[75,92] The incidence of dengue-associated cerebrovascular complications is unknown, although haemorrhagic stroke seems more common than ischaemic stroke. During an epidemic in India, 1148 laboratory-confirmed dengue patients were admitted to hospital and three had a stroke (0·26%).[93] During the 2003 epidemic in Brazil, only one patient with brain haemorrhage was registered among 1585 confirmed dengue cases.[94] However, in dengue-endemic countries, we assume that patients with haemorrhagic or ischaemic stroke are tested rarely for dengue.

Most patients have intracranial bleeding a week after fever onset.[92] Acute intracranial bleeding can arise without other (visible) haemorrhagic manifestations. Basal ganglia haemorrhages and multiple haemorrhagic foci in brain lobes are recorded.[4] Less common presentations of intracranial bleeding include bilateral cerebellar haemorrhage with oedema, mass effect, and obstructive hydrocephalus,[93] pontine haemorrhage,[94] acute subdural haematoma,[95–97] multiple acute subdural haematomas,[92] pituitary adenoma haemorrhage,[98] subarachnoid haemorrhage,[4,75] and focal subarachnoid haemorrhage associated with transient thrombocytopenia.[99] In some cases of fatal subarachnoid haemorrhage, post-mortem examination did not show intracranial aneurysm—eg, in a traveller returning to Norway.[100]

Cases of dengue fever with thrombocytopenia and ischaemic stroke are possible but infrequent.[101] Brain CT and MRI should be done to confirm a clinical suspicion of stroke. Several areas of watershed infarcts, small cortical infarctions, and dysarthria clumsy-hand syndrome due to corona radiata and putamen infarction have been reported.[93,102] Gradient-echo MRI can be useful to detect small bleeds, and diffusion-weighted images can show subacute infarctions.

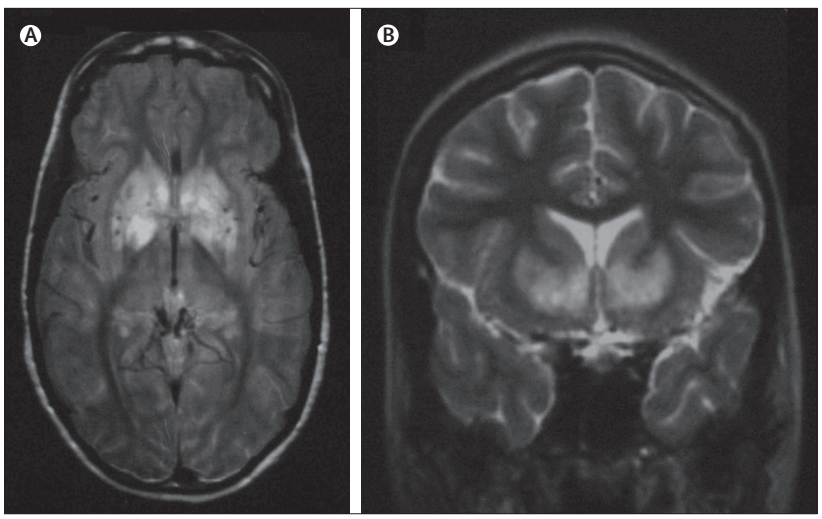

Figure 3: **FLAIR and T2-weighted MRI of acute disseminated encephalomyelitis**
(A) FLAIR MRI. (B) T2-weighted MRI. Images show involvement of bilateral lentiform nuclei in a 10-year-old girl with the rare post-dengue neurological manifestation acute disseminated encephalomyelitis. Reproduced from Palma-da Cunha-Matta et al,[70] with permission of Viguera Editores.

Dengue muscle dysfunction

Few epidemiological studies have been done to assess the incidence of neuromuscular complications after dengue virus infection. In a Saudi Arabian hospital-based study of 101 patients with dengue confirmed by serological analysis (42% dengue haemorrhagic fever, 58% dengue fever), raised amounts of creatine phosphokinase were recorded in 91%, myalgia in 63%, and mild proximal muscle weakness in 3%.[103] In India, of 39 cases of dengue confirmed serologically, 16 had clinical and 15 had subclinical muscle involvement.[104] Of these 31, eight people had severe weakness and five had hyporeflexia; severity correlated with creatine phosphokinase concentrations. In another study from India, of 40 children with benign acute childhood myositis, 20 were positive for dengue virus-specific antibodies, indicative of acute infection.[105]

Clinical studies based on case reports (n=1) and small case series (2–31 patients) describe pure motor weakness associated with dengue virus infection.[104–116] The clinical picture in these reports is highly variable. The weakness was generally referred to as dengue myositis, but recently, the term dengue-associated transient muscle dysfunction has been proposed because of the benign and self-limiting nature of the disorder.[104] Dengue virus could be one of the main causes of childhood benign acute viral myositis—also called myalgia cruris epidemica—in tropical regions.[105]

Dengue virus infection can present with varying degrees of transient myalgia, characterised by muscle tenderness on stretching, motor weakness, raised amounts of muscle enzymes, and—in very severe cases—rhabdomyolysis.[106,107,110] Motor weakness might range from mild hypotonia and proximal muscle weakness in both upper and lower limbs to asymmetrical weakness of lower limbs and severe quadriparesis.[108,110] Motor quadriplegia and neck, trunk, and respiratory muscle weakness that could lead to death have been noted in severe cases.[108,111] Amounts of creatine phosphokinase in serum can be raised during the first week of illness; in one case series, values ranged from 500 IU/L to more than 100 000 IU/L,[108] with a median of 837 IU/L in another study.[104] High concentrations of creatine phosphokinase might be secondary to intense muscle inflammation.[108] Dengue myositis and myocarditis, with augmentation of the creatine kinase muscle:brain ratio, can happen simultaneously.[104,112]

Dengue muscle dysfunction differs from typical inflammatory myopathy because of a paucity of findings on electromyography and an absence of spontaneous activity.[104] An electromyogram can show early recruitment of motor-unit action potentials with normal morphological findings and no spontaneous activity.[108] Motor-unit action potentials might be of normal-to-short duration and polyphasic with full recruitment, in accordance with mild myopathic changes.[104] Mild-to-moderate perivascular mononuclear infiltrates, interstitial haemorrhage with occasional myonecrosis, and lipid accumulation have been noted in muscle biopsy specimens.[110,113,117]

In general, dengue muscle dysfunction is judged a benign presentation of dengue virus infection, and spontaneous recovery happens in most patients within 1–2 weeks. Severe fulminant myositis and severe persistent steroid-responsive myositis are reported infrequently.[108,111,114] Differential diagnoses include bacterial myositis and leptospirosis muscle involvement. Normal findings on nerve-conduction studies and an

absence of albumin-cytological dissociation are useful to exclude Guillain-Barré syndrome.

Neuro-ophthalmic complications

Neuro-ophthalmic manifestations of dengue typically entail the posterior segment. Anterior uveitis without evidence of posterior segment involvement can happen rarely and be associated with progressive loss of vision.[118] Ocular complications include dengue maculopathy, retinal oedema, retinal haemorrhages, optic disc swelling, optic neuropathy, and vitritis. Incidence of these disorders is probably underestimated; neuro-ophthalmic complications usually develop during the convalescence stage of dengue virus infection and without systemic bleeding diathesis. Many patients with ocular complications have classic dengue fever with normal platelet counts and without substantial haemodynamic derangement.[119] In Singapore, the estimated prevalence of dengue maculopathy was 10% among 160 admissions for dengue.[120] In India, ocular involvement was noted in 40% of 134 dengue admissions.[121]

Retinal vasculopathy might be the most common ocular manifestation of dengue virus infection.[122] Another typical feature is retinal haemorrhage attributable to increased vascular permeability and breakdown of the inner blood–retinal barrier. Occlusion of precapillary arterioles can provoke microinfarctions of the nerve fibre layer, which can be detected as cotton wool spots on ophthalmological examination.[123] In case series, the most common ocular finding was dengue maculopathy presenting as macular oedema, haemorrhage, or both, yellow spots in the macula, and focal chorioretinitis with or without retinal vasculitis.[120,124] In a retrospective series of 41 patients with impaired vision from dengue-related maculopathy, blurring vision (21 cases) and central scotoma (14 cases) were the most frequent visual complaints.[124] Exudative maculopathy and small haemorrhages located in the optic nerve fibre layer can provoke reduced visual acuity.

Optic neuropathy has been described in a few cases.[125,126] Bilateral visual loss secondary to pituitary adenoma and bilateral vitreous haemorrhage associated with dengue fever have also been reported.[98,127] Most patients recover spontaneously to their best-corrected visual acuity without specific treatment between 1 week and 3 months after onset.[120] Nevertheless, some people might complain of persistent scotoma, and visual impairment could remain in cases of severe exudative maculopathy and retinal haemorrhage.[118,128]

Pathogenesis of neurological features of dengue

Dengue virus encephalitis

The pathogenesis of dengue neurological involvement and underlying virus–host interactions remain to be elucidated. For a long time, uncertainty surrounded whether dengue virus crossed the blood–brain barrier passively or whether active viral CNS invasion took place. Detection of dengue virus RNA in CSF, viral antigen in brain tissue, and concomitant pleocytosis lends support to the hypothesis of direct viral invasion of brain parenchyma (tables 1–3). Furthermore, the simultaneous finding of viral RNA in CSF and negative RT-PCR in serum samples suggests that dengue virus might enter the CNS actively and that the presence of virus in the CNS does not result from passive crossing of the blood–brain barrier or vascular leakage.[8,9]

From a pathological point of view, encephalitis is a histopathological diagnosis based on inflammation of brain parenchyma. Therefore, findings of autopsy studies provide substantive evidence for the neuroinvasive capacity of dengue virus, by showing dengue virus or dengue virus antigen in brain tissue concomitant with histopathological features of brain infection.[23,25,33,36] However, in some autopsy studies, dengue virus or dengue virus antigen have been reported in brain tissue without histopathological brain changes (table 3); non-specific lesions—oedema, vascular congestion, haemorrhagic foci, and perivascular lymphocytic infiltrates—were predominant features in these patients.

Dengue virus replicates within the cells of the immune system, particularly macrophages and monocytes. Virus entry via infected macrophages and histamine release have, therefore, been implicated as potential mechanisms.[36,129,130] Dengue virus antigen has also been detected in neurons of infected mice, and viral tropism for neurons of anterior horns, hippocampus, and cerebral cortex has been shown in vivo.[131] Viral factors are important in neuropathogenesis, and changes in dengue virus replication and assembly might augment apoptosis. In a murine model of dengue encephalitis, mutations of three aminoacids in DENV 1 produced a neurovirulent phenotype, resulting in extensive brain damage with encephalitis and leptomeningitis.[132] Similar to other flaviviruses, the envelope protein might have an important role in regulating CNS invasiveness and the neurovirulence of dengue virus.[133] However, since mice are not a perfect model for dengue virus, these findings cannot necessarily be extrapolated to account for the pathogenesis in human beings.

Other dengue-associated neurological complications

Pathogenic mechanisms of dengue cerebrovascular complications are not understood completely. Dengue virus infection might result in the release of mediators (including cytokines, chemokines, and complement-associated viral particles) with vasoactive or procoagulant properties, capillary leakage, increased fibrinolysis, and bleeding. Altered prothrombin time, severe thrombocytopenia, disseminated intravascular coagulation, and vasculitis can lead to haemorrhagic infarction and stroke.[129] The precise pathogenesis of acute disseminated encephalomyelitis remains unknown, but because virus has not been isolated from the CSF of patients infected with dengue virus and with acute disseminated encephalomyelitis, an immune-mediated cause is supported.[41,69,75]

Dengue virus could trigger a complex immune response, resulting in cytokine overproduction (interleukin 2, interferon γ, and tumour necrosis factor α) and inversion of the CD4:CD8 ratio.[134] Cytokines can provoke immune-mediated dysfunction of endothelial cells.[133] Furthermore, increased vascular permeability with subsequent hypotension and prolonged shock, metabolic disturbances, and hepatic dysfunction in patients with severe dengue might contribute to the pathogenesis and presentation of other neurological complications, such as encephalopathy or even rhabdomyolysis.[134]

Pathogenic mechanisms of neuro-ophthalmic dengue are poorly understood, although an immune-mediated process has been suggested.[120] Immunological activation response with release of cytokines with vasoactive and procoagulant properties could account for the occurrence of retinal vascular occlusion. The usual 1-week delay in appearance of neuro-ophthalmic symptoms after dengue disease onset favours the hypothesis of an immune-mediated process. Findings of an autoimmune screen in a patient with retinal vasculitis and macular detachment showed a low amount of C4 complement, suggesting that dengue virus infection could be the antigenic trigger for immune complex deposition and vasculitis.[135]

Diagnosis

Clinical suspicion is essential for diagnosis of dengue because many symptoms are non-specific. Various methods are available for laboratory confirmation. During the first days of infection, dengue virus is present in blood; thus, at that time, detection of NS1 antigen or RNA by RT-PCR and viral culture are appropriate diagnostic methods.[1] Dengue virus-specific IgM antibodies are present in serum samples 3–10 days after disease onset.[1] IgM capture (MAC)-ELISA is the most widely used serological test. Antibodies against other flaviviruses (eg, Japanese encephalitis, West Nile virus, yellow fever) might cross-react with dengue virus, leading to false-positive reactions.[136]

In endemic countries, or among travellers who recently (<14 days) returned from such regions, dengue should be ruled out in patients with fever and neurological features (panel 2). If possible, lumbar puncture should be done and CSF analysed for abnormalities and for dengue virus-specific antibodies, NS1 antigen, or dengue virus RNA, depending on available laboratory facilities. Differential diagnosis in patients with febrile encephalopathy includes malaria, tuberculosis, leptospirosis, rickettsial infection, and other bacterial or viral diseases (caused by, for example, Japanese encephalitis, West Nile virus, or herpes simplex virus [HSV]), depending on the local epidemiology. In a prospective hospital-based study in Vietnam, most children with acute encephalitis of presumed viral origin were infected with Japanese encephalitis (26%), followed by enteroviruses (9%) and dengue virus (5%).[30] In adults and adolescents in Brazil, dengue was the leading cause of viral encephalitis (47%), followed by infections with HSV-1.[31]

To differentiate dengue encephalitis from encephalopathy, detection of dengue virus, NS1 antigen, or dengue virus-specific IgM antibodies in CSF is helpful. Nevertheless, sensitivity of serological techniques can be low. Dengue virus-specific IgM antibodies have been recorded in CSF of 22–33% of patients diagnosed with dengue encephalitis (tables 1 and 2).[90] Detection of dengue virus in CSF could be hampered by low sensitivity of RT-PCR in CSF, compared with findings in serum, because of a lower viral load.[137] Moreover, measurement of IgM antibodies in CSF might not be a reliable diagnostic marker of dengue CNS involvement, owing to low titres in CSF.[138] Abnormalities in CSF—such as lymphocytic pleocytosis—support the diagnosis of dengue encephalitis, but they are not always present (tables 1–3). A mild increase in CSF protein has been recorded.[28] In a series of patients with neurological complications of dengue, four of seven with encephalitis had no alterations in CSF.[90] Therefore, normal CSF cellularity should not exclude dengue encephalitis.

The case definitions in panel 2 are designed to be used epidemiologically and clinically and to guide diagnosis and prognosis. Although we propose criteria for a classification scheme, a topic as challenging and as controversial as dengue encephalitis needs to be addressed in a standard way. Prospective studies are needed to assess the specificity and sensitivity of the proposed case definitions and to generate supporting evidence. Cases fulfilling neither the definition for encephalitis nor that for encephalopathy—eg, without CSF testing or when categories are overlapping—can be categorised as other or non-specified dengue CNS involvement.

Neuroimaging might provide additional clues in the diagnosis of neurological complications of dengue. In dengue encephalitis, brain MRI can be normal or show focal parenchymal abnormalities.[22,41] Nevertheless, no specific MRI findings suggestive of dengue encephalitis have been reported. Neuroimaging features of patients with dengue are diverse, with cerebral oedema the most commonly reported finding.[77] Meningeal enhancement on post-contrast MRI has been reported occasionally as well.[77]

Finally, EEG abnormalities can be seen in dengue patients with neurological complications. In a study of 23 patients with dengue virus infection and neurological symptoms, EEG abnormalities were recorded in 12 people.[139] Slowing on EEG can be seen, but this finding is unspecific and could be attributable to seizures, intracranial haemorrhage, and viral infection per se, besides encephalopathy.[77]

Management

Currently, no effective antiviral agents are available to treat symptomatic dengue virus infection.[140] Therefore, management remains supportive. In mild cases, antipyretic drugs and oral fluids could be useful. Acetyl-salicylic derivatives and other non-steroidal anti-inflammatory drugs should be avoided. Management

of haemorrhagic complications should be initially conservative. Precise management of intravenous fluids is needed, and blood or platelet transfusion is only necessary when severe bleeding takes place.[1]

In patients with severe dengue and signs of plasma leakage, prompt fluid resuscitation is imperative, with close monitoring of packed-cell volume to avoid fluid overload. Isotonic crystalloid solutions should be used, with isotonic colloid solutions reserved for patients presenting with profound shock or those who do not have a response to initial crystalloid treatment.[140,141] In a randomised controlled trial from Vietnam,[142] use of oral prednisolone during the early acute phase of dengue infection was not associated with a reduction in the development of shock or other recognised complications of dengue virus infection.

For supportive management of patients with neurological manifestations, possible underlying causes such as intracranial bleeding, liver failure, hyponatraemia, hypokalaemia, or metabolic acidosis should be ruled out and—if possible—corrected. Management of dengue encephalitis remains supportive and should include adequate hydration, nutrition, monitoring of consciousness, and maintenance of airways.[143] Symptomatic seizures should be treated with non-hepatotoxic anticonvulsants. Decompressive craniotomy and cerebral haematoma evacuation were done in two patients with dengue after correction of prothrombin time and platelet count.[92] Nevertheless, prognosis is not good and, in one case series, two of five patients died.[92] At this moment, haematoma surgery cannot be proposed as a routine treatment for dengue virus intracranial bleeding.

Some clinicians recommend treatment of immune-mediated dengue CNS involvement with pulses of intravenous methylprednisolone for several days.[50,69,72] However, up to now, no randomised controlled trial has been undertaken to show the efficacy of this approach in patients with dengue myelitis or acute disseminated encephalomyelitis. High doses of intravenous immunoglobulin might be useful to treat post-dengue Guillain-Barré syndrome. Supportive treatment—including hydration and analgesic drugs—is used for myalgia and transitory muscle dysfunction. The effectiveness of corticosteroids in dengue myositis remains to be proven.

No treatment has been approved for neuro-ophthalmic manifestations of dengue. Steroids have been administered previously because of possible underlying immune mechanisms, although up to now no randomised trials have been done. Topical steroids have been used to treat anterior uveitis, whereas pulsed intravenous methylprednisolone or systemic oral steroids might be indicated for extensive retinal vasculitis.[120]

Currently, no vaccine is available for protection against dengue. However, several vaccine candidates are in development.[144,145]

Search strategy and selection criteria

We searched Pubmed and Scopus for reports published between January, 1960, and June, 2013, with the terms ("dengue") AND ("neurolog*" or "encephal*" or "stroke" or "myositis" or "ophthalmic complications" or "ocular" or "unusual manifestations"). We did not include mental disorders after dengue virus infection in our search. We only considered original studies published in peer-reviewed journals in English, Spanish, Portuguese, German, or French. To verify our strategy, we hand-searched the reference lists of the 20 most cited primary articles on neurological manifestations in dengue patients and added relevant citations to our database. Next, we screened all titles and abstracts identified by the search and included those on dengue patients presenting with neuromuscular or immune-mediated complications; encephalitis, encephalopathy, or stroke; or neuro-ophthalmic complications. We excluded irrelevant articles or reviews. We then reviewed the full text of all included articles and abstracted relevant data. We presented articles in summary tables if they fulfilled the following criteria: (1) contained information on laboratory confirmation of dengue; (2) put dengue patients with neurological complications into context with either all dengue cases or all encephalitis cases presenting in a clinic; and (3) presented results of CSF testing (cells, dengue-specific antibodies, viral RNA) in a large proportion of dengue patients with suspected CNS involvement. Furthermore, articles presenting autopsy studies on fatal dengue cases with neurological manifestations were abstracted and summarised in a table.

Conclusions and future research

Dengue should be included in the differential diagnosis of acute febrile disease with neurological manifestations in dengue-endemic countries and in patients with a recent travel history to an endemic region. Many neurological manifestations of dengue have been recorded, ranging—with substantial overlap—from encephalitis and encephalopathy to immune-mediated syndromes and muscle involvement. Recent evidence suggests that dengue virus has neuroinvasive capacity. In several studies in endemic areas, a large proportion of viral encephalitis was caused by dengue virus.[26–32] However, even though CNS involvement is included now as a criterion for severe dengue in the 2009 WHO case classification,[1] no standardised case definitions or diagnostic criteria for dengue encephalitis or encephalopathy have been agreed, which leads to inconsistent use of these terms in published work.

An updated WHO dengue guideline should include a case definition for dengue encephalitis and encephalopathy, to guide clinicians and clinical epidemiological researchers into this topic. A case classification—such as the one proposed in panel 2—could serve as a starting point, which could be reviewed by WHO, agreed by consensus and best available current evidence, and refined as additional data become available from prospective studies. For this reason, assessment of CSF in patients with suspected neurological manifestations of dengue should be standardised. Very few published reports present findings of CSF testing for dengue virus, dengue virus-specific IgM antibodies, or NS1 antigen combined with CSF cellularity and confirmation of dengue in serum samples in a consistent way. Further epidemiological and neuropathological studies are needed to ascertain the true

incidence and burden of neurological complications of dengue, to elucidate the underlying pathophysiology, and to assess the sensitivity and specificity of diagnostic markers for dengue encephalitis.

Contributors

All authors contributed equally to writing of this Review, to preparation of the tables and figures, and to the literature search.

Conflicts of interest

We declare that we have no conflicts of interest.

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