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Review article

Acute disseminated encephalomyelitis in dengue viral infection

Wan Aliaa Wan Sulaiman [a,d,*], Liyana Najwa Inche Mat [a,d], Hasnur Zaman Hashim [a], Hoo Fan Kee [a,d], Ching Siew Mooi [b,d], Ramachandran Vasudevan [d], Mohd Hazmi Mohamed [c], Hamidon Basri [a]

[a] Department of Medicine, Faculty of Medicine and Health Sciences, University Putra Malaysia, Serdang, Malaysia
[b] Department of Family Medicine, Faculty of Medicine and Health Sciences, University Putra Malaysia, Serdang, Malaysia
[c] Department of Surgery, Faculty of Medicine and Health Sciences, University Putra Malaysia, Serdang, Malaysia
[d] Institute of Gerontology, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

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ABSTRACT

Dengue is the most common arboviral disease affecting many countries worldwide. An RNA virus from the flaviviridae family, dengue has four antigenically distinct serotypes (DEN-1–DEN-4). Neurological involvement in dengue can be classified into dengue encephalopathy immune-mediated syndromes, encephalitis, neuromuscular or dengue muscle dysfunction and neuro-ophthalmic involvement. Acute disseminated encephalomyelitis (ADEM) is an immune mediated acute demyelinating disorder of the central nervous system following recent infection or vaccination. This monophasic illness is characterised by multifocal white matter involvement. Many dengue studies and case reports have linked ADEM with dengue virus infection but the association is still not clear. Therefore, this article is to review and discuss concerning ADEM in dengue as an immune-medicated neurological complication; and the management strategy required based on recent literature.

1. Introduction

The growing global epidemic of dengue particularly in Asia and Central America, have caused substantial morbidity and mortality globally. The transmission of dengue virus to humans, occurs via adult female *Aedes* mosquitoes, with *Aedes aegypti* and *Aedes albopictus* being the primary vectors [1]. The population of *Aedes* mosquitoes and their breeding sites has been increasing as a consequence of the world population explosion and unplanned urbanisation. Vaccine for dengue is still under evaluation to be used in public immunisation programme [2,3]. Thus, prevention through control of disease transmission is the only method possible to reduce the burden dengue. A successful vector strategy is required to control and eliminate the *Aedes* mosquitoes and their breeding sites [4].

An RNA virus from the flaviviridae family, dengue has four antigenically distinct serotypes i.e. DENV 1, DENV 2, DENV 3 and DENV 4. Additionally, a possible fifth serotype has been found in 2013, but the virulence of the virus is still uncertain [5]. An infection by any serotype induces life-long protective immunity against subsequent infection to the homologous serotype [6]. However, re-infection with a heterologous dengue virus serotype is associated with severe disease, as more cytokines and inflammatory mediators are released via antibody-dependent enhancement [7].

Case fatality rate for severe dengue is from 0.2% to 5% [1], mainly caused by severe bleeding and plasma leakage that leads respiratory distress and multi-organ impairment. WHO classifies any severe involvement of organs such as liver, heart and central nervous system as one of the case definition for severe dengue. Neurological involvement in dengue can be further classified into dengue encephalopathy immune-mediated syndromes, encephalitis, neuromuscular or dengue muscle dysfunction and neuro-ophthalmic involvement. Most of these occur acutely during acute illness but immune-mediated syndromes typically occur following resolution of dengue fever. Acute disseminated encephalomyelitis (ADEM) characterised by multifocal CNS inflammatory white matter demyelination, is an immune mediated demyelinating monophasic disease that is commonly triggered by infections or vaccinations [8]. Recognised causative factors are mainly viral, such as influenza, measles and rubella [9]. Intriguingly, in the last few years, many dengue studies and case reports have linked ADEM with dengue virus infection but the association is still not well established. This review summarises current evidence and published literature of ADEM as the neurological complication dengue using PubMed and Scopus database, as well as describing

* Corresponding author at: Department of Medicine, Faculty of Medicine and Health Sciences, University Putra Malaysia, Serdang, Malaysia.
E-mail address: wanaliaa@upm.edu.my (W.A. Wan Sulaiman).

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its clinical features, diagnosis, associated neuropathology and management of the disease.

2. Literature review

2.1. Neurological complications of dengue

The neurological manifestations have long been observed among dengue cases [10,11]. The proportion of dengue cases with neurological involvement ranged between 0.5% [12] and 21% [13] and the neuropathogenesis has been mainly associated with DENV 2 and 3 serotypes [7]. The symptoms of neurological dengue involvement vary and often overlap, as both central and peripheral nervous system is affected [14]. The most common neurological diagnosis are encephalopathy and encephalitis followed by myositis, hypokalemic paralysis, Guillain–Barré syndrome (GBS), ADEM and transverse myelitis [15]. The pathogenesis of neurological involvement can be caused by the following factors; systemic metabolic disturbances; or direct viral invasion of nervous system; or post infectious autoimmune reaction secondary to dengue infection [16].

Nonetheless, until the revised dengue guidelines was published in 2009, neurological symptoms were not part of the previous WHO dengue classifications [17]. For the first time, neurological involvement is included in the case definition for severe dengue, although no detail neurological symptoms are described [1].

The subsequent WHO SEARO 2011 report has suggested a term i.e. expanded dengue syndromes, for atypical manifestations of dengue according to system involvement. Neurological complications such as seizures, encephalopathy, encephalitis, aseptic meningitis, intracranial haemorrhages or thrombosis, subdural effusions, neuropathies and transverse myelitis are described in this report [18,19].

Post infectious ADEM, one of the neurological complications, is categorised as an immune-mediated dengue CNS involvement under the proposed neurological case classification by Carod-Artal et al. [16]. Other post-dengue immune-mediated neurological syndromes include acute transverse myelitis, Guillain–Barré syndrome and rarely Miller-Fisher syndrome and mononeuropathies. These neurological symptoms are usually preceded by the dengue infection and will improve after few weeks [16].

The association of dengue virus with ADEM is very rare but has been increasingly recognised in literature. Using PubMed and Scopus database, this present review found a total of 13 publications on ADEM post dengue infection in addition to the 7 publications identified by Carod-Artal et al. [16].

Of these 20 publications, 5 were original studies and were published between 2005 and 2016 (Table 1), while 15 were case reports and were published between 2002 and 2015 (Table 2).

2.2. ADEM: post dengue immune mediated syndrome

ADEM is an acute para or post-infectious encephalopathy characterised by diffused inflammatory demyelinating lesions that mainly affects the white matter of the central nervous system [20]. ADEM is a rare disease that can occur at any age, but children and adolescents are more affected with the incidence of about 0.8 per 100,000 population [21].

However, majority of the reported cases on ADEM in the neurological dengue are adult patients, with the mean age of 21 years (Table 2). The youngest patient reported was a full term neonate of 9 days old, who had a vertical transmission of dengue [22], while the oldest patient was 58 years old [23].

There are 5 prospective and retrospective studies that have reported ADEM as one of the neurological complications of the dengue patients. Table 1 presents the proportion of neurological manifestations among the dengue patients and also the proportion of ADEM among the dengue patients with neurological features. The proportion of ADEM in neurologically involved dengue patients ranges from the lowest 2% in Brazil [24] to the highest 11% in India [25].

In a prospective hospital-based study from India, 21 of 799 adults admitted for dengue had neurological features and ADEM was the cause of neurological features in 2 of the 21 patients [26]. Higher cases of ADEM noted from prospective and later studies may be attributed to the increased awareness of physicians on the possibility of the ADEM in dengue since the first case reported in 2002 [23].

As shown in Table 2, 15 case reports presented clinical cases of 15 patients and an additional 7 patients were reported within the five studies. A total of 22 patients were diagnosed with ADEM between 2002 and 2016, reported from countries such as Brazil, Bangladesh, Japan and mainly India. Seven patients were females and 12 were males. Thirteen of the patients were adults, while 8 were paediatric patients.

The demography, clinical findings, investigations and outcomes of the patients with neurological involvement are listed in Table 2.

3. Discussion

3.1. Clinical presentation

The natural history of post-infectious ADEM is a monophasic illness that occurs 7–30 days after the acute episode of infection. Certain viruses and bacteria have been classically associated with ADEM, which includes measles, mumps, rubella, varicella zoster, Epstein Barr Virus, herpes simplex virus, parainfluenza, *Borrelia burgdorferi*, Chlamydia, Legionella, *Mycoplasma pneumoniae Rickettsia rickettsia,* Leptospira and Streptococcus [41]. Recently, den-

Table 1
Studies of dengue patients that had post dengue acute disseminated encephalomyelitis cases.

Publication	Country	Study design	Population	Proportion with neurological features	Proportion of neuro-dengue with ADEM
[24]	Brazil	Retrospective and prospective	41 dengue patients with neurological manifestations	Not applicable	1 of 41 (2%)
[27]	India	Retrospective study	109 children with severe dengue admitted to PICU	26 of 109 (24%)	2 of 26 (8%)
[26] 2010	India	Prospective study	799 adults admitted with serologically confirmed dengue	21 of 799 (2.63%)	2 of 21 (10%)
[15]	India	Retrospective study	26 children and adults with neurological complications and positive dengue serology	Not applicable	1 of 26 (4%)
[25]	India	Case based series (prospective)	9 adults (age > 12 years) with neurological complications and positive dengue serology	Not applicable	1 of 9 (11%)

Abbreviations: Paediatric Intensive Care Unit = PICU.