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## Neurobiochemical Cross-Talk Between Dengue Virus and the Nervous system

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### Abstract

Dengue, a severe and fatal viral disease, has become a global crisis. The notorious causative agent of dengue is the dengue virus (DENV). Though multi-organ manifestations of the dengue fever have been documented, less report has been publicized regarding the neuro-biochemical manifestations of DENV. This paper illustrates the neuro-biochemical, neuro-pathological and associated features with a view to aid in formulating the increasing dengue affected global populace.

### Keywords

Arbovirus; Immunoglobulin; Central nervous system; Peripheral nervous system; Serotype.

## Introduction

Dengue, the most common arboviral disease, has been taking a heavy toll globally [1]. Dengue is caused by the dengue virus (DENV) that is a single-stranded RNA virus and belongs to the family Flaviviridae [2]. Five serotypes of DENV (DENV-1, -2, -3, -4, -5) have been reported to be the culprit of this fastest spreading tropical disease and the second-most acute febrile disease of the travelers worldwide [3]. Though neurological involvement of dengue virus had been noticed since 1976, less attention had been paid towards amelioration of dengue-induced neurobiochemical alteration [4]. As currently, dengue has been plaguing different nations of the world severely, time is up to delve into the neuronal involvement and remedy of the dengue virus infection [5]. In 2009, the world health organization (WHO) classified dengue into three types: dengue with no signs, dengue with signs and severe dengue [6].

## Narcoviolence of the Dengue Virus

DENV is neurovirulent. Neurovirulence of this virus in the central nervous system (CNS) had been ascertained through presence of viral RNAs, proteins and host immunoglobulins generated against this virus [7]. DENV-2 and DENV-3 serotypes had been found to be most neurovirulent [8]. Presence of DENV in the cerebrospinal fluid (CSF) has confirmed this virus's neuropathological involvement [9]. DENV had been reported to disrupt the blood brain barrier of the experimental animals [10]. Autoimmune reaction leading towards immunoreactivity of the neurons and altered metabolic fates in the hemorrhagic dengue fever had been observed [11].

## DENV entry into the CNS

Hematogenous route has been considered to be the most direct entrance of the DENV to the CNS [12]. Normally, the blood brain barrier (BBB) prevents the entry of external components into the CNS. During DENV infection, the BBB might have been compromised anyway or the BBB might have undergone any alteration allowing the safe entry of the DENV as well as favoring the consequent neuro-inflammatory processes [13]. Dysregulation of the endothelial cell (EC) homeostasis directly by the DENV or DENV secreted components or pro-inflammatory mediators of DENV-infected cells could aid in ravaging the cascade [14]. Binding of the DENV to the EC activates the rho-associated coiled coil kinase (ROCK) as well as vimentin alteration that facilitates viral replication and assemblage of virion particles [15]. EC membrane sugars especially heparin sulfate acts as viral attractant. More advertantly, heat shock protein (HSP 70, HSP 90), CD 14, CD 60, ICAM 30, laminin act as EC receptor to the DENV [16]. Entrance of the DENV to the nervous system creates a "cytokine storm" that ultimately leads towards neuro-biochemical alteration leading towards physiological and psychological abnormalities of the dengue patient [17].

## CNS Complications

### Encephalitis

Encephalitis has been found common with all the three dengue types [18].

### Encephalopathies

Dengue virus induced encephalopathy had been manifested through behavioral alteration, cognitive impairment, anxiety, depression, aggression, mania and personality change [19]. About 50% of the dengue patients have been linked with encephalopathy and emotional alteration [20]. Dengue hemorrhagic

fever/dengue shock syndrome (DHF/DSS) correlate with anoxia, brain edema, hemorrhage, hyponatremia, renal or hepatic abnormalities [21]. Mutation of the envelope glycoprotein (replacement of alanine by valine at position 173) of DENV-2 had been implicated in encephalopathy [22]. Electroencephalograph (EEG) of the encephalopathics show epilepsia partialis continua, seizures and burst suppression [23].

### **Seizures**

Seizures alone or associated with encephalopathy and encephalitis have frequently been observed in dengue patients [24]. Children have been found much prone to seizures than the adults [25].

### **Meningitis**

Dengue associated meningitis, though previously less encountered, has become a commonplace nowadays [26]. Meningitis along with headache, neck rigidity, decreased platelet count are the common manifestations [27].

### **Stroke**

Hemorrhagic and ischemic strokes have been linked with DENV infection [28]. These may be due to increased permeability of blood vessels and leakage of plasma [29]. These type of dengue patients suffer from speech difficulty and paralysis [30]. Other cerebellar syndromes include nystagmus and gait abnormalities [31]. Hypokalemic paralysis of the dengue patients has been linked with increased catecholamine mediated increased urinary excretion of potassium and renal tubular acidosis [32]. Neuro-muscular consequence such as transient muscular dysfunction has also been manifested in dengue patients [33]. Elevated levels of creatinine phosphokinase (CPK) have been found in the serum of dengue patients suffering from neuro-muscular dysfunction [34].

## **PNS Complication**

### **Guillain-Barré Syndrome**

Guillain-Barré syndrome (GBS) is a peripheral polyneuropathy that causes paralysis through blockade of motor neurotransmission [35]. Among dengue patients, the children usually fall a victim to GBS [36]. Though the exact mechanism is yet to unveil, immunocytes and pro-inflammatory mediators such as tumor necrosis factors (TNF), interleukins (ILs) and cytokines might be involved in DENV induced GBS pathogenesis [37].

### **Neuritis**

Neuritis associated with dengue involve abducens, phrenic and thoracic nerve palsy, peripheral facial palsy and brachial neuritis [38]. Cranial nerve palsy, retinal vasculopathy and optic neuropathy are some neuro-ophthalmic complications of DENV infection [39].

### **Denv Induced Parkinsonism**

DENV-induced parkinsonism could be considered as a novel manifestation of this catastrophe [40]. Though the exact mechanism could not be outlined yet, disturbed neurotransmission and altered production and management of the neurotransmitters could lay the foundation of viral parkinsonism in dengue patients.

## **Conclusion**

Dengue has been creating global havoc. Neuro-biochemical manifestations of dengue and dengue virus

(DENV) has attracted less attention. Time is up for considering the neuro-biochemical underpinnings of dengue and DENV and chalking out appropriate measures for the betterment of global public health. Thus, the government and non-government organizations, policy makers, health professionals, care givers, donor agencies and research and development organizations should formulate necessary strategies to save the global populace from dengue and DENV-mediated patho-physiological and neuro-biochemical hallmarks.

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