Organ Dysfunctions in Dengue Infection

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Epidemiology

An estimated 500,000 people with severe dengue infection require hospitalization annually, with 2.5% case fatality each year.

Epidemiology

A global decline in case fatality (28%) have been recorded between 2010-2016 due to improvement in case management. Early detection and access to proper medical care lowers fatality rates below 1%

Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries.

OUTCOME OF DENV INFECTION

Bangkok, Thailand 80-81: DENV-1 and 2
Burke et al., Am J Trop Med Hyg 1988

Vietnam 04: DENV-2

Vietnam 07: DENV-1

Singapore 04: DENV-1
Yew et al., Ann Acad Med Singapore 2009

West Java, Indonesia 00-02: DENV-2
Porter et al., Am J Trop Med Hyg, 2005

ANAVAJ SAKUNTABHAI M.D., D.PHIL.
INSTITUT PASTEUR
PRESENTED AT THE 3RD ASIAN DENGUE SUMMIT,
KUALA LUMPUR, MALAYSIA MAY 7, 2018
Global Incidence of Dengue Infection

Indonesia, 2015
- Incidence 129,650
dengue cases
- IR 50.75/100,000 population;
- Attack 84.8% district,
- CFR 1.071 (0.83%)

WHO, 2013
## Diagnosis classification according to existing guidelines

<table>
<thead>
<tr>
<th>Year</th>
<th>Guideline</th>
<th>2009</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Dengue fever</td>
<td>Dengue without warning signs</td>
<td>Dengue fever</td>
</tr>
<tr>
<td>2011</td>
<td>DhF grade I</td>
<td>DhF grade I</td>
<td>DhF grade I</td>
</tr>
<tr>
<td></td>
<td>DhF grade II</td>
<td>DhF grade II</td>
<td>DhF grade II</td>
</tr>
<tr>
<td></td>
<td>DhF grade III</td>
<td><strong>Severe dengue</strong>: shock, resp distress</td>
<td>DhF grade III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➔ severe plasma leakage, severe hemorrhage and severe organ involvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DhF grade IV</td>
<td></td>
<td><strong>Expanded dengue syndrome</strong>: isolated organopathy</td>
</tr>
</tbody>
</table>
• **Severe dengue**: every dengue case that has one or more of the following manifestations (Pang et al, 2016, Martinez and Capo, 2018)

1. Shock or respiratory distress due to severe plasma leakage.
2. Severe bleeding (e.g. hematemesis, melena, ample metrorrhagia, and central nervous system bleeding).
3. **Severe organ involvement, such as major liver (AST or ALT >1000 IU), central nervous system, heart or kidney impairment.**


Complication among children with severe dengue infection (102)

<table>
<thead>
<tr>
<th>Complications</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>29 (11.1)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>31 (11.9)</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Hemophagocytic syndrome</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Refractory shock</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Myositis</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Disseminated intravascular coagulopathy</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Co-infections</td>
<td>19 (7.2)</td>
</tr>
</tbody>
</table>

Of 500,000 people with severe dengue infection require hospitalization annually, 90% of them are children <5 years of age

Severe dengue disease is characterized by circulatory damages, associated in most cases with hepatic dysfunctions.

These injuries may be a direct consequence of the virus presence and/or resulted by an exacerbation of the immune response after infection.

Pathologic feature:
- all showed severe parenchyma and circulatory alterations
- all showed hemorrhage and edema

Liver

Most important gastrointestinal manifestation

Clinical presentation:

- acute hepatitis with elevated liver enzyme values (AST being more significantly elevated than ALT)
- Jaundice
- altered mental status
- seizures
- severe hypoglycemia
- Acute liver failure (Manoj et al. 2014 and Kumarasena et al. 2010)

<table>
<thead>
<tr>
<th>Country</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>1049</td>
</tr>
<tr>
<td>Indonesia</td>
<td>354</td>
</tr>
<tr>
<td>Malaysia</td>
<td>969</td>
</tr>
<tr>
<td>Vietnam</td>
<td>3075</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>351</td>
</tr>
<tr>
<td>Brazil</td>
<td>540</td>
</tr>
<tr>
<td>El Salv.</td>
<td>716</td>
</tr>
<tr>
<td>Venezuela</td>
<td>360</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7414</strong></td>
</tr>
</tbody>
</table>

- **Lab-confirmed dengue**: 2691 (37%)
- **Not dengue**: 2561 (35%)
- **Acute flavivirus infection**: 327 (4%)
- **Recent flavivirus infection**: 827 (11%)
- **Inconclusive**: 923 (13%)
- **Insufficient data**: 266

- **>84 hours from disease onset**: 38
- **Lab diagnosis not available**: 53

**Prognostic analysis**: 2425

**Diagnostic analysis**: 5252

*Insufficient data = No information during DOI 4-7, OR <3 visits during DOI 4-7 with no summary*
Indonesia site → Yogyakarta

- > 5 yo patients presenting to outpatient clinics of PHC with fever < 72hrs, without focal infection
- 354 enrolled → 40.1% confirmed dengue (DF and DHF)
- **Prevalence of liver dysfunction : 42.79%**
- Significance increased of liver enzyme during fever defervescence
- No one with renal dysfunction/ AKI
Laboratory result of hepatic involvement

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients</th>
<th>Raised AST</th>
<th>Raised ALT</th>
<th>Hypoalbuminemia</th>
<th>Raised bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itha et al\textsuperscript{26}</td>
<td>45</td>
<td>96%</td>
<td>96%</td>
<td>76%</td>
<td>30%</td>
</tr>
<tr>
<td>Wong et al\textsuperscript{24}</td>
<td>127</td>
<td>90.6%</td>
<td>71.7%</td>
<td>16.5%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Saha et al\textsuperscript{21}</td>
<td>1226</td>
<td>52% (5 times normal was criteria)</td>
<td>50%</td>
<td>12.9%</td>
<td>16.9%</td>
</tr>
<tr>
<td>Kuo et al\textsuperscript{3}</td>
<td>270</td>
<td>93.3%</td>
<td>82.2%</td>
<td>-</td>
<td>7.2%</td>
</tr>
<tr>
<td>Souza et al\textsuperscript{4}</td>
<td>1585</td>
<td>63.4%</td>
<td>45%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Pathologic feature:
  - microsteatosis or macrosteatosis
  - focal areas of necrosis with mononuclear infiltrates
  - cell death (probably apoptotic process)
  - virus antigens in hepatocytes, Kupffer cells and endothelium
LUNG

- Hyaline membrane formation
- Hemorrhage
- Edema
- Hypertrophy of type II pneumocytes

- Mononuclear inflammatory infiltrate
- Hyperplasia of alveolar macrophages
- Hyaline membrane: in diabetes and obesity, probably due to DSS
- Virus antigens in alveolar macrophages, type II pneumocytes, and endothelium

Causes of acute respiratory distress and failure:

- severe metabolic acidosis from severe shock
- fluid overload – large pleural effusions and ascites
- acute pulmonary oedema
- acute respiratory distress syndrome (ARDS)
## Lung manifestation in 100 seropositive adult dengue patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Dengue fever (%)</th>
<th>Dengue hemorrhagic fever (%)</th>
<th>Dengue shock syndrome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult respiratory distress</td>
<td>0</td>
<td>19.4</td>
<td>53.3</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>0</td>
<td>21.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Unilateral pneumonitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bilateral pneumonitis</td>
<td>0</td>
<td>9.5</td>
<td>6.6</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>7.14</td>
<td>0</td>
</tr>
<tr>
<td>More than one presentation</td>
<td>0</td>
<td>38.1</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Heart

Miranda et al. 2013

Study over 81 dengue subjects

- 6 patients had acute heart failures (7%)
- 10 patients had high NT pro BNP (12%)
- 3 patients had chest pain (7%)
- 3 patients had shock and hypotension

• All patients with elevated biomarker showed:
  – more intense inflammatory activity confirmed by a higher leukocyte count and C-reactive protein levels.
  – lower viral load, suggesting no association between viral load and cardiac injury.

• Pathologic feature:
  - Myocarditis with cardiac fibers degradation
  - Virus antigens in
    - myocardial fibers
    - perinuclear region,
    - monocytes/macrophages
    - endothelium

Kidney

Renal involvement:
- Elevation of serum creatinine level
- **Acute kidney injury**
- Acute tubular necrosis
- Hemolytic uremic syndrome
- Proteinuria
- Glomerulopathy
- Nephrotic syndrome

Acute Kidney Injury (AKI)

Incidence: 14.2% among dengue patients aged ≥ 12 yo

Significant morbidity, mortality, longer hospital stay and poor renal outcomes

Etiopathogenesis
- direct action by the virus
- hemodynamic instability
- rhabdomyolysis
- hemolysis
- acute glomerular injury

Rare complication but poor prognosis....!

Prospective cohort study
Objective: predict renal involvement in dengue mortality
DSS patients 1mo-18 yo hospitalized in Dr Sardjito Hospital
August 2015- March 2017

Kidney involvement as AKI was prognostic factor of mortality in children with dengue shock syndrome (adjusted RR 11.93 CI 95% 1.76-80.71; p=0.011)
Kidney involvement occurred in dengue infection, from mild spectrum to severe

Budyarini et al, unpublished data
In Indonesia, 70% of fatal dengue infections (n=30) presented with one or more neurological signs, and 7% were admitted for viral encephalitis, which was listed as the cause of death.
• Central nervous system (CNS) disease is attributed to various factors, including direct viral invasion of the CNS, liver failure, electrolyte disturbances, and cerebral edema (AAP, 2010).

• Manifestation of encephalopathy were the same for all four serotypes but.... DEN-2 and DEN-3 are most frequently reported as the cause of severe neurological disease.
• Clinical manifestation
  – Dengue encephalopathy
  – DENV encephalitis
  – Immune-mediated syndromes (acute disseminated encephalomyelitis [ADEM], myelitis, neuritis brachialis, and GBS, among others)
  – Dengue-associated stroke
  – Neuro-ophthalmic complications

How to manage organ dysfunction?

• **Main principle:** supportive treatment

• **Acute liver failure:**

N-Acetyl cysteine (NAC): restore hepatocellular glutathione stores, free radical scavenger, improves antioxidant defense.

Kumarasena, et al.: 5 of 8 patients treated with NAC recovered from hepatic encephalopathy while 3 died.


• **Acute kidney injury**
  – Fluid adequacy, shock management, renal replacement therapy

• **Pulmonary oedema and ARDS**
  – Goals of therapy: optimize oxygenation and ventilation and stabilize the haemodynamic situation.
  – Indications for mechanical ventilation:
    • patients who have shock and are restless, combative or confused
    • respiratory failure from acute pulmonary oedema/ARDS ± shock
    • patients who fail to respond to non-invasive ventilation.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue encephalopathy</td>
<td>Correction of metabolic causes such as liver dysfunction, hyponatremia, metabolic acidosis, or hypokalemia</td>
</tr>
<tr>
<td>DENV encephalitis</td>
<td>Adequate hydration, nutrition, maintenance of airway, and monitoring of consciousness level</td>
</tr>
<tr>
<td>Dengue stroke</td>
<td>Treat as stroke</td>
</tr>
<tr>
<td>Guilain Barre Syndrome</td>
<td>Treat as Guilain Barre Syndrome</td>
</tr>
<tr>
<td>Dengue immune-mediated neurological complications</td>
<td>Steroids (intravenous methylprednisolone pulses, oral prednisolone) (safety and efficacy not established yet)</td>
</tr>
<tr>
<td>Myalgia and transitory muscle dysfunction</td>
<td>Hydration, resting, and analgesic drugs</td>
</tr>
<tr>
<td>Severe neurological complications including myelitis</td>
<td>Rehabilitation</td>
</tr>
</tbody>
</table>

Outcome

AKI was found to be an independent predictor [OR (95% CI): 1.3 (0.84–2.01), P = 0.044] of longer hospitalization.

Dengue patients with three or more organ failures on ICU admission were reported to have a 67% mortality rate.

ICU nonsurvivors were significantly associated with nonhematological organ failure → respiratory, cardiovascular, and neurological complications.

Summary

- Organ dysfunction in dengue can manifest from mild to severe organ impairment even with serious and fatal outcome.
- Organ dysfunction can occur in both DF and DHF.
- Proper supportive treatment is essential in dealing with organ dysfunction in dengue.
Thank You