Dengue in the New Millenium

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Factors to global resurgence of dengue

- Population growth
- Urbanization
- Mosquito control
- Travel
- Public health infrastructure

NATURAL HISTORY OF DENGUE INFECTION
**Spectrum of dengue infection**

- Asymptomatic
- Undifferentiated fever
- Dengue fever
- Dengue hemorrhagic fever

**WHO classification of dengue infection**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Platelet</th>
<th>Plasma leakage</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF</td>
<td>variable</td>
<td>absent</td>
</tr>
<tr>
<td>DHF grade I</td>
<td>&lt;100,000</td>
<td>present</td>
</tr>
<tr>
<td>grade II</td>
<td>&lt;100,000</td>
<td>present</td>
</tr>
<tr>
<td>DSS grade III</td>
<td>&lt;100,000</td>
<td>present</td>
</tr>
<tr>
<td>grade IV</td>
<td>&lt;100,000</td>
<td>present</td>
</tr>
</tbody>
</table>

**Dengue fever**

- Fever
- Muscle and bone pain
- Maculopapular rash

**Dengue infection during parturition complicated in severe hemorrhage and vertical transmission.**

Thaithumyanon P, Thisyakorn U, Deerojanawong J, Innis BL

Major pathophysiologic changes in DHF

- Leakage of plasma
- Abnormal hemostasis

Pathogenesis

- Immune: ADE
- Viral: loads, strains, virulence
- Host: genetic factors


Pathogenesis of DSS:
Immune Enhancement or Viral Virulence

Association between MBL gene polymorphisms and susceptibility to dengue.


HIV-infected children and healthy children had no different seroepidemiology of dengue virus infection.

Thisyakorn U, et al. Nutritional status of children with DHF

The study confirmed the observation generally made that most patients with DHF are not undernourished.

Clinical manifestations and severity of dengue infection varied with age.

The extent of endothelial cells, coagulation and fibrinolysis activation in children with dengue infection seems to be correlated to disease severity.

The d-dimer, a specific marker for cross-linked fibrin, is often used as a marker for DIC significantly correlated with disease severity.

Association of cytokine-related gene expression levels with dengue disease severity was demonstrated.
BLEEDING PRECAUTIONS

Mitrakul C, Thisyakorn U. Hemostatic studies in DHF
- Vasculopathy
- Coagulopathy
- Platelet abnormalities

Serial determinations of atypical lymphocytes (buffy coat), platelets, and hematocrit in DHF.

LABORATORY DIAGNOSIS OF DENGUE INFECTION

- Serology
- Virus isolation
- Molecular technique

Immune Response to Dengue infection

- Primary infection: High level of IgM that appears 4-6 days after symptoms and may persist for up to 10 weeks. IgG appears 2 weeks after onset and persists for life.

- Secondary infection: Low levels of IgM may not be produced or at undetectable levels in 20% of patients. IgG rise rapidly 1-2 days after onset of symptoms at higher levels than primary infection.

Interpretation Guide

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>Fever</th>
<th>PCR</th>
<th>NS1 Ag</th>
<th>IgM</th>
<th>IgG</th>
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<tr>
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<tr>
<td>Early Acute Primary</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Late Acute Primary</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Primary Convalescent</td>
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<tr>
<td>Very Early Acute Secondary</td>
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<td>-</td>
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<tr>
<td>Early Acute Secondary</td>
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<tr>
<td>Late Acute Secondary</td>
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<tr>
<td>Secondary Convalescent</td>
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<td>-</td>
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<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
DENGUE ENCEPHALITIS

A true entity?

Thisyakorn U, Thisyakorn C.
Dengue infection with unusual manifestations

Patients tended to be in the younger age group and had higher mortality.


Thisyakorn U, Thisyakorn C. Dengue infection with unusual manifestations

The unusual manifestations include encephalopathy, encephalitis and fulminant hepatitis


Thisyakorn U, Thisyakorn C., Limpitikul W, Nisalak A.
Dengue infection with CNS manifestations

Neurological manifestations of dengue including alteration of consciousness, seizures, pyramidal tract signs, meningeal signs and headache. CSF showed lymphocytic pleocytosis in 1/5 while presence of IgM in few patients.

Solomon T, et al. Neurological manifestations of dengue infection.

In dengue endemic areas patients with encephalitis and encephalopathy should be investigated for this infection, whether or not they have other features of the disease.

Innis BL, et al. Acute liver failure is one important cause of fatal dengue infection.

Liver injury is either a direct effect of virus replication in the liver or a consequence of host responses to infection.

Pancharoen C, Rungsarannont A, Thisyakorn U. Hepatic functions in dengue patients.

Hepatocellular injury manifested by hepatomegaly, elevation of ALT and coagulopathy are common in DHF and even in DF, though hepatomegaly is absent.

Pancharoen C, Thisyakorn U. Co-infection in dengue patients.

Co-infection can modify clinical presentations of dengue disease and result in missed or delayed diagnosis and treatment and possible misinterpretation as unusual manifestations.
Thisyakorn U, Thisyakorn C. Diseases caused by arboviruses

Successful treatment of DHF depends on early recognition and careful monitoring of the development of shock.

Prevention

- Control of mosquito
- Vaccine
Vaccines

- Two live-attenuated
- Mahidol-Aventis Pasteur
- Walter Reed
- Four chimeras

Lancet 2002;360:1243-5

Conclusion

The geographical expansion of DHF presents the need for well-documented clinical, epidemiological and virological description of the syndrome. Both biological and social researches are essential to develop effective mosquito control, medications to reduce capillary leakage and a safe vaccine.