Myocardial failure in tropical infections

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Tropical infections: What are they?

Definition:

Infections that are prevalent in, or are unique to tropical and subtropical regions

- Some of these occur throughout the year and some especially in rainy and post-rainy season.
- Most often disease is transmitted by an insect "bite“ / Vector borne
Tropical infections: What are they?

Malaria- Falciparum, also vivax some times

Dengue and other Hemorrhagic fevers

Rickettsial infection – Scrub Typhus

Leptospirosis

Typhoid fever

Diphtheria

Bacterial sepsis

Influenza, Hanta virus Fever and others
Tropical infections: a global concern?

Global importance

- Human exploration of tropical rainforests, deforestation, rising immigration and increased international tourism to tropical regions → increased incidence

- Climate changes and global warming → tropical diseases & vectors to spread to higher altitudes in mountainous regions and to higher latitudes like southern USA
Tropical Infections

- Dengue
- Scrub typhus
- Malaria
Tropical fevers & Myocardial failure

- Cardiac involvement is not uncommon: *reported from centres handling large number of tropical infections*
- Direct infective / toxic
- Tropical fevers in PICU: an observational study
  - Total 173 children
  - 40 children had shock required vasoactive agents
  - Myocardial dysfunction identified in 7 (17%)
  - LVEF < 45% (n=7), ECG changes (n=2)
    - (Scrub typhus -4, Dengue – 2, Sepsis – 1)
Tropical fevers & Myocardial failure

The challenges:

• Majority are subclinical, goes unidentified unless actively looked for.

• Lack of clear criteria to define cardiac involvement
  - Clinical features alone lacks sensitivity and specificity
  - ECG changes, elevated enzymes and echocardiographic evidence are not consistent in all cases
Tropical fevers & Myocardial failure

The challenges:

• Tropical infections are known to cause circulatory abnormalities, shock (capillary leak, vasodilation, bleeding) & pulmonary edema

• Even if myocardial dysfunction is present, the extent to which it contributes to shock is uncertain

• Involvement of multiple organs as well as the presence of metabolic derangement can further confuse the picture
Dengue & Heart: the problem

‘Myocarditis’ has now been included in the definition of severe dengue adopted in the 2009 WHO revised classification - but true incidence not known!

Studies: looked at functional myocardial impairment: identified both systolic and diastolic dysfunction

‘acute reversible myocarditis’
Dengue & Heart: the focus

• **Shock** in DHF has been attributed largely to decreased intravascular volume from capillary leakage

  But a small proportion: **Respond poorly to fluids**

Recent attention on possible impairment in cardiac function!


**Defining the role** of cardiac dysfunction in the haemodynamic compromise of severe dengue has potentially **important management implications.**
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Method of assessment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kabra et al. 1998</td>
<td>N=54; India</td>
<td>Echo</td>
<td><strong>LVEF &lt;50%</strong> in 16.7% and &lt;35% in 3.7%</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td></td>
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<tr>
<td>Khongphatthan-ayothin et al. 2003</td>
<td>N=24, Thailand</td>
<td>Echo</td>
<td><strong>Lower LVEF</strong>, VCFc/ESS, CI, EDV and higher SVR in critical phase vs recovery.</td>
</tr>
<tr>
<td></td>
<td>Children</td>
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<tr>
<td>Kularatne et al. 2005</td>
<td>N=120; Sri Lanka</td>
<td>ECG &amp; Biomarkers</td>
<td>ECG abnormalities – 62.5% (sinus bradycardia, ST-T changes, RBBB). Increased troponin levels in 29.4%</td>
</tr>
<tr>
<td></td>
<td>Older children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khongphatthan-ayothin et al. 2007</td>
<td>N=91, Thailand</td>
<td>Echo &amp; Biomarkers</td>
<td><strong>LVEF &lt;50% in 6.7%, 13.8%, and 36% of DF, DHF, and DSS</strong> during critical phase. Biomarkers were normal in all 11 tested</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td></td>
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<tr>
<td>Salgado et al. 2010</td>
<td>N=102, Columbia</td>
<td>ECG (n=11) Echo (n=7)</td>
<td><strong>Clinical Myocarditis -13.9%</strong> of DHF ECG: sinus bradycardia (82%, tachycardia 18%, and T inv. 64%) Echo: Pericardial effusions 71% diastolic dysfunction 28.3%</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>Clinical assessment (n=79)</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Study population</td>
<td>Method of assessment</td>
<td>Findings</td>
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<tr>
<td>La-Orkhun et al. 2011</td>
<td>N=35; Thailand Children</td>
<td>Holter 24 h ECG monitoring</td>
<td>Recovery phase: <strong>29% had ECG abnormalities.</strong> (sinus arrhythmias, 1° &amp; Mobitz type I 2° AV block, atrial and ventricular ectopics)</td>
</tr>
<tr>
<td>Yacoub et al. 2012</td>
<td>N=79, Vietnam Children &amp; Young adults</td>
<td>Echo &amp; Tissue Doppler imaging ECG, Biomarkers</td>
<td>Systolic impairment in 45%, diastolic impairment in 42%. Septal &amp; RV walls predominantly affected, worse in severe cases. <strong>ECG abnormal in 35%</strong>. Troponin elevation in 1 of 17</td>
</tr>
<tr>
<td>Wali et al. 1998</td>
<td>N=17, India Older children Adults</td>
<td>Echo, ECG Radio-nucleotide ventriculography, Tc- pyrophosphate imaging</td>
<td>LVEF = 41.7% using RNVgraphy , 47.1% using Echo. Global hypokinesia in 71% <strong>No myocardial necrosis in all 4 99mTc-pyrophosphate imaging.</strong></td>
</tr>
<tr>
<td>Miranda et al. 2013</td>
<td>N=81, Brazil Children &amp; Adults</td>
<td>Echo, Biomarkers CMR</td>
<td>Raised biomarkers in 15% . Abnormal echo 4 out of 10. <strong>CMR - myocardial enhancement in 4</strong></td>
</tr>
</tbody>
</table>
45 of 86 patients in DSS did not respond to fluid bolus, After CVP and optimization of fluids 21 cases Not improved at end of 2-3 hours –

Echocardiography – 22 cases**

- “Underfilled” left sided chambers: 8 cases: Slow fluid resuscitation continued,
- Diastolic dysfunction: 4 cases: Milrinone,
- Systolic dysfunction: 4 cases: Low dose nitroprusside added to epinephrine

Myocardial dysfunction- Ranjit et al (2005)
Myocardial dysfunction

(Int Care Med 2003, Khongphatthanayothin A et al, PCCM, 2007)

- ↓ Ejection fraction, and LV performance indices
- Transient myocardial depression is not uncommon

36% of patients with DSS had a LVEF <50%, compared with 13.8% of patients with DHF and 6.7% of those with DF during the toxic stage.
Left Ventricular Ejection Fraction (EF) at Toxic Stage and the Amount of Intravenous Fluid Given in the First 24 Hours

- Compared to patients with good ventricular function (EF ≥ 60%), the patients with depressed (EF < 50%) and fair (50 ≤ EF < 60%) ventricular function tended to receive larger amount and longer duration of intravenous fluid treatment during the toxic stage of DSS.

Scatterplot between

Myocardial dysfunction in acute dengue

- Study on 79 children and adults with Dengue – 42 dengue with warning signs, 15 severe dengue
- Echocardiography including tissue Doppler imaging
- Systolic impairment – 45% of patients, diastolic impairment in 42% of patients.
- Septal and right ventricular walls affected
- No correlation with cardiac biomarkers (16/17 patients had normal biomarkers)

Yacoub et al. Cardiac function in Vietnamese patients with different dengue severity grades. Crit Care Med 2012
Dengue & Heart: structural vs functional

- 79 children and young adults
- **Pre-load independent parameters** and tissue doppler imaging
- 45% had systolic and 42% diastolic impairment
- predominantly affecting the septal and right ventricular walls
- Changes were more frequent and pronounced in severe dengue
- None had elevation of troponin levels

  *Yacoub, S. et al. Cardiac function in Vietnamese patients with different dengue severity grades. Crit. Care Med. (2012).*

- 17 patients with dengue: 99mTc-pyrophosphate imaging showed no myocardial necrosis

  *Int. J. Cardiol. (1998)*
Dengue & Heart: proposed mechanism

Figure 2 | Proposed viral and immune mechanisms involved in the cardiac and vascular manifestations of dengue.

Nature Review Cardiology 2014
Dengue & Heart: Management

• Echocardiography: indicated

1. If fluid resuscitation is not successful in achieving hemodynamic stabilization
2. Children with clinical features of heart failure
3. Children with ECG changes of myocardial dysfunction
   → assess systolic and diastolic function to guide use of inotropes

Scrub typhus & myocarditis

Case reports and case series
Present in 2\textsuperscript{nd} week of illness – along with multi-system manifestations

Clinical presentation:

- Cardiogenic shock and refractory hypotension
- True incidence not known!
- Subclinical cases – not tested / not reported
Scrub typhus & myocarditis

Clinical findings:
Elevated JVP  n=7 (20%)
S3 Gallop      n=6 (17%)
Scrub typhus & myocarditis

Four children
- Signs and symptoms of myocarditis occurred on days 7–9 of fever
- Severe hypotension and required multiple vasopressor drugs or aggressive mechanical cardiac support.
- Abnormal ECG prior to hypotension in all cases
- Delay in appropriate antibiotics – poor prognostic indicator
ECG changes in scrub typhus

- > 30% patients with scrub typhus showed ECG changes
- Those with sustained ECG change had higher BUN and creatinine levels, and increased ICU admission rate and length of stay
- Another study from Thailand – 24% patients (7/29) had abnormal ECG findings
Histopathology in scrub typhus myocarditis

- Case report: Heart failure after 3 months of acute illness
- Endomyocardial biopsy: Small vessel vasculitis
- **Proliferation of Orientia tsutsugamushi** was observed in the **vascular endothelial cells** of the myocardium.
Typhoid fever: Myocarditis

• Long known to affect myocardium

  Typhoid Fever with Myocarditis *Am J Trop Med Hyg 1974*
  The heart in enteric (typhoid) fever. *J Trop Med Hyg. 1981*

• Toxic, infectious-toxic myocarditis

• Seen in late 2\textsuperscript{nd} week of illness

• Children more often affected

• Inflammation of the heart intramural vessels,
  lymphocytic-macrophageal infiltration of the stroma and
  necrotic changes of cardiomyocytes

  *Pathomorphology and morphogenesis of myocarditis in typhoid fever. Arch Patol 2005*
Cardiovascular complications in enteric fever

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG changes</td>
<td>40-80</td>
</tr>
<tr>
<td>Myocarditis (Clinical)</td>
<td>1-2</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Rare, exact incidence not known</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Rare, exact incidence not known</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>Case reports only</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0.83</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Rare, case reports only</td>
</tr>
</tbody>
</table>

*S. Singh, S. Singhi. Cardiovascular complications of enteric fever. Indian Pediatr 1992*
Typhoid fever: Myocarditis

More often subclinical than symptomatic

ECG changes: the most common abnormality

100 cases of proven enteric fever,
46% - had ECG changes suggesting myocarditis
7% - had clinical evidence of myocarditis

Myocarditis in enteric fever. *Indian J Med Sci 1995*

Clinical features:

Tachycardia – usually the first sign

Conduction abnormalities are common (Heart block)

CCF, Cardiogenic shock 1-5%
ECG changes (30 - 80% children)

### TABLE II—EKG Abnormalities Reported in Enteric Fever

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>Changes</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>QRS complex</td>
<td>11%-25% (6,12)</td>
<td>Low voltage graphs, improves with therapy</td>
</tr>
<tr>
<td>2.</td>
<td>QT&lt;sub&gt;c&lt;/sub&gt; interval</td>
<td>0-45% (7,13)</td>
<td>Prolongation with myocardial involvement; myocardial failure(6)</td>
</tr>
<tr>
<td>3.</td>
<td>ST segment and T wave</td>
<td>45%-55% (6)</td>
<td>Flat, diaphasic of inverted; depression of ST segment</td>
</tr>
<tr>
<td>4.</td>
<td>P-R interval</td>
<td>26%-50% (6,13)</td>
<td>Prolongation</td>
</tr>
</tbody>
</table>
Typhoid fever: Myocarditis

Electrocardiographic alterations
- have a direct relationship to the severity of disease
- occur at the height of illness
- have a bearing on the prognosis

Poor prognosis
- Persistent ECG abnormalities beyond 2-3 weeks
- Clinical evidence of myocardial failure
- Arrythmia
Diphtheria & Myocarditis

Diphtheria – still a disease to be eradicated in tropics

• Myocarditis occurs in 10-20% of patients presenting with oropharyngitic diphtheria

(Diphtheritic myocarditis, a review of 496 cases. J Pediatr. 1934)

• Higher figures in tropics: India reports 66% incidence of myocarditis

(Jayashree M, Shruti N, Singhi S. Predictors of Outcome in Patients with Diphtheria Receiving Intensive Care. Indian Pediatr 2006)
Diphtheria & Myocarditis

Predictors of Outcome in Patients with Diphtheria Receiving Intensive Care
M. Jayashree, N. Shruthi and S. Singhi

- Mean interval between onset of respiratory symptoms and myocarditis was 6.5 ± 2.4 days (range 1-11 days)
- 62.5% presented with conduction abnormalities and cardiogenic shock
  Bundle branch block (BBB) in 15 (47%) patients; 9 of them progressed to complete heart block
- 10 (32%) had tachyarrythmia (VT - 6, 2 SVT – 2)
# TABLE II – Comparison of Myocarditis vs No Myocarditis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Myocarditis (n = 32)</th>
<th>No myocarditis (n = 16)</th>
<th>‘P’ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean±SD (range)</td>
<td>5.1 ± 2.2 (1-9.5)</td>
<td>5.20 ± 1.81 (2.5-9)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Sex ratio (boys : girls)</td>
<td>2.5 :1</td>
<td>1.6 :1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Unimmunised, n(%)</td>
<td>22 (68.8)</td>
<td>11 (68.7)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Partially Immunised, n(%)</td>
<td>9</td>
<td>2</td>
<td>0.03 *</td>
</tr>
<tr>
<td>Adequately immunized, n(%)</td>
<td>1 (3.1)</td>
<td>3 (18.8)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Bull neck, n(%)</td>
<td>25 (78.1)</td>
<td>7 (43.8)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Duration of bull neck</td>
<td>3.34±4.5 (1-25)</td>
<td>1.06±1.61 (1-5)</td>
<td>0.011**</td>
</tr>
<tr>
<td>Duration of ADS with respect to</td>
<td>6.71±4.81 (2-30)</td>
<td>4.62±2.44 (1-11)</td>
<td>0.041**</td>
</tr>
<tr>
<td>onset of disease mean±SD (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths, n(%)</td>
<td>25 (78.1)</td>
<td>2 (12.5)</td>
<td>0.00001*</td>
</tr>
</tbody>
</table>
Diphtheria & Myocarditis

‘Myocarditis was the most important predictor of mortality’

→ Patients with complete heart block but none survived despite temporary pacing in all

→ Presence of cardiogenic shock was associated with the highest mortality (OR 33.3)
Myocarditis was the most common complication <10 years of age group, whereas neurological complication was mainly seen in adults.
Table 4: ECG abnormalities (patients had combinations of changes)

<table>
<thead>
<tr>
<th>ECG abnormalities</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>T wave inversion in precordial leads</td>
<td>54</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>38</td>
</tr>
<tr>
<td>A-V block 2\textsuperscript{nd} degree</td>
<td>10</td>
</tr>
<tr>
<td>“Sickle-shaped sagging” of ST segment</td>
<td>8</td>
</tr>
<tr>
<td>RBBB</td>
<td>4</td>
</tr>
<tr>
<td>Multiple Atrial Ectopic</td>
<td>4</td>
</tr>
<tr>
<td>Pseudo infarction pattern</td>
<td>2</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>2</td>
</tr>
</tbody>
</table>
Patients who had bull neck and extensive faucial patches had more incidence of cardiac involvement.

Patients who had developed frank features of heart failure showed persistently elevated SGOT level.

Table 5: Biochemical analysis in diphtheria patients

<table>
<thead>
<tr>
<th>Laboratory abnormalities</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT (raised)</td>
<td>38</td>
</tr>
<tr>
<td>CPK-MB (raised)</td>
<td>10</td>
</tr>
<tr>
<td>Troponin T (kit test)</td>
<td>5</td>
</tr>
<tr>
<td>Urea, creatinine (raised)</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
</tr>
</tbody>
</table>
Malaria: is it overlooked?

- Ehrhardt et al → raised cardiac enzymes in complicated malaria
  
  *(Trop Med Int Health 2004)*

- Yacoub et al → Ejection fraction by echocardiography significantly reduced on admission compared with discharge
  
  *(Cardiac function and hemodynamics in Kenyan children with severe malaria.*
  
  *Crit Care Med 2010)*
Malaria & Myocardial failure: Proposed pathogenesis

Intravascular fluid depletion & reduced preload

+ \rightarrow \textbf{Impaired microcirculation in heart}

Parasite sequestration in small capillaries

Excessive production of \textbf{pro-inflammatory cytokines} & \textbf{Lactic acidosis}

\textbf{Plasmodial toxin} glycosyl-phosphatidyl-inositol (GPI) augments \textbf{apoptosis} rates in cardiomyocyte
Malaria & Heart: clinical implications

→ During the acute phase ECG abnormalities were common
  - Non specific ST-T changes
  - Ventricular ectopics  (J Mol Med 1992)

→ Acidotic patients had worse haemodynamic indicators  
  (Crit Care Med 2010)

→ Children suffering from severe malaria those who died exhibited higher levels of cardiac markers (NT proBNP, CK-MB)  
  (Microbe Infect 2005)
Myocardial failure in tropical infections

Current status & future:

- Myocardial failure has been increasingly recognized to be a part of clinical manifestations in tropical infections.
- **Pathogenesis** is not clearly understood unlike in bacterial sepsis.
- **?** Part of multi-organ involvement.
- **?** Circulating substance.
- Difficulty in defining cardiac involvement in clinical settings --- ECG / Enzymes / Echo / Clinical features.
- Whom to test; whom to treat ‘asymptomatic vs symptomatic’.
- Early recognition is important, treatment remains largely supportive.
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