IMMUNOLOGICAL ASPECT AND COMPLEMENT IN THAI HEMORRHAGIC FEVER

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Shock and massive hemorrhage are the leading causes of death in Thai hemorrhagic fever (THF)\(^{(1,2,3)}\). From the pathophysiologic studies, it was concluded that shock in THF is due to hemocoagulation and decreased plasma volume which was resulted from the leakage of plasma into extracellular space\(^{(4)}\) through the damage capillaries. The causes of hemorrhagic phenomena in THF are capillary damage, thrombocytopenia, and decreased clotting factors I, II, V, VII, IX, X, of which are in part secondary to liver damage\(^{(5,6,7)}\). However, the mechanism for the damage of capillaries, platelets and liver is still not known. The observation that shock in THF is mostly associated with dengue virus infection rather than chikungunya virus\(^{(8)}\), raised the possibility that dengue virus

THE RELATION OF DENGUE VIRUS ISOLATION \\& ANTIBODY RESPONSE

IN THF

![Graph](image)

Figure I The relation of dengue virus isolation and antibody response in Thai hemorrhagic fever (T.H.F.). The cross bars represent percentages of dengue virus isolation from the plasma of T.H.F. patients\(^{(9)}\), represents serial reciprocal–hemagglutination inhibition (H.I.) titers to dengue type 1, 2, 3 and 4 from 12 T.H.F. patients plotted against day of disease. The solid line represents the approximation of the pattern of increasing HI titers in majority of cases.

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may directly cause severe tissue damage seen in THF. However, the findings that dengue virus disappeared rapidly from the blood\textsuperscript{[8]} as well as from the tissues of THF patients,\textsuperscript{[10,11]} cast some doubt on the direct tissue damage by dengue virus. When antibody response in THF was studied, it was found that majority of shock cases in THF had secondary dengue antibody response i.e. rapid increase antibody titer within 4–5 days of illness, convalescent antibody titer higher than acute serum titer four fold or over, and the antibody is IgG type\textsuperscript{[12,13,15]}. The relation of dengue virus recovery\textsuperscript{[9]} and the antibody response in THF patients is shown in Figure 1. It is clearly shown that in shock phase of illness (day 4 to day 7), dengue virus disappeared rapidly and dengue antibody rapidly increased at the same time. Thus, it is possible that during shock phase of THF there may be virus–antibody interaction to form circulating immune complex which may injure cells in the presence of a complement effector system.\textsuperscript{[14]} The studies of serum complement C3, a major component of complement system, revealed that C3 level was definitely decreased during the shock phase of illness in proportion to the severity of the disease\textsuperscript{[15,16,17]}. Figure 2 illustrates the examples of serial C3 concentrations in the individual cases of each grade of THF. The reduction of C3 level occurred during day 4 to day 7 of disease (critical phase) in all grades. However, the shock cases (grade III and IV) had significantly
### Table I

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>No.</th>
<th>C'(_3) mg % (mean ± S.D.)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>60</td>
<td>125.60 ± 26.57</td>
<td>-</td>
</tr>
<tr>
<td>GRADE I</td>
<td>21</td>
<td>92.26 ± 14.88</td>
<td>0.01</td>
</tr>
<tr>
<td>GRADE II</td>
<td>96</td>
<td>71.51 ± 19.81</td>
<td>0.005</td>
</tr>
<tr>
<td>T.H.F.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRADE III</td>
<td>28</td>
<td>54.10 ± 13.95</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GRADE IV</td>
<td>4</td>
<td>28.50 ± 25.99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CONVALESCENT</td>
<td>34</td>
<td>150.44 ± 52.66</td>
<td>&gt; 0.01</td>
</tr>
<tr>
<td>BACTERIAL INFECTION</td>
<td>18</td>
<td>133.87 ± 38.37</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>VIRAL INFECTION</td>
<td>10</td>
<td>154.80 ± 38.09</td>
<td>&gt; 0.01</td>
</tr>
</tbody>
</table>

Thus, the observations of rapid disappearance of dengue virus from the blood and tissues of THF patients of a secondary dengue antibody (IgG) response in most cases of severe THF and of the marked reduction of complement during shock phase of illness in proportion to the severity of the disease, are consistent with the possible role of circulating immune complex in causing changes seen in the shock cases of THF\(^{(18)}\). Although the direct demonstration of circulating immune complex was still unsuccessful due to technical difficulty, a search for such immune complex is in progress. The activation of coagulation system as well as kallikrein–kinin system by immune complex are also under current investigations.
Reference


