Letter to the Editor

Categorization of dengue fever according to phase of illness—a suggestion for clinical studies using single diagnostic sample

Dear Editor,

In 2008, World Health Organization (WHO) experts agreed that “dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome”.1 The development of a spectrum of laboratory methods to detect the first of seven non-structural proteins in dengue virus, NS1 (non-structural protein-1) leads us toward an opportunity to observe the features of dengue during viremic phase which corresponds to the first 3 days of illness.1 Prior to the availability of NS1 antigen assays for detection of dengue, the illness was confirmed only after the detection of IgM and (or) IgG antibodies. This also helps us infer that studies on dengue fever using positive serology as part of dengue case definition would have identified only features of dengue in the immune phase of the illness. Though inference based on paired sera is the ideal way to confirm dengue, our limited experience in dengue indicates that the concept of utilizing paired sera in dengue diagnosis is difficult to practice since obtaining a sample beyond the 10th day of illness in a patient who is free of symptoms raises consent related issues.2,3 WHO recommends classification of dengue as dengue fever ± warning signs and severe dengue.3 We suggest a further laboratory based categorization for dengue illness (both WHO categories) using a single diagnostic sample incorporating aspects related to dengue pathogenesis.

A brief overview on the immunology of dengue may help in understanding our classification.1,4 Dengue fever is characterized by an initial viremic phase which corresponds to the first 3 days of illness followed by immune phase (also called critical phase) spanning from 3rd to 6th day of illness. The phase of dengue beyond 6th day of illness is called recovery phase (though a sizable number of patients take longer to recover). When the dengue virus infects a previously non-infected person, it is inferred as primary dengue infection [PDI]. A patient with PDI will demonstrate NS1 antigen till the 3rd day of illness (sometimes as long as the 9th day), IgM antibodies detectable beyond the 3rd day of illness and IgG beyond the 7th day of illness. Though IgM and IgG are detectable by

<table>
<thead>
<tr>
<th>Phase of illness</th>
<th>Primary infection</th>
<th>Secondary infection</th>
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<tbody>
<tr>
<td>Viremic</td>
<td>NS1 positive</td>
<td>No isolated viremic phase since anamnestic IgG response often present at the onset of illness</td>
</tr>
<tr>
<td>Viremia-immune overlap</td>
<td>NS1 positive Plus One of the following: IgM positive (&gt;40 units) and IgG negative IgM/IgG optical density ratio &gt; cut-off value of assaya</td>
<td>NS1 positive Plus One of the following: IgG positive (&gt;100 units) and IgM negative IgM/IgG optical density ratio &lt; cut-off value of assaya</td>
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<tr>
<td>Immune</td>
<td>IgM positive (&gt;40 units) and IgG negative OR IgM/IgG optical density ratio &gt; cut-off value of assaya</td>
<td>IgM/IgG optical density ratio &lt; cut-off value of assaya</td>
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IgM and IgG detection by enzyme-linked immunosorbent assay (ELISA). NS1 detection by ELISA (further scientific inputs required).

a Studies have used a cut-off value of 1.2 with patient sera in 1/100 dilution or 1.4 with patient sera in 1/20 dilution.

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When, a laboratory immune rizing been (>40 assays, infection. course monitoring fying ance patient strated WHO the clarity factor importance viremia-immune response important observed and immunosuppresants) current interventions (anti-viral therapy, corticosteroids, immunosuppressants) during viremic phase and viremia-immune overlap which could lessen the complications observed in the immune phase. The classification does have important limitations. First one is the diagnosis of SDI, a factor which is difficult to address taking into account the complex IgM and IgG antibody response observed in secondary infection. Second is the lack of standardization of NS1 assays, though an ELISA based protocol is generally preferred. WHO recommendation on methods of NS1 detection will add clarity to the classification. Third, diagnostic accuracy compared to paired sample. Adopting a cut-off value for IgM (>40 units) and IgG (>100 units) in the classification has partially addressed the non-inclusion of paired sera for dengue diagnosis.

Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

5. Falconar AK, de Plata E, Romero-Vivas CM. Altered enzyme-linked immunosorbent assay immunoglobulin M (IgM)/IgG optical density ratios can correctly classify all primary or secondary dengue virus infections 1 day after the onset of symptoms, when all of the viruses can be isolated. Clin Vacc Immunol. 2006;13:1044–51.

Emmanuel Bhaskar a,*, Raveendran Praveena b, Gopalan Sowmya a, Swathy Moorthy a

a Department of Medicine, Sri Ramachandra Medical College and Research Institute, Porur, Chennai, India
b Department of Microbiology, Sree Balaji Medical College and Hospital, Chrompet, Chennai, India

* Corresponding author at: Sri Ramachandra Medical College and Research Institute, Porur, Chennai 600116, India.
E-mail address: drmeb1974@yahoo.co.in (E. Bhaskar).

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