Correspondence

Measuring Dengue Enhancing Antibodies: Caveats

To the Editor—Laoprasopwattana et al. [1] concluded that “levels of preillness plasma EA [enhancing activity] or DV [dengue virus] infection in K562 cells did not correlate with the clinical severity or viral burden of secondary DV infection” (p. 510). Sadly, serious flaws in their study’s design and methodology preclude rigorous interpretation of these data. Nonetheless, the authors have identified a research question of central importance to an understanding of the biology of DV infection enhancement in vivo and should be encouraged to continue this research. Comparative data permitting K562 cells, a stable line of human leukemia cells, to be accepted as a surrogate for primary human blood monocytes, which comprised the test system in an earlier study, will be important to future studies of DV enhancing antibodies [2].

With respect to the correlation between enhancing antibodies and disease severity during secondary DV serotype 3 (DV3) infection, the authors observed EA in all but 1 of 27 undiluted preillness plasma samples from children experiencing overt dengue illness. This result is similar to that obtained by Kliks et al. [2]. A challenge to the reader is how to interpret the results. Laoprasopwattana et al. obtained by testing plasma from only the 10 inapparently infected individuals in their study. First, these individuals may not have had secondary DV3 infection. The authors missed a crucial opportunity to document the etiology of these infections by failing to test posttransmission plasma for neutralizing antibodies. Importantly, all but 1 (case 31) of the 10 preseason plasma samples contained DV3 neutralizing antibodies, some at high titers. It was conjectured that both inapparently infected children and children with overt illness, because they were schoolmates, must have had secondary DV3 infection. However, as was illustrated in prospective cohort studies in Thailand and Indonesia, different DVs can be the cause of overt versus inapparent secondary infection during the same outbreak [3, 4].

With respect to attempts to correlate EA with viremia level, Laoprasopwattana et al. chose to measure viremia in a single acute-phase blood sample, labeling this as “peak viremia level.” In an earlier publication, many of these same authors established a reference standard in which a peak was observed in a viremia curve constructed by assaying virus in acute-phase plasma collected over a period of 5 consecutive days [5]. By these criteria, the present study did not measure peak viremia level. Further, “peak” viremia levels (see table 1 in their article) did not correlate with disease severity.

The authors’ methodology could have affected their results. Their Methods section and figures 1 and 4 indicate that preillness plasma from children with overt illness and from children with inapparent infection was studied for EA in separate tests. However, tests on plasma from inapparent cases did not include nonimmune control plasma and used only 8 comparison plasma samples from symptomatic children. No information is supplied to describe how these comparison samples were selected and whether they were representative of the larger group.

Peripheral to the above points but, yet, somewhat mysterious are individuals without any DV neutralizing antibodies in preillness plasma or with antibodies only to Japanese encephalitis who, a few months later, experienced an illness accompanied by a secondary DV antibody response. How is this possible? Did the authors rule out 2 closely spaced DV infections during the same transmission season as an explanation?

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References


Antibody-Dependent Enhancement in Dengue Virus Infections

To the Editor—Laoprasopwattana et al. [1] report that enhancing antibody activity in plasma does not predict subsequent disease severity or viremia in secondary dengue virus (DV) infection. They write that their “results do not support those of a