Virological Interpretations of Dengue Disease Spectrum in Infants in Chennai, Tamil Nadu, India, Need Reevaluation

We read with interest the study of Kabilan et al. (2) regarding the dengue disease spectrum in infants in Chennai, Tamil Nadu, India. However, certain points in this study regarding the virological investigations and their interpretations are not clear. As specified in the paper, the authors used dengue-specific immunoglobulin M (IgM) and IgG microenzyme-linked immunosorbent assay (microELISA) reagents for the detection of the respective antibodies. As a considerable number of cross-reactions occur between members of the flavivirus group, i.e., those causing dengue, Japanese encephalitis, and West Nile viral infections (1), it is worthwhile to look for specific IgM antibody against dengue viruses by the μ-capture technique. We have been working in the field of flaviviruses for the last decade (4, 5) and are using Pan-Bio μ-capture IgM microELISA reagents for the diagnosis of suspected dengue cases. In our experience, the μ-capture technique has been found to be better (94.7% sensitivity and 98.9% specificity, according to the manufacturer) than the technique has been found to be better (94.7% sensitivity and 98.9% specificity, according to the manufacturer) than the non-μ-capture microELISA system so far as diagnosis of dengue virus infection is concerned. Hence, it would have been more useful if the authors had used the μ-capture technique for the serological confirmation of dengue virus infection in their study.

As is evident from Table 2 in the original study (2), two cases of dengue shock syndrome were diagnosed as acute dengue virus infections based upon the dengue virus IgG antibody only. In areas where dengue is endemic, it appears to be difficult even among infants to exclude the presence of either passively transferred maternal IgG antibodies or IgG antibodies acquired due to past exposure in the form of clinical or subclinical infection. The first problem would be easily eliminated by determining the absence of dengue virus IgG antibodies in the maternal serum. Otherwise, the role of dengue virus IgG antibody in the diagnosis of acute infection lies with the demonstration of seroconversion or a significant rise in antibody titers in follow-up samples (1).

Since Kabilan et al. reported that the epidemic was due to dengue virus serotype 4, we would like to clarify that cross-reactions between flaviviruses as well as between dengue virus serotypes have been observed. It is difficult to type dengue viruses serologically by using the cross-reactive antigens that are available in many microELISA kits; i.e., the Pan-Bio dengue IgM kit utilizes dengue virus serotype 2 as the coating antigen, which cross-reacts with other dengue virus serotypes (serotypes 1, 3, and 4), whereas the Pan-Bio μ-capture IgM microELISA kit utilizes a pool of dengue virus serotypes 1 to 4 as the source of common dengue virus antigen. None of the kits mentioned above have the ability to differentiate between the serotypes unless serotype-specific antigenic determinants of dengue viruses are used individually in separate kits. At best, this type of kit can be used only for diagnosing acute dengue virus infection, not for serotyping. Conventionally, serotyping is done by neutralization, immunofluorescence tests using type-specific antisera (1), or reverse transcriptase PCR using type-specific primers (3).

Hence, it would be worthwhile to know the type of antigens the authors used to determine the infection to be caused by dengue virus serotype 4. This information would be of much use to the researchers working in similar fields.

REFERENCES


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Author’s Reply

It is a great pleasure for me to respond to Dr. Mishra’s letter and to clarify the following points. First, in our study we used the μ-capture technique for serological confirmation. Second, what we said in the paper was that while dengue virus-specific IgM responses were predominant in most (23 of 24) dengue fever (DF) cases, the five infants with severe forms of dengue disease elicited IgG responses with or without IgM responses (Table 2 of reference 1), suggesting that the DF and dengue hemorrhagic fever-dengue shock syndrome cases were due to primary and secondary dengue virus infections, respectively. The cases were categorized by clinical and serological criteria. We fully agree with Dr. Mishra’s point of view as to the role of dengue virus-specific IgG antibody in the diagnosis of acute infection, which depends on demonstration of either seroconversion or a significant rise in antibodies in the paired sera. Collection of paired sera was not possible for us because of practical difficulties. Third, we are aware of the cross-reactions of antiflavivirus antibodies and among the dengue virus serotype-specific antigens as well. In our study, we used dengue virus serotype-specific antigens supplied by the Centers for Disease Control and Prevention, Fort Collins, Colo. In the absence of an immune response to the particular monovalent antigen, it has been claimed that the highest IgM responses were against the infecting dengue virus serotype in most of the individuals confirmed to have dengue virus infections (2). Following the report of our study (1), we isolated dengue virus of serotype 4 from a patient’s serum by using an insect bioassay system (i.e., an immunofluorescence assay using the larvae of Toxorhynchites splendens).

REFERENCES


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