Sequential Dengue Infection: Prevention Priorities

Sir,

We aim to draw your and readers’ attention to the repercussions of sequential dengue infection and its preventive measures.

Dengue is an infectious disease caused by one of four serotypes of the dengue virus (DENV): DENVs 1-4. It is a vector-borne disease transmitted mostly by the female Aedes mosquito to humans. Each of the four DENV serotypes is capable of causing a spectrum of mild to severe dengue disease. There are approximately 90 million symptomatic cases of dengue each year, 70% of which occur in Asia.1 Dengue is endemic in Pakistan, with 25,932 confirmed cases and 62 deaths from January to September 2022, placing a significant strain on the national health system.2

DENV infection produces both protective and pathogenic antibodies that target structural proteins E, prM, and a non-structural protein (NS1). The immune response to NS1 can cross-react, giving lifetime immunity to the same serotype but only short-term immunity to other serotypes. NS1 inhibits thrombin and causes bleeding diathesis by increasing fibrinolysis and promoting a vasoactive inflammatory response. Anti-prM antibodies induce antibody-dependent enhancement (ADE), but do not neutralise DENV because they enable non-neutralised and immature DENV to enter monocytes and macrophages.3 ADE may result in severe dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) following infection with a different serotype. The risk of DHF and DSS with sequential infection is 7.6 times higher in those with low anti-dengue virus antibody (anti-DENV) levels (1:21-1:80) compared to those with no antibodies, indicating no prior DENV exposure, or with exceptionally high anti-DENV levels (>1:1280). Also, it takes an average of three years post-infection to acquire the dangerous antibody titer range of 1:21-1:80.4

The only licensed live attenuated dengue vaccine (Dengvaxia®) is restricted by the CDC to be used only in children (9-16 years old) who have had previous laboratory-proven dengue infection. Dengvaxia® has about 80% efficacy against hospitalisation and severe dengue among these children.5 This approval is restricted out of concern that this vaccine may have sensitised some dengue-naive recipients to severe dengue fever after a subsequent infection through the same ADE. Antibodies produced by DENVS perform functions in both dengue illness prevention and pathogenesis. Protective immunity is determined by the equilibrium between these two antagonistic antibody functions. A safe and effective dengue vaccine must provide long-lasting protection against all four DENV serotypes without causing ADE.3

Dengue fever has no definitive treatment; supportive therapy is the only option once symptoms and complications appear. Healthcare professionals and the general public exhibit a lack of awareness and concern for the dire consequences of sequential dengue infection. We intend to counsel our dengue patients to be extra vigilant in the future to avoid reinfection. This dilemma must be highlighted in dengue awareness seminars, advertisements, and educational materials distributed by public health authorities. Positive dengue IgG antibodies indicating a previous infection should alert physicians to the possibility of severe disease.

Our earnest hope is that these measures can mitigate the severity of dengue infections in Pakistan, consequently saving lives and reducing the burden on our healthcare system.

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REFERENCES

Javaria Aslam1, Khawaja Hassam2 and Muhammad Abdullah Naeem3

1Department of Medicine, Quaid-e-Azam Medical College, Bahawalpur, Pakistan
2Liver Centre Beth Israel Deaconess Medical Centre, Boston, Massachusetts, USA
3Department of Surgery, Sadiq Abbasi Hospital, Bahawalpur, Pakistan

Correspondence to: Dr. Javaria Aslam, Department of Medicine, Quaid-e-Azam Medical College, Bahawalpur, Pakistan
E-mail: javaslam50@gmail.com

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