Pathophysiology of Severe Dengue

Antibody-Dependent Enhancement of Disease and Severe Dengue

Severe dengue most commonly occurs among infants and patients with secondary dengue virus (DENV) infections (i.e., infection with a DENV type different from what they were previously infected with earlier in life). The most widely-cited hypothesis for this occurrence is antibody-dependent enhancement (ADE) of disease. ADE occurs when nonneutralizing anti-DENV antibodies bind to but do not neutralize an infecting DENV. This virus-antibody complex allows for enhanced viral entry into host cells, specifically dendritic cells and macrophages. Once inside the cell, the virus replicates and generates higher virus titers in the blood than when anti-DENV antibody is not present, which results in a "cytokine storm" and ultimately leading to more severe disease.

Infants and Severe Dengue

Infants in dengue endemic areas have anti-DENV IgG antibodies at the time of birth. Anti-DENV IgG antibodies are passed from a mother to her fetus (IgM does not cross placenta). This passively transferred maternal anti-DENV IgG can protect the infant for the first few months after birth, which is why dengue in infants less than 4 months of age is unusual. However, as the maternal anti-DENV IgG titer falls 4-6 months after birth, ADE outweighs neutralization and the infant is at risk for severe disease even with a primary DENV infection. At about one year, the infant is no longer at increased risk.

Risk Factors for Severe Dengue

Viral characteristics

• Viral titer correlates with disease severity

• There may be strain and serotype differences in pathogenicity

Host factors

• Age (infant)

• Women, especially pregnant women

• Patients with chronic medical conditions, including diabetes, asthma, obesity, and heart disease

• Patients with secondary DENV infection

Level of neutralizing antibody

• Timing of infection relative to the previous DENV infection (the longer, the higher the risk)

• There are no tests or biomarkers to identify which patients will experience severe disease

Centers for Disease Control and Prevention
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