Apoptosis, vascular leakage and increased risk of severe dengue in a type 2 diabetes mellitus patient

Dear Sirs,

Diabetes mellitus (DM) is reported to be a risk factor for increased dengue severity in dengue epidemics both in Cuba and elsewhere. Dengue is a major cause of morbidity and mortality throughout tropical and subtropical regions of the world. Four distinct dengue viral serotypes (DENV1–4), transmitted principally by Aedes aegypti mosquitoes, cause dengue fever (DF) and dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). DF is a self-limited febrile disease. However, the most severe clinical form of dengue (DHF) is defined mostly by the hallmark pathological characteristic of vascular leakage, represented by ascites and hydrothorax. Some severe DHF cases progress to the life-threatening disease, DSS, which is associated with hypovolaemic shock.

The pathogenesis of DHF/DSS involves viral, immunological and host factors. Sequential DENV infections by distinct serotypes constitute the most important risk factor for DHF/DSS. It is possible that interactions between high viral load and altered immune response, including cytokine overproduction, might trigger vascular leakage. Individuals with chronic diseases such as DM are at high risk of severe dengue.

Very recently, in vivo apoptosis in cerebral cells, leukocytes and microvascular endothelial cells (MECs) has been demonstrated for the first time in tissues from fatal cases of DHF/DSS. Apoptotic cells were detected in five out of six individuals studied. These subjects died during the DENV-2 epidemic in Santiago de Cuba in 1997. One of them suffered from type 2 DM. Apoptosis of MECs was demonstrated in the intestinal serosa of this individual. Thus, the serosal oedema and ascites described in the post-mortem study were associated with apoptosis in the serosal MECs. Prior studies have shown endothelial dysfunction and increased production of cytokines in patients with type 2 DM. In vitro induction of apoptosis in endothelial cells by serum tumour necrosis factor (TNF)-α was observed. Additionally, high levels of monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF) have been reported in type 2 DM patients.

Similarly, in vitro induction of apoptosis in endothelial cells associated with a high level of TNF-α in dengue patients’ serum has been reported. Very recently, high expressed levels of MCP-1 have been found in DHF/DSS patients, which were also related to the in vitro increase of vascular endothelial cell permeability, probably an effect on the endothelial cell tight junctions. Also VEGF, a cytokine that enhances permeability, has been linked to vascular permeability regulation in DHF/DSS. These data together suggest cytokines present in sera from type 2 DM patients might predispose them to vascular leakage and consequently to severe dengue and death during DENV infection.

To our knowledge, this is the first post-mortem study to report apoptosis findings in a type 2 DM case dying of DHF/DSS. Notably, apoptosis in intestinal MECs was found in this fatal case in which the presence of ascites was described at autopsy. It is very likely that pathophysiological features and increased risk of severe dengue in type 2 DM patients may be related to microvascular endothelium abnormalities and cytokine overproduction. Further studies are required to address the high risk of severe dengue in diabetic patients and the plausible immunopathological links between dengue and diabetes.

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Conflict of interest
None declared.

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LETTER TO THE EDITORS

Improving diabetes care and prevention in the 21st century

The Global Partnership for Effective Diabetes Management was founded in 2004 as a multidisciplinary taskforce of internationally-respected diabetes experts from leading institutions and diabetes organisations, committed to improving outcomes for people with type 2 diabetes.

To build on the momentum generated by the recent UN resolution on diabetes, the Global Partnership has developed three short presentations to provide inspirational, yet practical, direction for the global diabetes community. Offering ‘real world’ guidance, underpinned by motivational success stories from around the world, the presentations aim to raise diabetes awareness from grassroots to governments, improve clinical practice, increase understanding and stress the urgent need for action.

The three presentations are designed to help all diabetes healthcare professionals communicate with as wide an audience as possible, including policy makers, fellow healthcare professionals and the general public.

Together we can continue the current momentum and improve diabetes care and prevention in the 21st century.

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