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Inducible nitric oxide synthase (iNOS) in peripheral blood cells as an early predictive biomarker of dengue hemorrhagic fever

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Dengue is the most common flaviviral disease transmitted by mosquitoes in the endemic areas. Dengue can manifest clinical symptoms ranging from mild dengue fever (DF) to severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue patients present symptoms of hemorrhagic manifestations only after 3-5 days from fever onset. Lack of effective vaccines and antiviral therapy makes severe manifestations of dengue more life threatening. However, early fluid management can drastically mitigate the disease outcome of severe dengue. Therefore, an early prognostic marker of disease severity has the potential to reduce complications of severe dengue.Nitric Oxide (NO) is a molecule involved in cellular signaling that has been implicated in pathogenesis of several viral infections including dengue. Our studies have shown significantly ($P<0.05$) low NO levels present in plasma of patients who later developed DHF compared to DF patients within 4 days from fever onset. NO is believed to increase the vascular permeability of endothelial cells, which is one of the main symptoms of hemorrhagic manifestations of dengue infection. NO is produced by three isoforms of nitric oxide synthase (NOS), namely, inducible NOS (iNOS), endothelial NOS (eNOS) and neuronal (nNOS). iNOS activity and plasma NO has been implicated in inflammatory responses and plasma leakage. Therefore, we have evaluated the expression of iNOS in PBC collected from NS1 antigen positive, DF patients (n = 19) and patients who later developed DHF (n = 20) within 4 days of fever onset using qRT-PCR. Relative expression of iNOS was normalized against the expression of GAPDH as a reference gene. Consistent with the levels of NO in plasma, iNOS showed over 2 fold down regulation of expression in the DHF patients within 4 days of onset of fever ($P < 0.05$) andwithin 2 and 3 days of fever onset as well. But there was no relative expression difference in the patients presented with thrombocytopenia (platelet count ≤ 100000/mm^3)compared to those with platelet count >100000/mm^3during the course of illness. Therefore, iNOS may serve as an early prognostic marker for DHF.

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