Dengue: Cardiac Manifestations and Implications in Antithrombotic Treatment

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Introduction

Dengue is a disease caused by a virus of the *Flavivirus* genus that consists of an RNA virus transmitted mostly by arthropods. Other clinically important diseases caused by these viruses are yellow-fever and Japanese encephalitis[1].

Dengue is widely disseminated, occurring endemically or sometimes epidemically in tropical regions. It is transmitted by mosquitoes of the *Aedes* genus, mainly *Aedes aegypti*, and its distribution and adaptation in urban and domestic environments help to explain the predominance of dengue in cities. The disease occurs when a viremic patient enters an environment where there is a sufficiently large concentration of vectors, and becomes epidemic when there is a significant increase in the number of vectors. The virus is subdivided in 4 serotypes that do not provide cross-immunity.

In Brazil, similar to other countries in the tropical zone, the disease is endemic with epidemic outbreaks. According to data from the Ministry of Health, until March 12th of this year, 85,018 cases had been reported, which represents an increase of nearly 30% relative to the same period of 2006. The states with the largest numbers of cases are: Mato Grosso do Sul (50.4%), Mato Grosso (7.2%), Rio de Janeiro (5.2%), Paraná (4.7%), Minas Gerais (4.6%), and São Paulo (3.6%). The only states where autochthonous transmission of dengue has not been documented are Rio Grande do Sul and Santa Catarina. Due to the unspecific clinical presentation of milder cases, most certainly these numbers are underestimated[2].

Clinical aspects of dengue

Most cases of dengue are self-limited, and the course of the disease is a nonspecific febrile state, general malaise and weakness. Patients may feel severe muscle pain and retro-orbital pain, with or without skin rash. Laboratory tests may reveal increased hepatic enzyme levels, leukopenia and thrombocytopenia, which are abnormalities consistent with but nonspecific for dengue fever[1].

Key words

Dengue; dengue hemorrhagic fever/complications; arrhytmia; heart block; fibrinolytic agents.

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The most severe forms of the disease are dengue shock syndrome and dengue hemorrhagic fever. The shock syndrome is due to an important alteration in capillary permeability and significant capillary leakage of plasma into extra-vascular spaces, and is associated with immune activation and high serum levels of tumor necrosis factor-α (TNF) receptor, interleukin (IL)-8, and other factors.

Dengue hemorrhagic fever typically develops together with shock and occurs 2 to 7 days after defervescence. From a clinical point of view, it is not possible to distinguish those patients who will progress to the hemorrhagic form of the disease from those with the self-limited illness. This year in Brazil (from January to May), only 55 cases of dengue hemorrhagic fever and 6 deaths were reported[2].

Physiopathology of dengue hemorrhagic fever

The hemorrhagic form of dengue is rare and affects almost exclusively patients with a prior episode, suggesting a physiopathology associated with an exacerbated immune response mediated by heterologous antibodies. Increases in TNF, IL-2, and soluble CD8 are suggestive of hyperactivation of memory CD4 and CD8 cells. There is evidence of overexpression of Fc receptors and class I and II MHC antigens, as well as a serum increase of several inflammatory mediators, as a result of endothelial and mononuclear cell lysis. The result of the immune over-response is a combination of vasculopathy and consumption coagulopathy. The hemorrhagic diathesis in dengue is caused by vasculopathy, thrombocytopenia, and mild coagulopathy, which are responsible for skin and mucous membrane bleeding[3]. The greater vascular fragility is probably a result of the direct action of the virus, which would occur as early as the viremic or initial febrile phases.

Thrombocytopenia and platelet disorders

As to platelets, there may be thrombocytopenia and platelet disorders. Thrombocytopenia may be secondary to decreased platelet production by the bone marrow, as well as increased peripheral destruction of platelets. It has already been observed that during the acute febrile phase of dengue hemorrhagic fever, bone marrow is markedly hypocellular, with a drop in the production of all cell lines. These findings were later shown to result from direct action of the virus on the medullary stroma and on the hematopoietic progenitor cells. Two days before the defervescence phase,

bone marrow hypercellularity is noted, with an enhanced production of precursor cells of the three medullary cell lines. Hemophagocytosis is another possible explanation for the reduced platelet count, which can also occur due to immune destruction (IgM class antiplatelet antibodies and dengue-specific antibodies). Platelet counts return to normal within 7 to 10 days after the defervescence phase[4,5].

Alterations in platelet function are also described; these are evidenced by ADP-induced platelet hypoaggregation, a drop in the secretion of intra-platelet ADP, and a rise in plasma concentrations of β-thromboglobulin and platelet factor-4. These findings are consistent with *in vivo* platelet activation resulting from activation by immune complexes. Platelet function resumes its normal conditions 2 to 3 weeks after the initial convalescence period[5].

Alterations in coagulation

During the febrile period, variable reductions are observed in the different coagulation factors, such as fibrinogen, factor V, factor VIII, factor IX and factor X, besides antithrombin and α_2-antiplasmin. These changes explain the discreet prolongation in prothrombin time and activated partial thromboplastin time. Elevations in the concentrations of fibrinogen/fibrin (FDP) degradation products and D5-dimer have also been described[5].

Due to these alterations in hemostasis, the use of acetylsalicylic acid, non-hormonal anti-inflammatory agents, and large quantities of volume expanders (Dextran 40 and Haemacel) is considered as risk factors for bleeding[6].

Immunity and inflammation

The mechanisms involved in the development of severe dengue hemorrhagic disease are not fully understood, but it is suggested that a secondary infection induced by another dengue serotype is the main risk factor for dengue hemorrhagic fever and dengue shock syndrome. Cross-reactive non-neutralizing antibodies from a previous infection bind to the new serotype, increasing capture by monocytes and macrophages, thus resulting in the amplification of the cytokine cascade and activation of the complement[7]. However, as only 2% to 4% of individuals with a second infection develop the severe form of the disease, the antibody-dependent increase alone can not explain the whole process. Significant differences in antibody, cytokine, and T-cell responses are observed between patients with the non-complicated form of the disease and those with the complicated forms.

Monocytes, B lymphocytes, and mastocytes infected by the dengue virus produce different cytokines, and some authors show that the largest increases in concentrations of TFN-α, IL-2, IL-6, and interferon (IFN)-γ take place during the first 3 days of the disease, followed by the appearance of IL-10, IL-5 and IL-4. Patients with the hemorrhagic form of the disease present larger concentrations of TNF-α, IL-6, IL-13, IL-18, and cytotoxic factor, and these cytokines are involved in the increased vascular permeability and shock that occur during the infection. Additionally, by producing T CD4+ cells, the cytotoxic factor induces macrophages to produce IL-1α, TNF-α, and IL-8. Concentrations of IL-6 (of endothelial and mastocyte origin) are higher in patients with shock and dengue hemorrhagic fever. The highest levels of TNF-α and IL-10 correlate with hemorrhagic manifestations and thrombocytopenia, respectively. IL-10 also reduces platelet function and contributes to dengue platelet defects[4].

There is much evidence linking inflammation and coagulation, and the main interfaces for this are the tissue factor (TF) pathway, the C-protein system, and the fibrinolytic system. Proinflammatory cytokines can affect all these coagulation mechanisms, whereas activated coagulation proteases, physiological anticoagulants, or components of the fibrinolytic system can modulate inflammation through specific cell receptors.

The main inflammatory mediators involved are IL-6, in coagulation activation, and TNF-α and IL-1 in physiological anticoagulant regulation. Several studies demonstrate the importance of IL-6 in the induction of TF expression in many cells, such as mononuclear cells, leading to systemic activation of coagulation. Once TF is expressed, the coagulation cascade is triggered, as well as the formation of enzymatic complexes on a phospholipid surface which, ideally, is presented by the platelets. During the inflammatory process, platelets can be directly activated by endotoxins, thrombin, and inflammatory mediators, such as the platelet activating factor. By expressing P-selectin, the activated platelets mediate platelet adhesion to the endothelium and leukocytes. The binding of activated platelets to neutrophils and mononuclear cells induces activation of nuclear factor κB, thus increasing the expression of TF in monocytes. During the acute inflammatory process, concentrations of antithrombin are significantly decreased due to the reduced synthesis, degradation by neutrophil elastase released from activated neutrophils, and consumption. The C-protein system is also blocked, as the endothelial expression of thrombomodulin is reduced by the action of TNF-α and IL-1β. TNF-α and IL-1β also have a role in regulating plasminogen inhibitors and activators. Cytokines induce secretion of tPA and uPA from their storage sites in endothelial cells. However, this increase in fibrinolytic activation is counterbalanced by a delayed and sustained rise in PAI-1[7].

Cardiac manifestations of dengue

Dengue rarely affects the heart. In 1996, during an epidemic outbreak of dengue in India, 206 patients were evaluated and only one had cardiac symptoms[8]. Medical literature has reports of isolated cases of atrioventricular conduction disorders (junctional rhythm and atrioventricular block), supraventricular arrhythmias, and myocarditis[9].

On the other hand, the ventricular dysfunction associated with the acute phase of dengue hemorrhagic fever has been described by several authors and is probably underdiagnosed in clinical practice. During the 1996 epidemic, 54 children with dengue of varied degrees of severity underwent evaluation of the ventricular function. Approximately 16% had ejection fractions under 50%[10]. In that same period, 17 subjects with dengue hemorrhagic fever or dengue shock syndrome underwent myocardial scintigraphy, which showed that 70% of them had diffuse hypokinesia, with a mean ejection fraction of 40%[11]. After three weeks, the myocardial

function of all patients had normalized. More recently, 24 patients with dengue hemorrhagic fever were evaluated and underwent serial echocardiograms during the acute phase of the infection and convalescence. In the study, a transient reduction in ventricular ejection fraction and in cardiac index during the infection was observed[12].

Although cardiac manifestations specific to dengue are rare, depression of myocardial function is frequent in the hemorrhagic form of the disease or in the associated shock. The "dengue-related shock syndrome" is due to the increased vascular permeability and hypovolemic pattern[13]. However, an adequate approach to the hemodynamic instability associated with dengue requires not only a significant volemic expansion, but also evaluation and treatment of the accompanying ventricular dysfunction, as in the current treatment of sepsis.

Implications of the interruption of antithrombotic agents used in cardiac patients with dengue

The decision to interrupt the use of platelet antiaggregants and anticoagulants in patients with dengue depends on a complex assessment of the risks and benefits of these treatments. The risk of interrupting the use of antithrombotics in different clinical conditions and the risk of hemorrhage in an acute virus infection should also be taken in consideration.

Patients who have recently undergone angioplasty, with chronic atrial fibrillation (CAF) and those with metal valvar prostheses are the ones who benefit most from the use of antiaggregants and anticoagulants in the long run. Treatment interruption increases the risk of thrombosis in different ways in each of the clinical conditions described below.

After stent implantation, treatment with acetylsalicylic acid (ASA) and thienopyridines (ticlopidine or clopidogrel) is mandatory, as it significantly reduces the risk of acute and subacute stent thrombosis, as well as adverse cardiovascular events[14]. A study conducted with 1,653 patients who had undergone stent angioplasty revealed a reduction from 3.6% to 0.5% in the risk of adverse events within 30 days, with the use of thienopyridines combined with aspirin[15]. Besides the use of aspirin, current recommendations are to add clopidogrel for at least one month after the implantation of non drug-eluting stents, three months after the implantation of sirolimus-coated stents, six months for plaxitaxel and, ideally, 12 months for all of them, provided they do not represent a high risk of hemorrhage[16]. Recently, the occurrence of late (after one year) drug-eluting stent thrombosis raised a discussion about the possibility of long-term treatment with clopidogrel for an unlimited time. On the other hand, early interruption of treatment with platelet antiaggregants during the first month after stent implantation can be devastating, with an incidence as high as 30% of acute or subacute stent thrombosis[17].

Patients with CAF must be treated with platelet antiaggregants or anticoagulants to prevent atrial thrombosis and cardioembolic cerebrovascular accidents (CVA) Anticoagulants should be preferred for patients at a higher risk of embolism (patients with ventricular dysfunction, who are elderly, hypertensive, diabetic, have valvar disorders or a prior CVA). Depending on the number of risk factors, the annual risk of CVA in patients who have not undergone treatment with anticoagulants may vary from 3% to 20%[18]. A meta-analysis demonstrated that patients with CAF had a 62% reduction in the risk of CVA with the use of anticoagulants[19].

Patients with metal valvar prostheses may benefit from the use of anticoagulants to prevent valvar thrombosis. Patients with mitral prostheses are at higher risk than those with aortic prostheses. Patients with implanted Starr-Edwards prostheses, prior CAF or thromboembolism, more than one mechanical valve, and tricuspid involvement are also at a higher risk of thromboembolism. However, even in patients with mechanical valves, the annual risk of thrombosis without warfarin protection is approximately 20%[20]. Therefore, interrupting the use of warfarin for a few days does not represent a significant risk of thrombosis.

Conclusion and recommendations

Due to the low incidence of dengue hemorrhagic fever and the difficulty to initially predict which patients will progress to the hemorrhagic form of the disease, we suggest the following measures regarding the interruption of antithrombotics in these clinical cardiac situations:

1) All patients with dengue

The use of AAS should be avoided by patients with dengue for two reasons: the first one, the possibility of developing Reye's syndrome. Although rare, Reye´s syndrome, a severe encephalopathy associated with hepatitis, may be triggered by the use of aspirin in patients with several types of virus infections, such as varicella, influenza and dengue. It is a condition that affects mostly children, but adults may also be affected. The second reason is the risk of thrombocytopenia due to dengue, which can be worsened by the concomitant use of platelet antiaggregant agents.

Recommendation: All patients with dengue should avoid using AAS for one week to reduce the risk of developing Reye's syndrome and severe thrombocytopenia. In patients at high risk of thrombosis, treatment with antiaggregant agents may be maintained provided platelet counts are regularly monitored (see below).

2) Patients with dengue and at a high short term risk of thrombosis:

- Patients who have recently undergone coronary angioplasty with stent implantation (1 month for non-pharmacological stents, and 3-6 months for pharmacological stents).
- Patients with mechanical valvar prostheses, especially in a mitral or tricuspid position, or with associated CAF, prior thromboembolism or more than one mechanical valve.
- Patients with CAF and multiple thrombotic risk factors (patients with ventricular dysfunction, who are elderly, hypertensive, diabetic, have valvar disorders, prior CVA or intracavitary thrombus).

Recommendation: Keep clopidogrel and AAS, in those patients already taking these agents. Interrupt warfarin use

and replace it with heparin as soon as the INR level is below the therapeutic range. Reintroduce warfarin after one week. Perform serial platelet monitoring and coagulogram during one week. Interrupt use of medications if platelet count is equal to or less than 50,000/mm^3, and if there is bleeding or shock. Clopidogrel and AAS interruption may be considered depending on the intensity of progressive reduction in the number of platelets.

3) Patients with dengue and at low short term risk of thrombosis:

- Patients with stable coronary artery disease.
- Patients who have undergone coronary angioplasty with stent implantation more than six months before.
- Patients with CAF and no risk factors for thrombosis (or only one risk factor).
- Patients with biological valvar prostheses.

Recommendation - Interrupt the use of aspirin. Consider interrupting clopidogrel and warfarin for one week.

4) Patients with dengue hemorrhagic fever

Recommendation - Interrupt immediately the use of all antithrombotic agents.

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