Asymptomatic myocardial involvement in acute dengue virus infection in a cohort of adult Sri Lankans admitted to a tertiary referral centre

RAVINDRA L SATARASINGHE, KANAGASINHAM ARULTNITHY, NEOMALI L AMERASENA, UDITHA BULUGAHAPITIYA, DESHU V SAHAYAM

Abstract

Viral myocarditis is a well-recognised complication of many viruses leading to subsequent cardiomyopathies (dilated type). There are limited data available with respect to dengue virus involvement,[1,2] an infection which can be asymptomatic and can lead to undifferentiated viral fever syndrome, dengue fever, dengue haemorrhagic syndrome or dengue shock syndrome. Dengue has probably been endemic in Sri Lanka for a long time[3] although no cases of dengue haemorrhagic fever was reported until 1965. Now, several hundred cases a year have been reported annually from 1991.[4] The only two published articles from Sri Lanka on myocardial involvement described cardiac sequelae, diagnosed quite late, retrospectively, in the non-active phase of the illness.[5,6] Recent epidemics of the disease in Sri Lanka led us to design a study to look at myocardial involvement in clinically and serologically confirmed cases of dengue infection.

Br J Cardiol 2007;**14**:171–3

Subjects and methodology

All patients suffering from an acute febrile illness admitted to the principal author's unit from 1st June 2002 to 1st June 2003, who satisfied the criteria for the diagnosis of dengue fever, were selected for the study. These criteria included an acute febrile episode lasting two to seven days and a platelet count of less than 100,000/mm.[1] Full blood count, liver function tests, renal profile, a 12- lead electrocardiogram (ECG), cardiac enzymes (creatine phosphokinase [CPK] and its MB isoenzyme [CPK-MB]), two-dimensional (2-D) echocardiography during the acute phase of the febrile illness, and dengue IgM antibodies by ELISA method using the haemaglutinin inhibition method, were the investigations carried out in all patients included in the study.

Any patient who showed 2-D echocardiographic abnormalities unlikely to be due to chronic cardiac pathology, such as chronic valvular heart diseases, evidence of cardiomyopathies, ischaemic heart disease and hypertension, were assumed to have dengue virus related acute myocarditis. Their ECG, CPK and CPK-MB values, liver function tests, and clinical symptoms and signs related to cardiovascular system were analysed. Patients had repeat 2-D echocardiographic examination three to four weeks later and were then followed up for one to two years for clinical and symptomatic cardiovascular abnormalities.

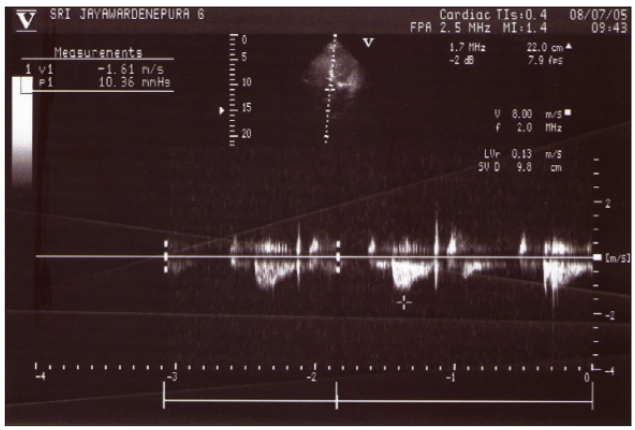
Results

Some 217 patients satisfied the minimum criteria of dengue fever, of whom 85% had undergone 2-D echocardiography. Dengue IgM antibody was positive in 95% of patients, with the remaining 5% having either negative results or results that were unavailable. The major reason for the latter was sending blood samples too early in the disease. Evidence of 2-D echocardiographic myocarditis was present in 24% of patients, with a male:female ratio of 2:1, and an age distribution of 12–65 years, of whom 65% were in the 12–30 years age group. None had clinical features of overt myocarditis, such as significant sinus tachycardia, raised jugular venous pressure, triple rhythm, bilateral pulmonary crepitations and peripheral oedema. None complained of any chest discomfort or dyspnoea of any grade. All had a relative bradycardia of around 50–60 beats per minute despite 2-D echocardiographic abnormalities suggestive of acute myocarditis. Only one patient had a regularly irregular pulse rate which was subsequently diagnosed to be due to Wencheback's phenomenon. There were no other ECG abnormalities in the myocarditis group.

The 2-D echocardiographic abnormalities showed chamber dilatation, an irregular jerky movement of the ventricular wall, and a minor degree of atrioventricular valvular regurgitation (figure 1). Dominantly, the right ventricle (RV) showed dilation with associated tricuspid regurgitation in 57% (35/61) of patients, left ventricular dilation was observed less often in 21% (13/61) of patients, followed by duel chamber dilatation in 16% (10/61) of patients and isolated tricuspid regurgitation in 6% of patients. All had a satisfactory ejection fraction. CPK-MB values were not helpful in diagnos-

Sri Jayewardenepura General Hospital (Postgraduate Teaching & Tertiary Referral Centre), Kotte, Sri Lanka.
Ravindra L Satarasinghe, Consultant Physician and Gastroenterologist
Kanagasinham Arultnithy, Registrar
Neomali L Amerasena, Consultant Cardiologist
Uditha Bulugahapitiya, Registrar
Deshu V Sahayam, Senior House Officer
Correspondence to: Dr RL Satarasinghe
(E-mail: pubsy@sltnet.lk)

Figure 1. Two-dimensional echocardiographic features of tricuspid regurgitation in a patient having asymptomatic dengue myocarditis as a result of atrioventricular valvular annulas dilatation which occurred either as an isolated phenomenon or combined with right ventricular dilatation



ing myocardial involvement. All myocarditis patients were found to have dengue virus infection of the D2 serotype.

Follow-up showed that 96% and 100% of the myocarditis group had normal 2-D echocardiographic findings within three weeks and three months, respectively. Tricuspid regurgitation was the last to disappear. In the entire period of follow-up (up to 1st June 2005), there were no cardiovascular symptoms and signs in any patient who had had evidence of 2-D echocardiographic myocardial involvement. There was no bias to any particular blood group in the myocarditis group but asymptomatic elevation of hepatic transaminases was seen in 30% of the myocarditis group compared to 76% of the total population; and raised CPK in 9% of the myocarditis group compared to 30% of the normal population. Nobody in the study group had pericardial effusions.

Discussion

Dengue fever is known to affect several systems in the human body. There is little published data on myocardial involvement in acute dengue infection. Obeysekara and Yvette[5,6] did not describe any features of myocardial involvement, which we have seen during acute dengue virus infection confirmed by positive dengue IgM antibodies. Also 2-D echocardiography was not available in Sri Lanka at the time of their studies. Whether these patients also had previous undiagnosed myocardial disease is unknown. As in any viral myocarditis, only a portion of the patients (24%) had 2-D echocardiographic evidence of myocarditis. A clear male dominance was noted and also a younger age group of 12–30 years (65%). Why certain individuals had a predilection for myocardial involvement is unknown. As all affected individuals had D2 virus infection. Virulence factors and geographic variation seem unlikely. We could not find any other associated factors.

Myocardial involvement may be a result of the direct effect of the dengue virus in susceptible individuals, or due to the effects of cytokine mediators and/or cellular components of the immune response. The possibility of IgM antibodies produced against the dengue virus cross-reacting with a myocardial antigen is unlikely, as echocardiographic improvement was seen within three weeks of the illness, when these antibodies were still in circulation. Dengue viral antigen, associating with a myocardial receptor site, thereby triggering off an immunological response is also another possibility in susceptible individuals. This myocardial inflammation ceases when the viral antigen disappears from the circulation. Dengue haemmorrhagic fever patients have higher levels of TNF-α, interleukins-6, -13 and -18, and cytotoxic factor. These cytokines are implicated in causing increased vascular permeability and shock during dengue infection[7-9] but their contribution towards development of myocarditis remain undefined.

Dengue virus can infect both CD-4 and CD-8 T cells.[10] Following primary infection both serotype-specific and serotype-cross-reactive-memory T cells are formed and the latter, on secondary exposure to the virus, augment infection by producing various cytokines.[11] These mechanisms may have a role in the pathogenesis dengue associated myocarditis, although the exact pathophysiology is undefined. Liver injury during dengue infection could also be due to a T-cell immune response.

In our study, transient chamber dilatation with a good ejection fraction and jerky wall motion were the major abnormalities, which dominantly involved the right ventricle. Its thinner musculature may make the right ventricle more susceptible to dilatation. Isolated valvular regurgitation could represent a form of localised valvulitis, which also subsequently disappeared. The study group had grade I to II atrioventricular valvular regurgitation according to colour Doppler criteria. Acute rheumatic fever and associated carditis was unlikely due to the non-fulfilment of the Dukett-Jones criteria, absence of characteristic echocardiographic features of acute or chronic rheumatic valvular disease, and the prevailing background dengue epidemics in the country with investigations suggestive of a viral rather than a bacterial aetiology. Relative bradycardia is a well described association with dengue fever[12] but heart rate not useful in predicting myocarditis. Likewise, CPK-MB was unhelpful in predicting myocarditis and CPK, which reflected presence of asymptomatic viral myositis, had no linear relationship with 2-D echocardiographic abnormalities or the time taken for the evidence of myocarditis to disappear.

In this cohort of patients, none has yet had any residual cardiac complication as long-term sequelae nor presented with shock syndrome or other cardiovascular abnormalities of the myocardium.

In an Indian study, Wali *et al.*[13] described cardiac involvement in dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) in 17 patients, which showed global hypokinesia in 70.6%. ^{99}Tc pyrophosphate imaging carried out in four patients showed no myocardial necrosis. Only five patients showed ST and T wave changes with ECG changes, echocardiographic and radionuclide ventriculography all returning to normal within three weeks, as in our study, contradicting predictions made by Obeysekara *et al*. It is also important to note that, in spite of presence of dengue haemorrhagic fever and DSS in the Indian study, only 5/17 (29%) had ECG changes. In another Indian study by Kabra *et al.*,[14] which

Key messages

- Dengue myocarditis was exclusively asymptomatic with no long-term sequelae
- Two-dimensional echocardiography was the only reliable tool of investigation
- Sinus bradycardia was the most conspicuous ECG finding
- Right ventricular involvement dominated over left ventricular involvement

looked at the myocardial dysfunction in children with dengue haemorrhagic fever, again, found no correlation between myocardial involvement and clinical severity. It is also evident from this study that only 2-D echocardiography should be the tool of investigation to diagnose dengue virus-related asymptomatic acute myocarditis as other ancillary investigations, such as ECGs and cardiac enzymes, proved unhelpful in the diagnosis.

Conclusions

The results and follow-up of this study revealed that myocardial involvement of dengue infections run a benign course without long-term complications, contrary to what was believed in the past. The shock syndrome in severe dengue infections is most likely to be due to hypovolaemia and internal fluid extravasation than due to carcinogenic shock.

Acknowledgements

We thank all the junior medical officers attached to ward – 06 and staff of the cardiac investigation unit at the Sri Jayewardenepura General Hospital, who extended their support during the study. The study received no financial support.

Conflict of interest

None declared.

References

1. Buan WH, Ton G. Cardiac involvement in haemorrhagic fever. *J Singapore Paed Soc* 1967;**9**:28.
2. Hyman AS. The heart in dengue. Some observations made among Navy and Marine combat units in South Pacific. *War Medicine (Chicago)* 1943; **4**:497.
3. Mendis NMP. Epidemiology of dengue like fever in Ceylon. *Ceylon Med J* 1967;**12**:67-74.
4. Clinical management of dengue fever and dengue haemorrhagic fever – Epidemiology unit – ministry of health – Sri Lanka 1997.
5. Obeysekara I, Yvette H. Myocarditis and cardiomyopathy after arbo virus infection, (dengue and chickengunya fever): *Br Heart J* 1972;**34**:821-7.
6. Obeysekara I, Yvette H. Arbovirus heart disease. Myocarditis and cardiomyopathy following gangue fever and chickengunya fever. A follow up study. *Am Heart J* 1973;**85**:186-94.
7. Mustafa AS, Elbishbishi EA, Agarwal R *et al*. Elevated levels of interleukin-13 and IL-18 in patients with dengue hemorrhagic fever. *Immunol Med Microbiol* 2001;**30**:229-33.
8. Vitarana T, de Silva H, Withana N *et al*. Elevated tumour necrosis factor in dengue fever and dengue haemorrhagic fever. *Ceylon Med J* 1991;**36**: 63-5.
9. Christine A King, Marshall JS, Alshurafa H *et al*. Release of vasoactive cytokines by antibody-enhanced dengue virus infection of a human mast cell/basophil line. *J Virol* 2000;**74**:7146-50.
10. Mentor NA, Kurane I. Dengue virus infection of human T lymphocytes. *Acta Virol* 1997;**41**:175-6.
11. Kurane I, Innis BL, Nimmannitya S *et al*. Human immune responses to dengue viruses. *Southeast Asian J Trop Med Public Health* 1990;**21**:658-62.
12. Nimmannitiya S. Dengue, and dengue hemorrhagic fever. In: Manson's Tropical Diseases 20th edition, London: WB Saunders, 1996;712-29.
13. Wali JP, Biswas A, Chandra S *et al*. Cardiac involvement in dengue haemorrhagic fever. *Int J Cardiol* 1998;**64**:31-6.
14. Kabra JK, Juneya R, Madhulika J *et al*. Myocardial dysfunction in children with dengue haemorrhagic fever. *Natl Med J India* 1998;**11**(2):59-61.