

Review Article

Dengue and the heart

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Abstract

Dengue is a neglected viral arthropod-borne tropical disease transmitted by the bite of infected *Aedes* spp. mosquitoes. It is responsible for a significant global burden of disease and corresponding socio-economic implications. There are four different virus serotypes, all of which are found predominantly in countries with tropical climates. Patients with dengue may present with cardiovascular (CV) manifestations, contributing to associated death and disability. A systematic review was conducted to identify CV manifestations of dengue, wherein 30 relevant studies were identified in the MEDLINE and PubMed databases. CV complications of dengue include rhythm abnormalities, hypotension, myocarditis, pericarditis and deterioration in myocardial function. Prompt recognition and treatment of CV complications of dengue are essential to reduce morbidity and mortality in these patients, who are at risk of progressing to cardiogenic shock and heart failure.

Keywords: dengue, cardiovascular involvement, myocarditis, neglected tropical diseases

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Dengue: A neglected tropical disease

Dengue is a neglected tropical disease (NTD), which is predominantly spread through bites of *Aedes* spp. mosquitoes that have previously bitten an infected person. The four serotypes of dengue (DENV 1 to 4) are considered a major public health problem due to their geographical breadth, large number of cases, and disease severity in severe dengue forms.¹ The disease is endemic to tropical regions of over 100 countries in Africa, Central and South America, the Middle East, south-east Asia and the Pacific Islands (Fig. 1).² Dengue transmission is influenced by weather, rain, temperature, urbanisation and distribution of the principal mosquito vector *Aedes aegypti*.²

The majority (80%) of dengue cases are asymptomatic or present with mild symptoms.¹ A small proportion of patients may experience severe dengue (approximately 5%), which is characterised by the presence of either severe plasma leakage (with shock or fluid accumulation with respiratory distress), severe bleeding or severe organ impairment. These include hepatitis, neurological dysfunction, coagulopathy and cardiovascular (CV) complications.² CV manifestations have been reported in up to 12.5% of patients with severe dengue.³ However, research regarding the clinical presentation, pathophysiology, diagnosis and prognostic significance is scarce. The majority of literature about CV involvement comes from case reports and small studies.

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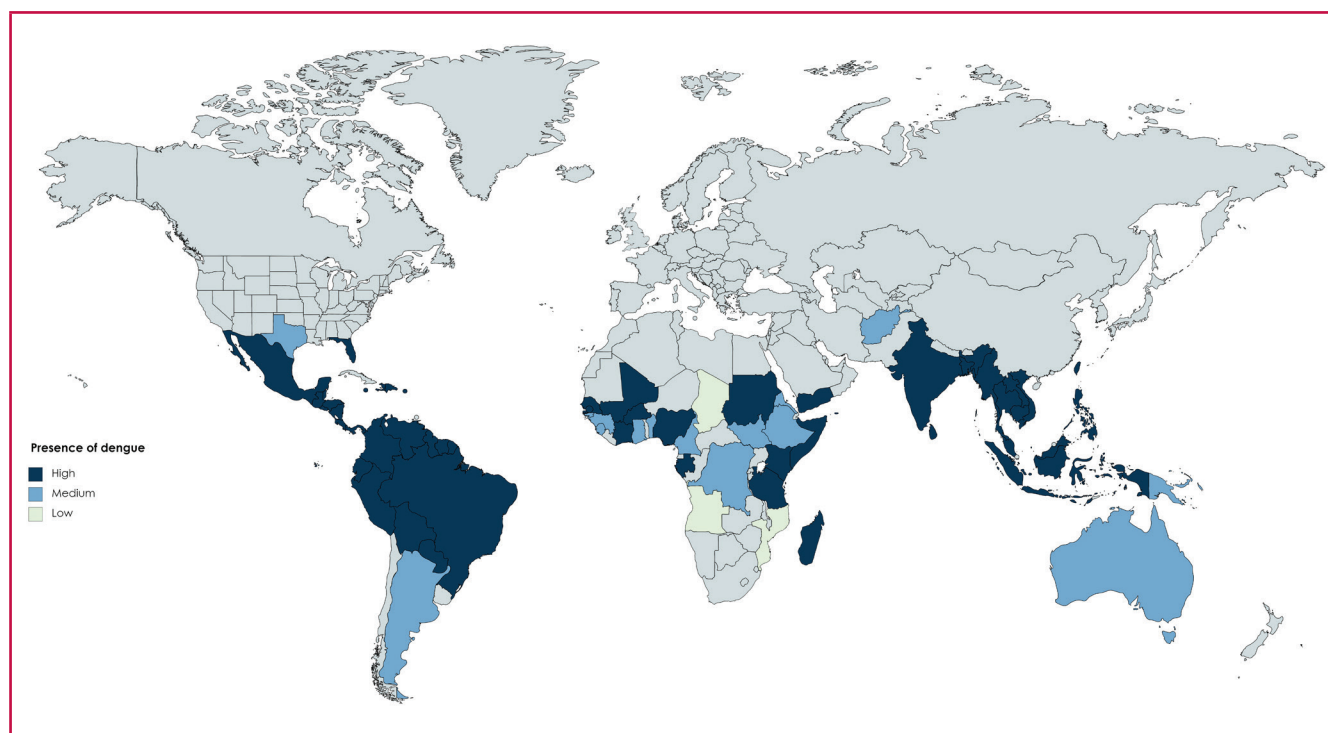


Fig. 1. Global dengue burden, 2014. Adapted from Guzman MG and Harris E. *Lancet* 2015; **385**: 453–465.²

The Neglected Tropical Diseases and other Infectious Diseases involving the Heart (the NET-Heart) project is an initiative of the Emerging Leaders section of the Inter-American Society of Cardiology (IASC) whose purpose is to expand knowledge on CV involvement of infectious diseases and to help identify barriers to diagnosis and treatment.⁴ This review is part of the NET-Heart project and describes the epidemiology, pathophysiology, diagnosis, treatment and prognosis of CV manifestations of dengue. An algorithm is also proposed for the detection and treatment of CV complications with dengue.

Methods

An electronic systematic review of the literature was conducted in PubMed, MEDLINE, Cochrane and Lilacs databases to identify any relevant studies or reviews detailing an association between dengue and CV involvement. The selection of articles was made according to the following criteria: (1) publications issued from 1980 to the present; (2) case series, case reports, clinical trials, systematic reviews and pronouncements of professional associations and scientific societies; (3) human studies; (4) English and Spanish language; and (5) articles referring to CV involvement in dengue. Studies were excluded if the full text was not accessible. The keywords used were chosen according to the MESH terminology: ‘abnormalities, heart’, ‘cardiac’, ‘heart failure’, ‘pericarditis’, ‘pericardium’, ‘endocardium’, ‘conduction disorders’, ‘arrhythmias’, ‘syncope’, ‘blood vessels’, ‘acute stroke’, AND ‘Dengue’.

The search was conducted by two blinded authors (DAG and CEGM). First, relevance based on title and abstract was determined. Selected publications were then further reviewed for relevance using the full text. Kappa interobserver was calculated and disagreement was solved by consensus. A secondary search

was conducted by reviewing the reference lists of the included articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used in conducting and reporting this systematic review.⁵

Results

The study selection flow chart for the different phases of the systematic review is presented in Fig. 2. From a total of 160 studies obtained in the initial search, 28 documents fulfilled the

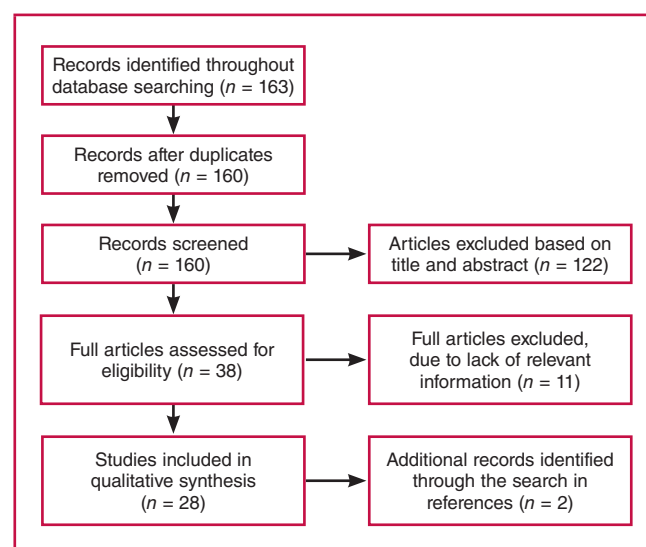


Fig. 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram for the evidence review selection of the literature.

study inclusion criteria and we selected: seven observational studies, eight case series, 11 case reports, one narrative review and one systematic review. From manual reference lists search, two additional documents were selected. A table (Table 1) of the original articles was made with the principal CV findings in dengue. Interobserver variability was assessed using Cohen's

kappa. Percentage overall agreement was 85%; free-marginal kappa was 0.70 (0.38, 1.00) (moderate) for observers.

Epidemiology of cardiovascular manifestations

CV manifestations of dengue are uncommon and almost

Table 1. Summary of original studies selected presenting cardiovascular complications of dengue

Study (year)	Type of study (participants)	Country	Disease severity	Cardiovascular findings	Co-morbidities
Datta <i>et al.</i> (2019)	Prospective study (n = 15)	India	Asymptomatic (n = 4) Symptomatic (n = 11)	Asymptomatic sinus bradycardia (n = 4); symptomatic bradyarrhythmias (n = 4); left ventricular systolic dysfunction (ejection fraction 35–45%) (n = 4); pericardial effusion (n = 2); atrial fibrillation (n = 1)	Not reported
Wali <i>et al.</i> (1998)	Cohort (n = 17)	India	Severe (n = 17)	Ejection fraction < 40% (n = 7); global hypokinesia (n = 12); ST and T changes in the ECG (n = 5)	Not reported
Sheetal <i>et al.</i> (1998)	Observational (n = 100)	India	Mild (n = 33) With warning signs (n = 58) Severe (n = 9)	Sinus bradycardia (n = 32)	Not reported
Kularatne <i>et al.</i> (2007)	Cohort (n = 120)	Sri Lanka	Mild (n = 120)	Patients with ECG changes such as T inversion, ST depression and bundle branch blocks (n = 75). Of this group, 17 (23%) patients had hypotension and 58 (77%) developed tachycardia and bradycardia, suggestive of significant cardiac dysfunction	Not reported
Satarasinghe <i>et al.</i> (2007)	Cohort (n = 217)	Sri Lanka	Mild (n = 217)	Myocarditis (n = 44); bradycardia (n = 44)	Not reported
Da Costa <i>et al.</i> (2012)	Case series (n = 5)	Brazil	Mild (n = 5)	Ileo-femoral deep-vein thrombosis (n = 2); pulmonary thromboembolism (n = 2); mesenteric vein thrombosis (n = 1)	None
Guadalajara <i>et al.</i> (2014)	Case report	México	Severe (n = 1)	Myocarditis characterised for: S3 gallop rhythm, generalised lung rales and shock; ECG showed sinus tachycardia, ST depression in V1–V3, and ST elevation in aVR and aVL.	None
Kularatne <i>et al.</i> (2018)	Case series (n = 3)	Sri Lanka	Severe (n = 3)	Tachycardia in three cases. Myocarditis confirmed by troponin estimation and echocardiogram in one case, and in the other two also was confirmed histopathology	Type 2 diabetes (n = 1) Bronchial asthma (n = 1)
Marques <i>et al.</i> (2013)	Case reports (n = 2)	Singapore	Severe (n = 2)	Myocarditis (n = 2). ECG with widespread ST-segment elevations and T-wave inversions and echocardiography with left ventricular systolic dysfunction with mild hypokinesia and an ejection fraction of 45% (n = 1). Acute fatal myocarditis (n = 1)	Asthma (n = 1)
Bich <i>et al.</i> (2015)	Case report (n = 1)	Vietnam	Severe (n = 1)	Acute cardiac failure due to dengue myocarditis. ECG showed inverted T waves in the inferior leads, and troponin I was raised	Hyperthyroidism Three miscarriages
Naresh <i>et al.</i> (2008)	Case report (n = 1)	New Delhi	Severe (n = 1)	Myocarditis	Not reported
Chou <i>et al.</i> (2016)	Case report (n = 1)	Taiwan	Severe (n = 1)	Takotsubo cardiomyopathy. ECG showed sinus bradycardia, inverted T-wave changes (V3–V6), and prolonged QT interval (QTc = 597 ms). Elevated cardiac enzymes. Left ventriculography shows apical hypokinesia with preserved contractility at basal portion and left ventricular apical ballooning appearance	Hypertension and diabetes
Ramanathan <i>et al.</i> (2015)	Case report (n = 1)	Singapore	Severe (n = 1)	Dengue myopericarditis mimicking acute myocardial infarction. Hyperacute ST changes in the inferolateral leads. Echocardiogram with severe global left ventricular dysfunction with moderate pericardial effusion and no cardiac tamponade. The serum troponin I level elevated.	None
Tayeb <i>et al.</i> (2011)	Case report (n = 1)	France	Mild (n = 1)	Acute pericarditis. Consulting with acute chest pain. ECG revealed negative antero-lateral T waves with long QT segment	Hypertension
La-Orkhun <i>et al.</i> (2011)	Prospective study (n = 35)	Thailand	Mild (n = 12) Moderate (n = 18) Severe (n = 5)	Holter study in children. Sinus pause (n = 1), first-degree (n = 2) and Mobitz type I second-degree atrioventricular block (Wenckebach) (n = 3) and atrial (n = 4) and ventricular ectopic beats (n = 5)	Not reported
Dhariwal <i>et al.</i> (2016)	Case report (n = 1)	India	Moderate (n = 1)	Repeated symptomatic episodes of high-degree atrioventricular block with ventricular asystole	None
Navinan <i>et al.</i> (2015)	Case report (n = 1)	Sri Lanka	Severe (n = 1)	Bradycardia with dynamic ECG changes, which evolved into complete heart block with atrioventricular dissociation and a junctional rhythm with a short P-R interval.	None
Sharda <i>et al.</i> (2013)	Case series (n = 8)	India	Not specified	Sinus bradycardia (n = 8). Echocardiography showed decreased ejection fraction (LVEF = 42%) (n = 1)	Not reported
Khongphattathallayothin <i>et al.</i> (2000)	Case reports (n = 2)	Thailand	Severe (n = 2)	Mobitz type I second-degree atrioventricular block. Patient 1 also had occasional monomorphic premature ventricular contraction	None
Promphan <i>et al.</i> (2004)	Case report (n = 1)	Thailand	Severe (n = 1)	Myocarditis with bradycardia, showed a junctional rhythm with a rate of 50 beats/minute	None
Kaushik <i>et al.</i> (2010)	Case report (n = 1)	India	Severe (n = 1)	Sino-atrial block and atrioventricular dissociation	None
Mahmod <i>et al.</i> (2009)	Case report (n = 1)	Malaysia	Moderate (n = 1)	Atrial fibrillation	None
Horta Veloso <i>et al.</i> (2003)	Case report (n = 1)	Brazil	Moderate (n = 1)	Atrial fibrillation	Diabetes mellitus

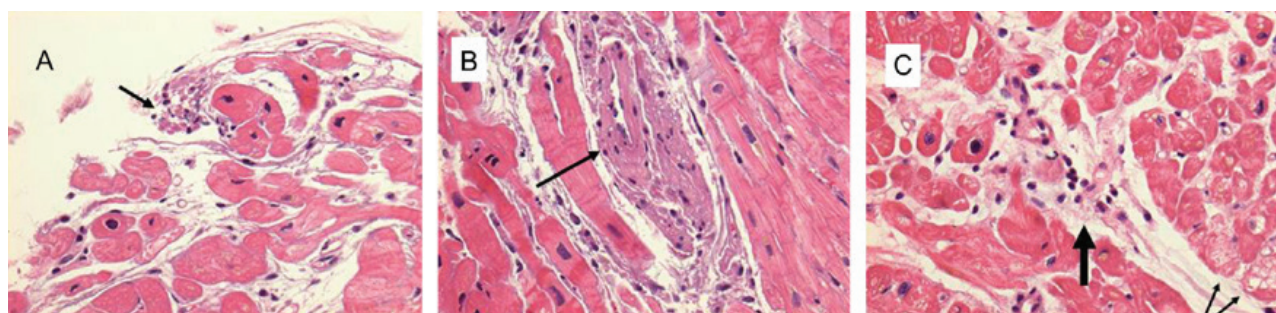


Fig. 3. Left ventricular endomyocardial biopsy (Masson 40x) shows necrosis of myocardial fibres (arrow in A) with inflammatory cell infiltration and marked interstitial oedema causing fibre separation (A), perivascular inflammatory infiltrate (arrow in B) with a necrotic fibre (B), and perivascular lymphocytic infiltrate (thick arrow in C), and vacuolisation of myocardial fibres corresponding to cellular oedema (narrow arrows in C). Reproduced with permission from reference 13.

exclusively associated with severe disease.⁶ A prospective observational study including 120 patients hospitalised with dengue in a tertiary centre in India showed that 12.5% had CV manifestations, including bradyarrhythmia (6.6%), left ventricular systolic dysfunction (3.3%), pericardial effusion (1.6%) and atrial fibrillation (1.0%). Among those with bradyarrhythmia, sinus bradycardia was the most common form reported. Only one patient developed a heart rate of less than 40 beats per minute and required a transient pacemaker; in the rest of the cases, the evolution was uneventful, and abnormalities resolved within days. Similarly, in a prospective study of consecutive, serologically confirmed cases of dengue ($n = 220$ with nine severe cases), up to 62.5% demonstrated electrocardiogram (ECG) changes (including T inversion, ST depression and bundle branch blocks) and 24% had echocardiographic findings consistent with myocarditis (chamber dilatation and motion abnormalities).^{7,9}

While previous reports suggest that 3.3 to 24% of hospitalised patients with dengue may present with myocarditis, the prevalence of CV manifestations in ambulatory patients has not been reported. Major limitations of previous studies include the lack of a standardised definition for CV involvement and the inclusion of exclusively hospitalised cases in which the disease had already progressed in severity.⁹ There are no quality studies that evaluate the role of age and gender on the appearance of CV manifestations in dengue.

Pathophysiology of cardiovascular involvement

Both systemic CV injury (such as endothelial dysfunction and alterations in vascular permeability) and localised cardiac injury (including myocardial necrosis and inflammation) may contribute to the appearance of CV manifestations in dengue.^{9,10} Understanding of dengue pathogenesis has been hindered by the lack of an animal model that accurately represents the increased capillary permeability and decreasing viral burden seen in patients.²

Minor non-specific changes in histopathological studies of the microvasculature suggest that transient disruption in the function of the endothelial glycocalyx layer occurs. The glycocalyx functions as a molecular filter, selectively restricting molecules within the plasma according to their size and three-dimensional characteristics.² Hypo-albuminaemia and proteinuria are

observed during dengue, which is consistent with a change in the filtration characteristics of the glycocalyx. Both the virus itself and dengue non-structural protein 1 (NS1) are known to adhere to heparan sulfate, a key structural element of the glycocalyx, and high-level early viraemia and NS1 antigenaemia have been associated with more severe clinical presentations.²

Patients with severe dengue are at higher risk of CV involvement than those who are asymptomatic or experiencing mild symptoms. It follows that the pathophysiological mechanisms of severe dengue likely have CV consequences.⁷ NS1, which plays a crucial role in severe dengue, may have a role in CV involvement, accordingly. High circulating NS1 levels and hyaluronan (a component of the extracellular matrix) are indicative of perturbed endothelial intercellular junction and disease severity.¹¹ Other vascular anomalies found in severe dengue include alterations of actin filaments and vascular-endothelial cadherin, increased paracellular gaps and enhanced vascular permeability, which may explain vascular leakage and shock.¹²

Common pathophysiological mechanisms of severe dengue and CV manifestations may include endothelial dysfunction, systemic hypoperfusion and systemic hypoxaemia. However, the specific mechanisms that are responsible for CV manifestations of dengue have not yet been fully described. Histology from endomyocardial biopsies in a patient with dengue myocarditis has been studied (Fig. 3). Necrosis of myocardial fibres, inflammatory cell infiltration, marked interstitial oedema and perivascular inflammatory infiltrate have been found.¹³ However, it is not yet determined if dengue myocarditis is the result of a direct viral invasion of tissue or of the immunological response mediated by cytokines through complement activation.

Clinical manifestations

Clinical manifestations of dengue range from asymptomatic to mild and severe cases. The symptoms of dengue are comparable to a common cold and/or gastroenteritis. The syndrome starts abruptly with fever, headache, retro-orbital pain, muscle ache, arthralgia, vomiting, diarrhea and/or rashes. A small proportion of patients, usually less than 5%, progress to severe and life-threatening manifestations.^{6,14} In severe forms, multiple organs and systems may be affected, with several reports describing encephalopathy, encephalitis, fulminant hepatitis, splenomegaly and ocular complications.^{6,15-18}

CARDIAC INVOLVEMENT:

From silent disease to severe myocardial dysfunction.

Symptoms suggesting cardiac involvement: chest pain, palpitations, pleurisy, hypotension, pulmonary oedema, and features of shock

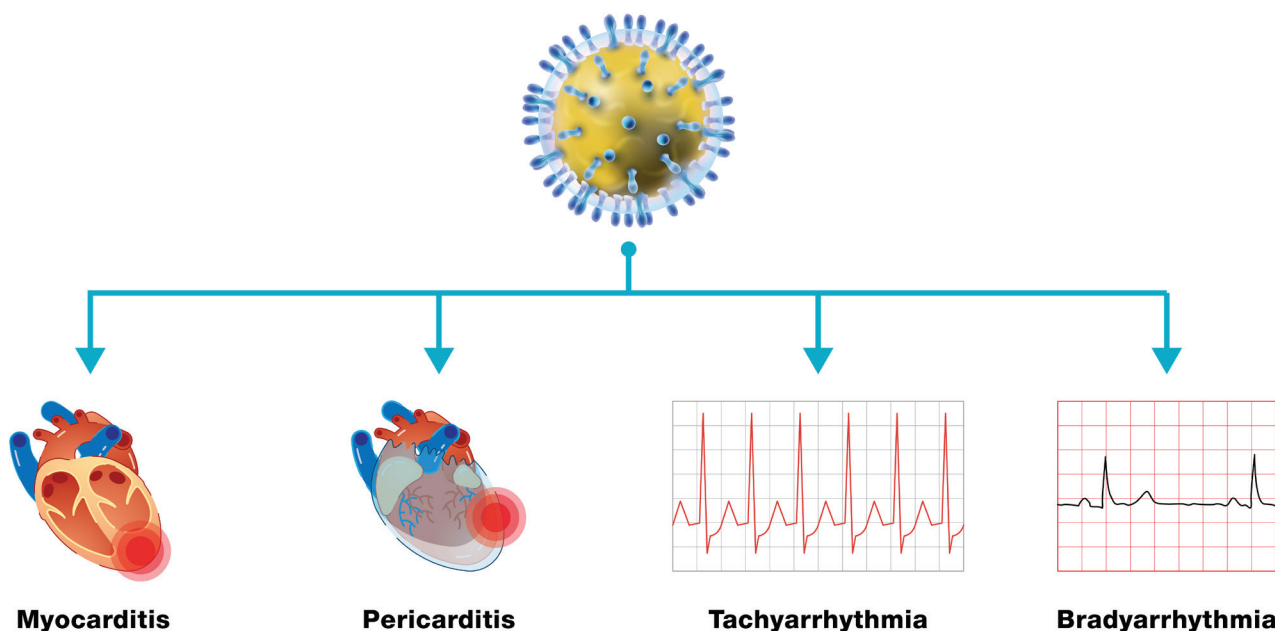


Fig. 4. Cardiovascular manifestations of dengue.

Dengue cases follow a common course: a febrile phase, critical phase and recovery (convalescent) phase. In the first phase (febrile) the patient exhibits a biphasic fever ($> 40^{\circ}\text{C}/104^{\circ}\text{F}$), associated with generalised, retro-orbital pain and headache lasting two to seven days. Skin manifestations, such as rashes or petechiae, can be present in 50 to 80% of the patients.^{6,14} Light rash is likely observed early in the course of infection (day one to two) and it progresses to a measles-like rash at day four to seven. Petechiae and bleeding from the mucous membranes of the mouth and nose also appear at this point.

After resolution of the high fever, a small proportion of patients progress to a critical phase, which typically lasts for 24 to 48 hours. This phase is characterised by plasma leakage with or without bleeding. There may be significant accumulation of fluids in the thoracic and abdominal cavities, leading to hypovolaemic shock that can result in organ dysfunction, metabolic acidosis, disseminated intravascular coagulation and severe bleeding, typically from the gastrointestinal tract. The last phase is the recovery, which lasts for two to three days.^{6,14} CV manifestations of dengue can be present in any of the different phases.^{2,6,14}

Clinical manifestations of CV involvement can vary widely, from silent disease to severe myocardial dysfunction and arrhythmias, resulting in death.¹⁵ Symptoms suggesting CV involvement include chest pain, palpitations, pleurisy, irregularities of the pulse, hypotension, pulmonary oedema and features of shock.¹⁴ Although the cardiac complications of dengue are rare, asymptomatic myocardial involvement has been documented. Acute myocarditis is the most common cardiac

pathology described in cases of severe dengue.¹⁶ The earliest CV manifestation typically seen is tachycardia. Other abnormalities such as bradycardia, hypotension, myocarditis, pericarditis, myocardial depression with symptoms of heart failure, and shock have been reported within the spectrum of associated CV manifestations.¹⁵ (Fig. 4).

The presence of tachycardia and progression to shock early in the disease should increase clinical suspicion of myocarditis.^{15,17,18} Additionally, there have been cases of reported Takotsubo cardiomyopathy and myopericarditis mimicking acute myocardial infarction associated with dengue.^{19,20} Finally, pericarditis (without myocarditis) has been reported both at the onset of dengue and in the following days.²¹

Asymptomatic ECG changes and arrhythmias are the predominant CV manifestations associated with dengue, and sinus tachycardia is reported most frequently. The majority of the cardiac rhythm abnormalities secondary to dengue have been reported in children.^{8,22} Bradyarrhythmia, such as sinus bradycardia, first-degree heart block, Mobitz type I second-degree atrioventricular block, bundle branch blocks, complete atrioventricular dissociation and ventricular asystole have been reported.^{8,23-26} Additionally, there is a case report of junctional rhythm of 50 beats per minute following a patient's recovery from dengue.²⁷ Ventricular arrhythmia, atrial fibrillation and atrioventricular block have been primarily observed during the acute stage of severe dengue.²⁸⁻³⁰

In the convalescent stage of dengue, most of the cardiac rhythm abnormalities reported are bradyarrhythmia or premature atrial and/or ventricular beats.²² Other manifestations

include T-wave abnormalities, ST-segment depressions and elevation, sinus pauses, atrial or ventricular ectopic rhythms, ventricular trigeminy and atrial fibrillation.²⁴

Diagnosis: an original algorithm to detect CV involvement in dengue

The gold standard for the diagnosis of dengue is the demonstration of viral fragments by real-time polymerase chain reaction (RT-PCR). This test is limited to the acute viraemic phase, which is usually restricted to a few days (one to five days after the onset of fever). In the convalescent phase or in the case of a negative RT-PCR result with high clinical suspicion, immunoglobulin M is diagnostic.^{1,2} The identification of CV involvement due to dengue can be complex due to: (1) the absence of universal diagnostic criteria; (2) different forms of presentation; and (3) other diseases that can alter the diagnostic findings such as the presence of pre-existent ECG abnormalities.

The appearance of arrhythmias has been reported to be in the range of 34 to 75% of severe dengue cases, which can be identified through 12-lead ECG and 24-hour Holter monitoring.^{3,4,22,29} The severity of heart rhythm disorders is not related to the severity or phase of dengue.^{3,4}

In addition to ECG abnormalities, elevation of cardiac biomarkers may indicate the presence of dengue CV involvement. A prospective study in Sri Lanka evaluated several cardiac biomarkers (myoglobin, creatine kinase-muscle brain-type, N-terminal pro-brain natriuretic peptide, heart-type fatty acid-binding protein, troponin T) in patients with dengue; 25% of patients had abnormal results in one or more biomarkers. Conversely, the correlation between biomarkers and cardiac function has not been clearly demonstrated in dengue.¹⁴ ECG and cardiac biomarkers are particularly helpful in cases of myocarditis and left ventricular dysfunction.

Transthoracic echocardiography is a non-invasive imaging method through which ventricular anatomy and function and some haemodynamic variables can be evaluated. The frequency of appearance of myocardial damage due to dengue seems to be directly related to the severity of the disease. Up to 36% of children with severe dengue have a left ventricular ejection fraction (LVEF) less than 50% compared to only 6.7% of cases with mild dengue. Up to 21% of patients may have dilated cardiac cavities and valve regurgitation, believed to be due to myocarditis.¹⁴

In children hospitalised with severe dengue and depressed LVEF (< 50%), tachycardia and respiratory symptoms, pleural effusions, lower cardiac outputs and the need for greater fluid requirements were more likely to occur in patients with low LVEF.¹⁴ Myocardial injury secondary to dengue can be fatal, therefore it is vital to assess ventricular function during infection. Echocardiography is also an important tool to assess and rule out other causes of heart failure, such as valve or ischaemic heart disease.^{3,7,14,16}

Cardiac magnetic resonance (CMR) is a useful tool for confirming suspected myocarditis, however its application in cases of dengue is limited. The main associated findings are hyperintensity in T2-weighted signals with late gadolinium enhancement. CMR is considered the gold standard for evaluation of the function of both ventricles.⁶

Histological findings of the CV involvement of dengue include

the appearance of petechial haemorrhage, interstitial oedema and infiltration of inflammatory cells such as neutrophils and lymphocytes in the myocardial tissue.⁷ Although the number of deaths associated with severe forms of dengue is elevated, reports of post mortem findings are scarce.

The prevalence of CV disease due to dengue is low, so the indiscriminate application of diagnostic tests can lead to erroneous conclusions. Patients with ECG alterations and those with clinical characteristics of heart failure should have an echocardiogram done. Additionally, if myocarditis is suspected, echocardiography should be conducted if available.¹⁴ In Fig. 5, we propose an algorithm to guide the decision to use diagnostic tests in patients with suspected or confirmed dengue and possible CV involvement.

Treatment

No specific treatment exists for dengue. During the febrile phase, liberal oral fluid administration and antipyretic treatment with paracetamol is recommended. As for the severe forms, the mainstay of treatment is intravenous fluid management. Episodes of myocardial damage, associated or not with myocarditis, may be asymptomatic and treatment is unnecessary in most cases.^{6,14} Dengue prevention using vaccines could be associated with a decrease in symptomatic cases, thus preventing CV manifestations. However, its use has not been authorised worldwide and remains controversial and limited to seropositive patients.³¹

Supportive treatment is based on maintaining an adequate intravascular volume status through the administration of intravenous fluids, avoiding volume overload. Judicious use of diuretics should be considered where indicated, although they are associated with worse outcomes in patients with severe dengue.¹⁴ Cases of severe dengue, if untreated, can cause a mortality rate as high as 20%. Appropriate case management and intravenous rehydration can reduce the mortality rate to less than 1%.⁶

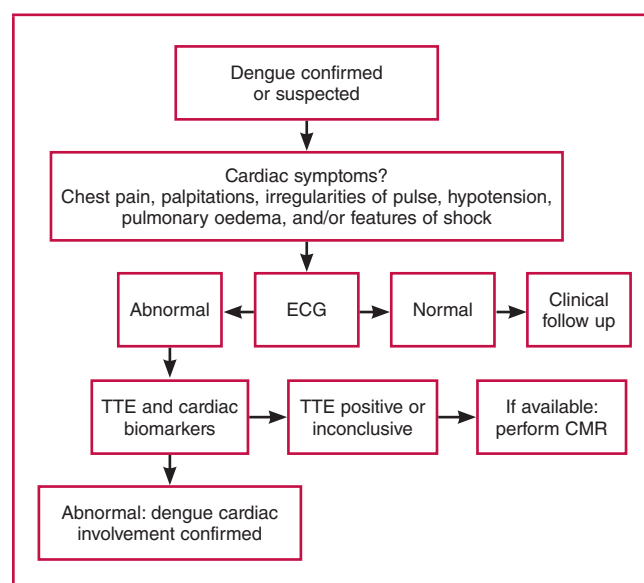


Fig. 5. Diagnosis of dengue and its cardiac involvement. ECG: electrocardiogram, TTE: transthoracic echocardiogram, CMR: cardiac magnetic resonance.

In the case of lack of response to interventions based on fluid resuscitation, the presence of CV dysfunction should be considered, and inotropic support can be considered if appropriate. Medications with inotropic effect, such as dobutamine or levosimendan can be administered. The choice of drug should be based on knowledge of the history and particular clinical setting. Due to the lack of controlled clinical trials, no recommendation can be made on this topic.¹⁴

The correction of abnormalities in serum potassium and calcium levels must be taken into account to reduce the appearance of arrhythmias, especially in the case of suspected myocarditis.¹⁴ In cases of symptomatic bradyarrhythmia or complete heart block, it has been reported that the use of atropine and transient or permanent pacemakers have been effective in management.^{23,24,30}

Discussion

Early detection of myocardial damage should be a main objective in patients with severe dengue, to prevent the development of multiple organ failure and death. The main limitation in achieving this objective is that the manifestation of CV consequences is subtle and can be confused with other diseases. Clinicians should be cognisant of atypical manifestations of CV involvement in dengue.^{2,6,14}

The low prevalence of CV disease due to dengue infection may result in a poor performance of most diagnostic tests.¹⁴ Additionally, resources and availability may be limited in dengue-endemic countries. Application of imaging should be guided by clinical judgment and the findings of the physical examination. To date, there are no image-guided protocols for the diagnosis and tailored treatment of dengue.^{2,14}

Similar to other manifestations of dengue, myocardial damage is transitory and can resolve spontaneously in the first 48 hours after the onset of fever. However, in some cases they can complicate the clinical course of the disease and affect treatment decisions. In patients without response to fluid resuscitation, myocardial damage will mainly manifest with pump failure. Inotropes may be needed to control hypotension.¹⁴

The role of heart rhythm disturbances in dengue outcomes is unknown. Factors that cause its appearance or aggravate its manifestations, such as electrolyte imbalance (hypocalcaemia for example) should be intentionally screened in hospitalised patients. Medications that prolong the QT interval should be avoided, such as amiodarone, chloroquine and quinolones.^{14,24}

Conclusions

Dengue is a NTD that may have severe manifestations and cause seasonal outbreaks in endemic countries. Severe forms of dengue can progress to CV involvement. Detection of CV involvement through non-invasive imaging methods, such as echocardiography and CMR should be the objective in patients with severe forms of dengue, for diagnostic purposes, to inform treatment and to improve outcomes.

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Striking association of cardiovascular risk factors with late-life cognitive decline

An increase in risk factors for cardiovascular disease (CVD) during young adulthood is associated with cognitive decline in late life, a US data analysis shows. Investigators found a ‘novel, striking’ association between high body mass index (BMI), elevated systolic blood pressure, and high glucose levels among adults in their 20s and 30s and a doubling of the average rate of cognitive decline over a 10-year period in late life.

‘These results are striking and suggest that early adulthood may be a critical time for the relationship between these health issues and late-life cognitive skills,’ study investigator Dr Kristine Yaffe, professor of psychiatry, neurology, and epidemiology, University of California-San Francisco, said. ‘It’s possible that treating or modifying these health issues in early adulthood could prevent or reduce problems with thinking skills in later life,’ she added.

The investigators noted that CVD risk factors are associated with an increased risk for cognitive decline, but little is known as to how early CVD risk factors influence late-life cognition.

To examine the impact of these risk factors on cognition, the researchers pooled data from four prospective studies: the Coronary Artery Risk Development in Young Adults (CARDIA) study, the Multi Ethnic Study of Atherosclerosis (MESA), the Cardiovascular Health Study (CHS), and the Health, Aging and Body Composition (Health ABC) study (*n* = 15 001 participants aged 18–95 years).

On the basis of previous epidemiologic research of CVD risk factors associated with cognitive decline, the investigators focused on BMI, fasting glucose level, systolic blood pressure and total cholesterol level. They used data from the four studies to examine early adult and mid-life trajectories of these risk factors for each participant in the two older cohorts, those of the Health ABC and CHS studies.

To assess cognitive outcomes, the investigators examined participants’ scores on the Digit Symbol Substitution Test (DSST) and the Modified Mini-Mental State Exam. The former test measures processing speed and executive function; the latter evaluates global cognition. These tests were administered every one to two years.

Levels of CVD risk factors were higher among older participants than among their younger counterparts, but

smoking was more prevalent among younger participants. The mean age of the two pooled older cohorts was 72 years. BMI, fasting glucose level and systolic blood pressure were elevated in fewer than 5% of these participants during early adulthood. Among approximately 40% of older participants, cholesterol levels were elevated at that time.

Among approximately 20% of older participants, BMI and systolic blood pressure were elevated at mid-life. At mid-life, fasting glucose levels were elevated for 10% of participants, and cholesterol levels were elevated for 68%.

In late life, BMI was elevated for 15% of participants, fasting glucose levels were elevated for 9%, systolic blood pressure was elevated for 24%, and cholesterol levels were elevated for 43%.

Elevated BMI during early adulthood was associated with an increase in cognitive decline of three to four points over 10 years in late life. High systolic blood pressure was associated with a four-point increase in decline on DSST in late life.

Although fasting glucose levels were elevated in few participants during early adulthood, the data suggest such elevations are associated with increased late-life cognitive decline. However, high cholesterol levels in early adulthood were not a significant risk factor for cognitive decline.

‘The evidence for cholesterol and late-life cognitive decline is mixed, but our findings may suggest that other cardiovascular risk factors, such as blood pressure, BMI and fasting glucose level in early adulthood, are more critical than cholesterol,’ said Yaffe.

The associations between elevated cardiovascular risk factors at mid-life and cognition in late life were less consistent. Elevated BMI, systolic blood pressure and fasting glucose levels in late life were associated with cognitive gains in very late life.

‘Clinicians could be more aware that cardiovascular health is important for brain health, even if you’re not an older adult, and also share this information with their patients,’ said Yaffe.

Yaffe added that her team plans to investigate associations between CVD risk factors and cognition throughout life. In particular, they want to examine the transition of cognitive

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