DENGUE AND THE CARDIOVASCULAR SYSTEM

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Abstract. Dengue is a mosquito-borne viral disease which is currently an important and rapid growing health problem across the globe. It is one disease entity with different clinical manifestations, often with unpredictable clinical evolutions and outcomes. Hypovolemia plays an important role in hemodynamic changes of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) as seen by a favorable response to appropriate volume replacement in majority of dengue patients with DHF and DSS. Cardiac involvement secondary to dengue virus infection is not uncommon and is often transient. It may vary from functional myocardial impairment, both self-limiting and arrhythmias that need treatment to severe and even fatal myocarditis. Successful treatment, which is mainly symptomatic and supportive, depends on early recognition of the disease and careful monitoring for the disease severity. For patients with severe myocarditis, in addition to intensive care and careful vasopressor and catecholamine therapy, mechanical circulatory support such as intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO) or ventricular assist device can be beneficial.

Keywords: dengue, cardiac, arrhythmias, myocarditis

INTRODUCTION

The World Health Organization (WHO) has declared dengue the most rapidly spreading mosquito-borne viral disease with a 30-fold increase in global incidence over the past 50 years (WHO, 2012). Infection with any one of the 4 antigenically-related serotypes: DEN-1, DEN-2, DEN-3, and DEN-4 can produce a broad spectrum of effects from mild to severe dengue which includes asymptomatic infection, undifferentiated febrile illness, dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). (WHO, 1997, 2009). The pathogenesis of dengue disease is still not clearly understood (Thisyakorn and Thisyakorn, 2015a).

Despite being traditionally considered a disease of children, dengue is now known to affect individuals of any age and cardiac involvement is not uncommon especially in adult who can present with fulminant myocarditis, which sometimes can masquerade as acute myocardial infarction (Lee *et al*, 2009). Clinical presentation in adult older than 65 years can be even more complicated because of higher frequency of comorbidities such as hypertension, ischemic heart disease, and diabetes mellitus.

The clinical course of dengue is divided into 3 phases: febrile, critical, and recovery. Febrile phase: the patient develops high-grade fever suddenly. This phase usually lasts 2-7 days. The patient has anorexia, nausea and vomiting, facial flushing, skin erythema, generalized body ache, myalgia, arthralgia, and headache. Critical phase: around the time of defervescence, usually on days 3-7 of illness, an increase in capillary permeability in parallel with increasing hematocrit level may occur. Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage. Those patients who deteriorate will manifest with warning signs such as abdominal pain and tenderness, persistent vomiting, clinical

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fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement, increase in hematocrit concurrent with rapid decrease in platelet count. Recovery phase: if the patient survives the 24-48 hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48-72 hours. General well-being improves, appetite returns, hemodynamic status stabilizes and diuresis ensues. An extremely important point is that a drop in the hematocrit level at this stage not be taken as a sign of internal hemorrhage. A strong pulse and blood pressure, with a wide pulse pressure and diuresis, indicate good vital signs. They rule out the likelihood of gastrointestinal hemorrhage, which is mostly found during the critical or shock stage (Thisyakorn and Thisyakorn, 1994). Bradycardia and electrocardiogram (ECG) changes are common during this stage (WHO, 2009).

Severe dengue.

Although majority of dengue virus infections are either asymptomatic or mild, an estimated 1-5% of patients admitting to hospital develop complications including organ impairment, bleeding and plasma leakage that can result in potential cardiovascular collapse if severe (Yacoub *et al*, 2014).

Severe dengue is defined by one or more of the following (WHO, 2009):

1. Plasma leakage that may lead to shock if fluid replacement therapy is not enough for maintaining adequate circulating blood volume. Shock can be intractable culminating death.
2. Severe bleeding usually does not happen in children unless they have pathologic bleeding site or have disseminated intravascular coagulation (DIC) leading to death.
3. Severe organ impairment is not a usual finding in dengue infection, it can be a result of prolonged shock of any origin or can be severe disease from direct involvement of that organ by dengue, *eg*, fulminant myocarditis that can be fatal.

CARDIAC INVOLVEMENT

Dengue virus affects the heart functionally and structurally. It is difficult to define cardiac involvement in dengue virus infection due to lack of clear criteria. Cardiac involvement of dengue include functional myocardial impairment, both self-limiting and arrhythmias that need treatment (Mahmod *et al*, 2009) to fulminant myocarditis leading to hypotension, cardiac failure, pulmonary edema, cardiogenic shock, and death (Miranda *et al*, 2013b; Guadalajara-Boo *et al*, 2014; Bich *et al*, 2015; Shivanthan *et al*, 2015).

FUNCTIONAL MYOCARDIAL IMPAIRMENT

Functional myocardial impairment usually results in a benign and self-limiting disease (Wali *et al*, 1998; Khongphatthanayothin *et al*, 2007; Kirawittaya *et al*, 2015). Myocardial dysfunction has been documented in dengue virus infection by using a variety of methods including 12-lead ECG, 24-hour Holter, echocardiography, radionucleotide ventriculography, Tc pyrophosphate imaging, cardiac magnitic resonance (CMR) imaging (Kabra *et al*, 1998; Wali *et al*, 1998; Khongphatthanayothin *et al*, 2003; Khongphatthanayothin *et al*, 2007; Kularatne *et al*, 2007; Lateef *et al*, 2007; Satarasinghe *et al*, 2007; Salgado *et al*, 2009; Salgado *et al*, 2010; La-Orkhun *et al*, 2011; Yacoub *et al*, 2012; Miranda *et al*, 2013a; Sengupta *et al*, 2013; Yadav *et al,* 2013).

The dysfunction can be found in different severity of dengue infection but is more prevalent in disease with more severity (Khongphatthanayothin *et al*, 2007). Cardiac functional abnormalities were found related to the severity of plasma leakage (Kirawittaya *et al*, 2015). In most patients the dysfunction is asymptomatic, requires no treatment and usually the abnormal findings revert to normal during the follow-up (Wali *et al*, 1998) or even as rapid as 24-48 hours after the toxic or critical stage (Khongphatthanayothin *et al*, 2007). Except in the rare case of fulminant myocarditis, the patient is usually symptomatic, needs treatment, and abnormal findings may last longer.

There was statistically significant correlation between cardiac manifestations and all the

warning signs except persistent vomiting (Sheetal and Jacob, 2016). Myocardial functions need to be accessed in patients with this disease especially those who have persistent hypotension in spite of adequate intravenous fluid resuscitation since more severe concurrent involvement such as myocarditis should be considered, it can progress to cardiogenic shock and death.

The postulated mechanisms for myocardial dysfunction include direct viral invasion, immune mechanisms, electrolyte imbalance (Shivanthan *et al*, 2015), myocardial edema from capillary leakage, presence of myocardial depressant factor, coronary hypoperfusion, altered calcium homeostasis (Salgado *et al*, 2010), lactic acidosis, or a combination of these factors. Another possibility is non-fulminant myocarditis, which can be the sole factor or a contributory factor of myocardial dysfunction.

ELECTROCARDIOGRAPHIC ABNORMALITIES

Just like the functional myocardial impairment, ECG abnormalities are quite common in dengue virus infection. Most of the ECG abnormalities are benign, asymptomatic and self-limiting but some may cause symptoms and need treatment (Mahmod *et al*, 2009). The reported ECG abnormalities are diverse and include rate and rhythm abnormalities, sinus bradycardia is the commonest (Sheetal and Jacob, 2016), waveform and voltage abnormalities. These ECG abnormalities can be detected during both the critical and the recovery phases. The possibility that these ECG abnormalities can be caused by concealed dengue myocarditis cannot be ruled out since myocarditis can be asymptomatic and undiagnosed.

Although ECG is an easy and useful test to screen for cardiac abnormalities, the use of ECG changes alone to denote cardiac involvement is inaccurate. ECG abnormalities were found in 5-of-17 patients of DHF/DSS studied with horizontal ST elevation and T inversion and the changes reverted back to normal within 3 weeks (Wali *et al*, 1998). Reported rhythm abnormalities include relative bradycardia (Lateef *et al*, 2007), sinoatrial block (Kaushik *et al*, 2010), disorders of atrioventricular conduction (Junctional rhythm) (Donegani and Briceno, 1986; Promphan *et al*, 2004; Kaushik *et al*, 2010), first degree (Naresh *et al*, 2008), second degree (Khongphatthanayothin *et al*, 2000), and complete heart block (Virk *et al*, 2016), monomorphic premature ventricular contractions on a background of heart block (Khongphatthanayothin *et al*, 2000), transient (Pahadiya *et al*, 2015) and non-self-limiting (Mahmod *et al*, 2009), atrial fibrillation, self-limiting tachy-brady arrhythmia (Lee *et al*, 2010), sinoatrial block and uniform ventricular ectopics progressing to ventricular bigemini (Chuah, 1987), ventricular trigeminy (Matthias *et al*, 2014).

Electrocardiographic features mimicking acute myocardial infarction have also been reported (Lee *et al*, 2009). In a prospective study in Thailand, overnight 18-24 hour Holter monitoring was performed in 35 clinically diagnosed dengue virus infection children (mean age 11.7 years) at least 24 hours after defervescence, Cardiac rhythm abnormalities were found in ten patients (29%), including sinus pause (1), first degree (2) and Mobitz type I second-degree AV block (Wenckebach) (3), and atrial (4) and ventricular ectopic beats (5).

There was no relationship between the clinical severity of dengue virus infection (DF, DHF without shock, and DSS) and the incidence of cardiac arrhythmia. All patients were asymptomatic during episodes of cardiac arrhythmia (La-Orkhun *et al*, 2011). In another case series of 120 patients with dengue, 62.5% showed ECG abnormalities: T inversions, ST depression, bundle branch blocks (Kularatne *et al*, 2007).

Arrhythmia management

The reported ECG abnormalities may be asymptomatic or go undetected, most of the patients only need conservative follow-up of the ECG abnormalities that are usually self-limiting and revert to normal without any treatment (Wali *et al*, 1998). However, some types of arrhythmia should be treated aggressively. Supraventricular tachyarrhythmias may respond to digitalis or other

medications. Ventricular arrhythmias have been known to respond to lidocaine or intravenous amiodarone. Despite aggressive treatment of these arrhythmias, rapid deterioration to ventricular fibrillation may occur and should be treated immediately by direct current defibrillation. Complete atrioventricular block requires a temporary transvenous pacemaker (Vashist *et al*, 2009).

MYOCARDITIS

Cardiac involvement in dengue patients can range from benign myocardial impairment and arrhythmias to fulminant myocarditis (Miranda *et al*, 2013a; Yacoub *et al*, 2014). Dengue myocarditis can present at any time during the illness, unlike other severe manifestations that present during the critical phase around defervescence (Simmons *et al*, 2012). The incidence of dengue myocarditis is unknown, but the prevalence of myocarditis in hospitalized dengue patients is 11.28% (Li *et al*, 2016) according to the European Society of Cardiology myocarditis criteria (Caforio *et al*, 2013) using ultrasound cardiogram as the imaging diagnosis method of myocarditis rather than cardiac magnetic resonance (CMR) imaging and no endomyocardium biopsy (EMB) was performed.

Dengue myocarditis can be found both in primary and secondary dengue infection and cardiac involvement was not more prevalent in dengue patients with secondary infection (Miranda *et al*, 2013a; Sane *et al*, 2015). All four serotypes of dengue virus can cause myocarditis (Weerakoon *et al*, 2011; Marques *et al*, 2013; Bich *et al*, 2015; Sane *et al*, 2015). Myocarditis presents in many different ways. It can be completely asymptomatic, as shown by a study in Sri Lanka, revealing 24% of dengue patients with echocardiographic evidence of myocarditis without any cardiac complaints and with complete resolution during convalescence (Satarasinghe *et al*, 2007).

The main mechanism of dengue myocarditis is still unknown though both direct viral infection and immune mediated damage have been suggested to be the cause of myocardial damage (Hober *et al*, 1993; Hober *et al*, 1996). The histopathological findings of dengue myocarditis include: areas of myocytolytic necrosis of myocardial fibers with inflammatory cell infiltration and marked interstitial edema causing fiber separation (Weerakoon *et al*, 2011; Guadalajara-Boo *et al*, 2014). One report also included electron microscopic findings showing clusters of dengue-like virus particles inside the cells and in the interstitial space, providing evidence of a possible direct action of dengue virus on myocardium (Miranda *et al*, 2013b).

Diagnosis of myocarditis

Non-invasive imaging techniques such as cardiac magnetic resonance (CMR) imaging can be useful in making the diagnosis of myocarditis and for monitoring disease progression, but endomyocardial biopsy (EMB) should be the gold standard for the diagnosis of definite myocarditis (Caforio *et al*, 2013).

Standard 12-lead ECG should be performed in all patients with clinically suspect myocarditis. ECG is usually abnormal in myocarditis though ECG signs are neither specific nor sensitive. Echocardiography helps to rule out non-inflammatory cardiac diseases such as valve disease. Global ventricular dysfunction, regional wall motion abnormalities, and diastolic dysfunction with preserved ejection fraction may occur in myocarditis. Fulminant myocarditis often presents with a non-dilated, thickened, and hypocontractile left ventricle as the intense inflammatory response results in interstitial edema and loss of ventricular contractility (Pinamonti *et al*, 1988; Felker *et al*, 2000).

Cardiac magnetic resonance (CMR) imaging provides non-invasive tissue characterization of the myocardium and can support the diagnosis of myocarditis. One study has demonstrated good correlation between CMR and EMB in troponin-positive patients without coronary artery disease (Baccouche *et al*, 2009).

Troponin and Brain Natriuretc Peptides (BNP) levels: while cardiac troponins are more sensitive of myocyte injury in patients with clinically suspect myocarditis than creatine kinase level (Lauer *et al*, 1997), they are nonspecific and when normal do

not exclude myocarditis (Heymans, 2007). This also applies to cardiac hormones such as brain natriuretic peptides.

Endomyocardial biopsy (EMB) should be the gold standard for the diagnosis of definite myocarditis. Besides confirming the diagnosis of myocarditis, it identifies the underlying etiology and the type of inflammation, which implies different treatment and prognosis. EMB should be performed early in the course of the disease and multiple specimens should be taken. At least three samples, each 1-2 mm in size, should be taken from the right or from the left ventricle for light microscopy; additional samples should be snap frozen in liquid nitrogen and stored at -80ºC or store in RNA later tubes at room temperature for viral PCR (Leone *et al*, 2012). EMB has been rarely reported in dengue myocarditis (Guadalajara-Boo *et al*, 2014).

TREATMENT OF MYOCARDITIS

Most patients with acute myocarditis do not require therapy. For dengue patients with myocarditis and hemodynamically stable heart failure should be treated with diuretics, angiotensin converting enzyme inhibitor, or angiotensin receptor blockage and beta-adrenergic blockage with or without aldosterone antagonists. For dengue patients with myocarditis and hemodynamically unstable, heart failure should be treated aggressively and supportive care is indicated for fulminant myocarditis. In cases with cardiogenic shock and severe ventricular dysfunction, norepinephrine should be the first choice as a vasopressor because treatment with dopamine in comparison with norepinephrine was associated with significant more arrhythmic events (De Backer *et al*, 2010).

Because myocardial oxygen consumption increases under catecholamine therapy and vasoconstrictors may impair the microcirculation and tissue perfusion, their use should be restricted to the shortest duration and the lowest possible dose. Inotropic dobutamine may be administered in addition to norepinephrine in an attempt to improve cardiac contractility, which is often performed in clinical practice. In fulminant cases with cardiogenic shock and severe ventricular dysfunction, mechanical circulatory support such as intra-aortic balloon pump (IABP), ventricular assist device or extracorporeal membrane oxygenation (ECMO) may be needed to provide a bridge to heart transplantation or to recovery (Japanese Circulation Society Joint Working Group, 2011).

Immunomodulatory therapy

Therapy to enhance immune function may benefit patients with myocarditis, especially during the viral replication phase (Liu and Mason, 2001).

Interferon

An uncontrolled trial of interferon in humans with biopsy-positive enteroviral or adenoviral myocarditis demonstrated clearance from the myocardium with a decrease in left ventricular size and improvement in left ventricle ejection fraction (Kuhl *et al*, 2003).

Intravenous immunoglobulin

High dose intravenous immunoglobulin (IVIG) modulates the immune and inflammatory response by a variety of mechanisms and is used in a number of systemic autoimmune diseases (Orange *et al*, 2006). Its use has been associated with improved left ventricular ejection fraction in chronic symptomatic heart failure of various causes (Gullestad *et al*, 2001). A Cochrane review analyzing the use of IVIG for presumed viral myocarditis in children and adults concluded that evidence from one trial does not support the use of IVIG for the treatment of adults with presumed viral myocarditis.

The only pediatric trial had high risk of bias but suggested that benefit may be seen in the select group of children beyond the neonatal period who have viral encephalitis with myocarditis. Until higher-quality studies have demonstrated benefit in a particular group of patients, IVIG for presumed viral myocarditis should not be provided as routine practice in any situation (Robinson *et al*, 2015).

Immunosuppressive therapy

The recognition that the pathogenesis of myocardial dysfunction in myocarditis is at least

partially the result of an immune activation or autoimmune process (Liu *et al*, 2001) led to attempts to ameliorate this process with a variety of immunosuppressive regimens using prednisone or various combinations of steroids, azathioprine, and cyclosporine (Maisch *et al*, 1995). A single-center controlled trial suggested a beneficial effect of combined steroid and azathioprine therapy in virus-negative myocarditis (Frustaci *et al*, 2009)

Heart transplantation

Despite advances in therapy and the high rate of improvement in patients with myocarditis, some patients with myocarditis will require cardiac transplantation.

PREVENTION

There is currently no specific antiviral treatment against dengue and successful treatment, which is mainly supportive, depends on early recognition of the disease and careful monitoring for shock and treatment of complications. Main public health preventive interventions consist of mosquito control while safe and efficacious dengue vaccine is seen as the best hope to fight this disease (Thisyakorn and Thisyakorn, 2015b).

CONCLUSION

Dengue virus is the causative agent of a very wide spectrum of clinical manifestations, ranging from asymptomatic illness, to undifferentiated febrile illness, DF, DHF, and DSS. Cardiac involvement in dengue virus infection is also very difficult to define since cardiac manifestations can be either caused by direct pathology of the heart or indirectly from the pathophysiologic changes of the cardiovascular system secondary to the dengue virus infection.

Although severe cardiac impairment in dengue patients is not commonly seen, it can cause significant morbidity and even mortality. Careful interpretation of clinical parameters will help avoid unnecessary invasive interventions. Successful treatment that is mainly symptomatic and supportive depends on early recognition of the disease and careful monitoring for the disease severity.

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