DENGUE: PITFALLS IN DIAGNOSIS AND MANAGEMENT

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Abstract. Dengue is a mosquito-borne viral disease, which is currently an important and rapidly growing health problem across the globe. Four closely related dengue serotypes cause the disease, which ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). Specific antiviral medications are not available for dengue and successful treatment, which is mainly supportive, depends on early recognition of the disease and careful monitoring for shock. In 2009, the World Health Organization (WHO) developed a severity-based revised dengue classification for medical interventions, which is used in most countries. Laboratory diagnosis includes virus isolation, serology, and detection of dengue ribonucleic acid. Since dengue poses a heavy economic cost to health systems and societies, the potential economic benefits are associated with promising dengue preventive interventions such as dengue vaccines and vector control innovations.

Keywords: dengue, diagnosis, management

INTRODUCTION

Dengue is the most common arboviral infection of humans transmitted by *Aedes* mosquitoes, principally *Aedes aegypti*. There are four antigenically distinct serotypes of dengue virus (DEN 1–4), which belong to the genus *Flavivirus* in the family Flaviviridae. Global phenomenon such as urbanization and international travel are key factors in facilitating the spread of dengue. The pathogenesis of dengue hemorrhagic fever (DHF) is complex and is the product of host determinants, dengue serotype, and environmental factors.

The continuum of dengue disease includes dengue fever (DF), which causes fever, rash, muscle or joint pain, headache, and eye pain, as well as DHF, which causes abnormal hemostasis and increased vascular permeability with severe cases leading to dengue shock syndrome (DSS). Because the age of dengue patients in several countries has increased from children to adolescents and adults,

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the proper diagnosis and management of dengue patients must consider the age-specific variance of clinical manifestations (Thisyakorn and Thisyakorn, 2015a).

CLINICAL FEATURES

There is significant variance in clinical manifestations and severity of dengue infection in different age groups. DF has been known in Asia for more than a century, and its severity is largely age-dependent. This disease is mild in children and more severe in adults. Infants and children with DF have symptoms ranging from an undifferentiated fever to a mild febrile illness, sometimes associated with a rash. Older children and adults frequently suffer a more severe form with high fever, pain in various parts of the body, and a maculopapular rash. However, the infection is only rarely fatal. DSS is more common in children than in adults. Infants with dengue infection present more frequently with convulsions, diarrhea, rash, cyanosis, and splenomegaly while co-morbidities that are more likely to be present in adults than in children such as peptic ulcers and preexisting liver disease can aggravate the disease severity. Thus, proper management of dengue patients must consider the different age-specific clinical manifestations and

severity of dengue disease (Panpitpat *et al*, 2007; Tantawichien, 2015)

Dengue patients with severe organ involvement such as liver, kidneys, brain, or heart have been increasingly reported. These organopathies may be associated with co-infections, co-morbidities, or complications of prolonged shock. Organopathies can modify clinical presentations of dengue disease and result in missed or delayed diagnosis. Exhaustive investigations are usually needed in these cases. Patients from dengue endemic areas with encephalitis and encephalopathy should be investigated for dengue infection whether or not they have other features of dengue disease.

The clinical spectrum of the infection undermines surveillance activities, particularly because the majority of cases are asymptomatic and remain undetected. A large proportion of infected individuals have a mild form of the disease, which is perceived as insufficiently serious enough to warrant professional care, and this may cause misdiagnosis and underreporting. Over half of the world's population lives in areas at risk of infection. Complex disease presentation and sudden development of hemorrhagic symptoms in a seemingly stable patient can cause fatal outcome even in well-prepared hospitals (Thisyakorn and Thisyakorn, 2015a, b).

An echocardiographic study regarding hemodynamic profiles of DHF patients during the toxic stage shows that the mechanism of decreased cardiac output is complex. Decreased preload is accompanied by decreased left ventricular performance and possibly a subnormal heart rate response in some patients (Khongphatthanayothin *et al*, 2003). Transient myocardial depression is not uncommon in patients with DSS. Cardiac dysfunction in children with DSS may contribute to the clinical severity and the degree of fluid overload in these patients (Khongphatthanayothion *et al*, 2007). Various benign bradyarrhythmias and ectopic beats are detected in dengue patients during the convalescent stage (La-Orkhun *et al*, 2011).

Special consideration for dengue patients during pregnancy are as the following (Royal College of Physicians of Thailand, 2014): Physiologic hemodilution in pregnancy may obscure hemoconcentration in DHF. Differential diagnosis of pregnancy-related conditions should be considered, *eg*, hemolysis, elevated liver enzymes, and thrombocytopenia syndrome (HELLP). There is an increased risk of abortion, premature uterine contraction, intra-partum and post-partum hemorrhage, maternal death, fetal distress, low birth weight, death fetus *in utero*, as well as vertical transmission of dengue virus.

DIAGNOSIS

The incubation period of dengue infection is usually 4-7 days but can range from 3-14 days. Clinical and laboratory criteria for the diagnosis of DHF/DSS as established by the World Health Organization (WHO, 1997) are as follows.

Clinical manifestations:
- Fever: acute onset, high and continuous, lasting 2-to-7 days in most cases.
- Any of the following hemorrhagic manifestations including one positive tourniquet test, petechiae, purpura, ecchymosis, epistaxis, gum bleeding, as well as hematemesis and/or melena.
- Enlargement of the liver is observed at some stage of the illness in 90-98% of children. The frequency varies with time and/or the observer.
- Shock manifested by tachycardia, poor tissue perfusion with weak pulse, as well as narrowed pulse pressure or hypotension with the presence of cold, clammy skin, and/or restlessness.

Laboratory findings:
- Thrombocytopenia (100,000 cells per mm^3 or less).
- Hemoconcentration; a hematocrit increase of more than 20% from the baseline of patient or population of the same age.

A severity-based revised dengue classification for medical interventions has been developed by the WHO and has been adopted in most countries (Fig 1) (WHO, 2009).

Other common laboratory findings are hypoproteinemia, hyponatremia, elevated hepatic enzymes, and elevated blood urea nitrogen level. Metabolic acidosis may be found in patients with prolonged shock. White blood cell count is variable, ranging from leukopenia to mild leukocytosis with an increased percentage of lymphocytes and the presence of atypical forms (Well *et al*, 1980; Thisyakorn *et al*, 1984).

Hematological findings include vasculopathy, reduction of several coagulation factors, reduced platelet count, and platelet dysfunction. Tendency toward bleeding should be monitored in any dengue patient since it may cause severe, uncontrollable hemorrhage. The pathogenesis of bleeding in a dengue patient is not fully understood (Mitrakul and Thisyakorn, 1989). The extent of endothelial cells, coagulation, and fibrinolysis activation in children with dengue infection seems to be correlated with dengue disease severity (Sosothikul *et al*, 2007).

The laboratory diagnosis of dengue infection can be confirmed by serological testing, isolating the virus, and detecting viral RNA by reverse transcriptase polymerase chain reaction. Virologic tests have a high yield in the first few days of illness. However, this yield decreases thereafter, so serological tests should be considered. Commercial kits for rapid dengue diagnostic tests are also available for routine use. However, the sensitivity, specificity, and accuracy vary among these tests. Therefore, these tests are suitable for screening and should be confirmed by the above.

MANAGEMENT

Successful treatment, which is mainly symptomatic and supportive, depends on early recognition of the disease and careful monitoring for shock.
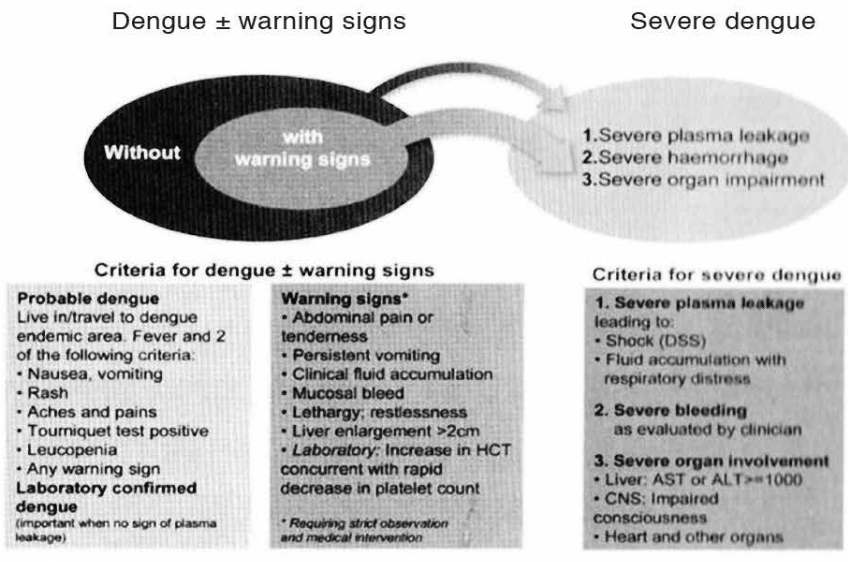

Fig 1–The 2009 WHO dengue case classification (WHO, 2009).

In DHF, early and effective replacement of lost plasma with fluid and electrolyte solutions, plasma, and/or plasma expanders results in a favorable outcome. Blood transfusion is indicated for patients with significant clinical bleeding, mainly from the gastrointestinal tract. Blood components are required when disseminated intravascular coagulation (DIC) causes massive bleeding. Persistent shock despite adequate fluids and a declining hematocrit level suggest significant clinical bleeding requiring prompt treatment. DIC occurs in cases with severe shock and may play an important role in the development of massive bleeding and irreversible shock. Coagulation tests should be monitored in all cases of shock to document the onset and severity of DIC. Blood grouping and matching should be performed as a routine precaution for every shocked patient. The rate of fluid infusion needs to be carefully tailored according to the patient's vital signs, hematocrit, and urine output.

Generally, there is no need for fluid therapy beyond 48 hours after the cessation of shock. Reabsorption of extravasated plasma occurs, which is manifested by a further drop in the hematocrit level. Excessive fluids during the recovery phase may cause hypervolemia, pulmonary edema, or heart failure. An extremely important point is that a drop in the hematocrit level at this stage should 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 shock stage (Thisyakorn and Thisyakorn, 1994).

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. Main public health preventive interventions consist of mosquito control, while a safe and efficacious dengue vaccine is seen as the best hope to fight this disease (Thisyakorn and Thisyakorn, 2015c).

CONCLUSION

Dengue is a disease entity with different clinical manifestations often with unpredictable clinical evolutions and outcomes. Successful treatment of clinical dengue virus infection, which is mainly symptomatic and supportive, depends on early recognition of the disease and careful monitoring of disease severity.

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