UPDATE: CLINICAL MANIFESTATIONS OF DENGUE FEVER 2013

Tran Xuan Chuong
Hue University of Medicine and Pharmacy Vietnam

Summary
Dengue is a mosquito-borne infection found in tropical and sub-tropical regions. In recent years, transmission has increased predominantly in urban and semi-urban areas and has become a major international public health concern. In the last years, the clinical picture of dengue fever is clearly changed. The average age of patients is increased every year. Some changings in clinical symptoms and signs were reviewed in this paper.

Key words: *Dengue fever.*

1. INTRODUCTION

Dengue is a mosquito-borne infection found in tropical and sub-tropical regions around the world. In recent years, transmission has increased predominantly in urban and semi-urban areas and has become a major international public health concern [10].

Dengue fever is a disease caused by dengue virus that are transmitted by mosquitoes. It is an acute illness of sudden onset and follows a benign course with symptoms such as headache, fever, exhaustion, severe muscle and joint pain and rash. The presence of fever, rash, and headache is characteristic of dengue. The dengue fever with warning signs can have several kinds of bleeding, include petechiae, nose or gums bleeding, gastrointestinal bleeding, vaginal bleeding ect.

The *Aedes aegypti* mosquito is the primary vector of dengue. The virus is transmitted to humans through the bites of infected female mosquitoes. After virus incubation for 4–10 days, an infected mosquito is capable of transmitting the virus for the rest of its life.

Because it is caused by one of four serotypes of virus (D1 to D4), it is possible to get dengue fever multiple times. However, an attack of dengue produces immunity for a lifetime to that serotype to which the patient was exposed. [1]

GLOBAL BURDEN OF DENGUE

The incidence of dengue has grown dramatically around the world in the last century and also in beginning of XIX century. Over 2.5 billion people - over 40% of the world's population - are now at risk from dengue. WHO currently estimates there may be more than 50-100 million dengue infections worldwide every year. [9], [10]

Before 1970, only some countries had experienced severe dengue epidemics. The disease is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific. The American, South-east Asia and the Western Pacific regions are the most seriously affected.

Only in the Americas, South-East Asia and Western Pacific estimated about 1.2 million cases in 2008 and over 2.3 million in 2010 (WHO's Reports). Recently the number of reported cases has continued to increase. An estimated 500,000 people with severe dengue require hospitalization each year, a large proportion of whom are children. About 2.5% of those affected die [10].

In Vietnam, dengue fever epidemics were reported since the 60's years in the XX century, mainly in the South of country. In the last 20 years disease spreads to new areas, the Central and then the North. Not only is the number of cases increasing, but explosive outbreaks are occurring. The threat

- *Corresponding author: Tran Xuan Chuong, email: txchuongs@yahoo.com*
- *Received: 10/11/2013 * Revised: 15/12/2013 * Accepted: 27/12/2013*
DOI: 10.34071/jmp.2013.2e.1

of a possible outbreak of dengue fever now exists in every region, even in Central Highland. Every 3 – 4 years, a big outbreak appears. In 2010, a large outbreak of dengue resulted in over thousands cases. In 2013, a large outbreak appeared again in Central Vietnam. In Khanh Hoa and other provinces, some fatal cases were reported.

2. SYMPTOMS

After being bitten by *A.aegypti* mosquito, the incubation period ranges from three to 15 (usually five to eight) days before the signs and symptoms of dengue appear in stages. Dengue starts with chills, headache, pain upon moving the eyes, and low backache. Painful aching in the legs and joints occurs during the first hours of illness. The temperature rises quickly as high as 40°C, with relatively low heart rate (bradycardia) and low blood pressure (hypotension). The eyes become reddened. A flushing or pale pink rash comes over the face and then disappears.

Patients with dengue fever with warning signs or severe dengue fever often have evidences of plasma leakage and/or hemorrhage in the body. Petechiae (small red or purple splotches or blisters under the skin), bleeding in the nose or gums, black stools, or easy bruising are all possible signs of hemorrhage. These form of dengue fever can be life-threatening and can progress to the most severe form of the illness, dengue shock syndrome.

The principal symptoms of dengue are:

- High fever and at least two of the following:
  - Severe headache
  - Joint pain, Muscle and/or bone pain
  - Nausea, vomiting
  - Rash
  - Mild bleeding manifestation (e.g., nose or gum bleed, petechiae, or easy bruising)
  - Low white cell count
  - Low platelet count

Generally, younger children and those with their first dengue infection have a milder illness than older children and adults. [8]

Before 2009, dengue fever was classified into Dengue fever (DF) and Dengue hemorrhagic fever (DHF). The last form can lead to Dengue shock syndrome (DSS). Since 2009, WHO experts have revised the classification. Now the disease is classified into three form: dengue fever, dengue fever with warnings signs and severe dengue fever. [9]

Severe dengue is a potentially deadly complication due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Warning signs occur 3 – 7 days after the first symptoms in conjunction with a decrease in temperature (below 38°C/100°F) and include severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, fatigue, restlessness, bleeding vomiting. The next 24–48 hours of the critical stage can be lethal; proper medical care is needed to avoid complications and risk of death.

3. LABORATORY CRITERIA FOR DIAGNOSIS

3.1. Confirmatory

a. Isolation of virus from or demonstration of specific arboviral antigen or genomic sequences in tissue, blood, cerebrospinal fluid (CSF), or other body fluid by polymerase chain reaction (PCR) test, immunofluorescence, or immunohistochemistry, *or*

b. Seroconversion from negative for dengue-specific serum IgM antibody in an acute phase (≤5 days after symptom onset) specimen to positive for dengue-specific serum IgM antibodies in a convalescent-phase specimen collected ≥5 days after symptom onset, *or*

c. Demonstration of a ≥ 4-fold rise in reciprocal IgG antibody titer or hemagglutination inhibition titer to dengue antigens in paired acute and convalescent serum samples, *or*

d. Demonstration of a ≥ 4-fold rise in PRNT (plaque reduction neutralization test) end point titer (as expressed by the reciprocal of the last serum dilution showing a 90% reduction in plaque counts compared to the virus infected control) between dengue viruses and other flaviviruses tested in a convalescent serum sample, *or*

e. Virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF.

3.2. Presumptive/Probable

a. Dengue-specific IgM antibodies present in serum.

3.3. Criteria for Epidemiologic Linkage

a. Travel to an dengue endemic country or presence at location with ongoing outbreak within previous two weeks of dengue-like illness, *or*

b. Association in time and place with a confirmed or probable dengue case. [5], [9]

4. CHANGING OF CLINICAL MANIFESTATIONS

In the last 5 – 7 years, the clinical picture of dengue fever is clearly changed. Before, the majority of patients were children and young people. Now the percentage of adult is increased every year. The disease is reported in people older 50, even 70 years old. Tran T. Hien et al (Hospital for Tropical Disease, Hochiminh City) have recognized it some years ago. Annette Fox et al studied epidemiology of dengue fever in Hanoi from 1998 to 2009 and concluded that the average age of patients increased form 24 in 1998 to 32 in 2009 [2].

The duration of dengue fever was not around 7 days, but it can be longer than 8 days, sometimes patients have fever until the 10th day. Ho T. Thuy Vuong et al (Hue) recognized 9.1% of patients have fever more than 8 days in the 2010 - 2011 outbreak in Thua Thien-Hue [4].

The bleeding signs such as petechiae, nose and gums bleeding can disappeared until the 9th day.

Diarrhea was very rare reported in the last century. But now it becomes a common symptom. Many patients have mild diarrhea (2 – 4 times per day) without abdomen pain in the day 4 to 7. Nguyen V. Bang, Nguyen K. Hoi et al noted 28.1% patients with diarrhea [7]; Ho T. Thuy Vuong et al (Hue) recognized 52.6% of patients have mild to moderate diarrhea the same study [4]. Que A. Tram et al in Nghe An (2009 – 2010) saw 18.1% patients with diarrhea.

The bleeding is now very variable in patients with dengue fever. The frequency of vaginal bleeding tend to increase in the last years. About 20 – 25% of young female patients (age from 16 to 40) have mild to more severe vaginal bleeding. Nguyen T. Thu Oanh, Tran X. Chuong studied dengue patients with low number of platelet (≤50,000 per µl) in Binh Dinh Province (2010) showed that patients with number of platelet ≤30,000 per µl was 16.2%, patients with vaginal bleeding [6]. It appears outside the normal cycle, longer than 3 days, some times 5-6 days and the amount of losing blood is a little bigger than normal. Unfortunately, it's difficult to evaluate the losing blood. The female patients who have long vaginal bleeding feel weak and can have relatively low blood pressure, but rarely have shock.

Severe thrombocytopenia is also a new characteristics of dengue fever n the last years. Some years ago, it is not common to see a patient with platelet count under 15,000 per µl. Now we can see patients with very low number of platelet every day. Some patients have only 1 - 3,000 per µl. Ho T. Thuy Vuong et al recognized 31% of patients have low number of platelet (≤ 30,000 per µl) [4]. Que A. Tram et al in Nghe An (2009 - 2010) saw 27.5% patients with platelet under 30,000 per µl. Nguyen T. Thu Oanh showed that patients with number of platelet ≤ 30,000 per µl was 65.4%, patients with severe thrombocytopenia (number of platelet ≤ 10,000 per µl) was 23.1%. [6]

According the WHO recommendation, patients with platelet count under 5,000 per µl (and platelet count under 50,000 per µl if they have severe bleeding) should have platelet transfusion. But interestingly, we found that the low number of platelet was not correlated with the severity of patients state [8].

High transaminase level is recognized in the majority in patients with dengue fever. Ho T. Thuy Vuong et al recognized 82% of patients who have transaminase <400IU/mL and 7.1% ≥ 400 IU/mL [4]. Study of Nascimento Dd et al (Brasil) showed all the patients with hemorrhagic dengue grade II had AST and ALT alterations. AST variations reached 22.0 and 907.0, with an average value of 164.6. For ALT, we found variations between 25.0 and 867.0, with an average value of 166.07. There had been statistical significance between dengue clinical shapes and hepatic function markers [5]. Ho TS et al (Taiwan) also found elevated serum levels of aminotransferase (AST, 166 +/- 208 U/L; ALT, 82 +/- 103 U/L) in patients with dengue fever [3].

5. CONCLUSIONS

Dengue fever is still an important problem of public health in Vietnam and also in several regions in the world. The clinical pictures in the last years was clearly changed. The larger epidemiological and clinical researches on dengue fever are needed to confirm the new characteristics of this disease.

REFERENCES

1. Alexander N, Balmaseda A, Coelho IC, Dimaano E, Hien TT, et al. (2011) Multicentre prospective study on dengue classification in four South-east Asian and three Latin American countries. *Trop Med Int Health.* May 30, 2011 [Epub ahead of print].
2. Fox, Annette, Nguyen V Kinh et al (2011), The epidemiology of dengue emergence in Hanoi, Vietnam, 1998-2009, National Conference on Infectious diseases, Hanoi, Vietnam.
3. Ho TS, Wang SM, Lin YS et al (2013), Clinical and laboratory predictive markers for acute dengue infection, *J Biomed Sci.* Oct 20;20(1):75.
4. Ho T Thuy Vuong et al (2011), Studying of clinical and paraclinical characteristics in adult patients with dengue fever, *J. of Practical Medicine*, N.781, pp. 92-95.
5. Nascimento Dd, Castro AR, Froes ÍB et al (2011), Clinical and laboratory findings in patients with dengue associated with hepatopathy, *Rev Soc Bras Med Trop.* 2011 Nov-Dec;44(6):674-7.
6. Nguyen T. Thu Oanh, Tran X. Chuong (2011), Studying characteristics of dengue hemorrhagic fever with severe thrombocytopenia in Binh Dinh hospital 2010, *J. of Practical Medicine*, N.781, pp. 92-95.
7. Nguyen V. Bang, Nguyen K. Hoi et al (2010), Studying of some clinical characteristics in adult patients with dengue fever, *J. of Military Medicine*, N.35, pp. 98-103.
8. Rigau-Perez JG (2006) Severe dengue: the need for new case definitions. *Lancet Infect Dis* 6: 297–302
9. WHO (2009) Dengue guidelines for diagnosis, treatment, prevention and control. Third edition. Geneva: World Health Organization.
10. WHO (2013) World Health Statistics 2012, Geneva: World Health Organization.