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Original Article

Case Reports of Fatal Patients with Dengue Virus Infection in Taiwan, 2011

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Abstract

Dengue fever is the most important vector borne communicable disease. Outbreaks of different scales occurred every year in the past decade. Although most patients recovered gradually, some progressed to Dengue hemorrhagic fever or death. This article described the four fatal cases in Taiwan in2011, and made some recommendations on how to prevent the avoidable deaths.

Keywords: Dengue fever, Dengue hemorrhagic fever, gastrointestinal bleeding, mortality rate, warning signs

Introduction

Dengue fever (DF) is the most important vector-borne communicable disease. Outbreaks of different scales occurred every year in the past decade. Although most patients recovered gradually, some progressed to dengue hemorrhagic fever (DHF) or death [1-4]. In 2002, among the 5,388 domestic dengue cases, 241 were DHF and 19 died, resulting a DHF mortality of almost 8%. Ten years later, among the 1,543 domestic dengue cases diagnosed between summer of 2011 and March 2012, 20 were DHF and 5 died. Although most fatal patients had underlying medical conditions which could increase the risk of death, few studies addressed on the reversible and preventable factors. We reviewed the available medical records of four fatal patients in 2011, not only focused on the preventable risk factors, but also elucidated the problems in categorizing cases to DF or DHF based on the traditional classifications [5-6] and re-evaluated according to the new version of classifications made by World Health Organization in 2009 [7]. Some recommendations have been made to decrease the dengue associated mortality.

Description and analysis of the cases

A. Case 1

The patient was a 64-year-old male living in Ping-Tung, with history of hypertension, chronic kidney disease, and gouty arthritis. He presented with fever and bone pain on October 16, 2011 (Day 1) and visited emergency department (ED) of a hospital on the next day. At ED, his body temperature was 38^{o} C, heart rate was 83 beats per minute, respiratory rate was 19 times per minute, and blood pressure was 138/66 mmHg. In terms of his blood sampling results, his hemoglobin was 9.7 g/dL, platelet count was 121 K/uL, and serum creatinine was 7.3 mg/dL. The patient was discharged after injection of ketoprofen and infusion of normal saline. He went back to the ED three days later, on October 19, 2011 (Day4), complaining chest discomfort and short of breath. His body temperature was 37.4 ^{o} C, heart rate was 103 beats per minute, respiratory rate was 24 times per minute, and blood pressure was 116/94 mmHg. On physical examination, the patient had abdominal tenderness but without evidence of active bleeding. On laboratory examinations of blood samples, his white blood cell count was 6.5K/uL, hemoglobin was 15 g/dL, platelet count was 37K/uL, and blood urea nitrogen was 10 mg/dL. Abdominal ultrasonography showed presence of ascites. The patient was admitted under the impression of DF. On the next day, the patient started to have bloody stool and was transferred to other hospital, where his hemoglobin had once dropped to 6.2g/dL, and the levels of liver transaminases, amylase, and lipase had increased to more than a thousand. The patient passed away on October 24 (Day 9). About the results of tests for Dengue fever, he was positive for NS1, but negative for IgM, IgG or PCR.

Commentary: Because the patient did not present with active bleeding the second time he visited ED, the possibility of hemorrhagic fever could easily be overlooked. However, the presence of ascites and abnormal elevation of hemoglobin level both hinted plasma leakage, and the blood pressure of 116/94 mmHg could be the result of shock with compensation. The clinical picture was compatible with DHF according to the diagnostic criteria. Abdominal pain, change on levels of hematocrit and platelet count were dangerous signs.

B. Case 2

The patient was a 60-year-old male living in Kaohsiung City, with history of hypertensive cardiovascular disease and diabetes. He visited a private clinic because of fever on August 27, 2011 (Day 1) and presented to the ED with short of breath, nasal and anal bleeding on August 31, 2011 (Day 5). He had recent family history of confirmed DF. On arrival, his body temperature was 37.8 ^{o} C, heart rate was 138 beats per minute, respiratory rate was 30 times per minute, and blood pressure was 116/76 mmHg. The patient was found collapsed with massive oral bleeding soon, with pulseless electrical activity on monitor. Cardiopulmonary resuscitation was done but failed. On laboratory examination, his white blood cell count was 9.2 K /uL, hemoglobin level was 17.8 g/dL, hematocrit level was 51.5%, platelet count was 20 K/uL. His serum was positive for IgG, IgM, and PCR of DF infection.

Commentary: The patient had dangerous signs such as short of breath and hemorrhage on the day he visited ED, but should we notice any dangerous signs that appeared earlier, we could remind the patient earlier. The presence of bleeding but with elevated hematocrit level indicated plasma leakage. Despite the patient had a normal blood pressure of 116/76 mmHg, we did not know his baseline. The clinical picture was compatible with DHF according to the diagnostic criteria, and the circulatory shock could be contributed to large amount of plasma leakage accompanied with gastrointestinal bleeding.

C. Case 3

The patient was a 66-year-old female living in Kaohsiung, with history of hypertension and diabetes. She visited a private clinic as well as an ED because of fever on October 19, 2011 (Day 1) and presented to the ED again with bloody stool in the morning on October 22, 2011 (Day 4). On arrival, her body temperature was 37.1 ^{o} C, heart rate was 103 beats per minute, respiratory rate was 16 times per minute, and blood pressure was 103/66 mmHg. On laboratory examination, her white blood cell count was 3.2 K /uL, hematocrit level was 40.7%, platelet count was 49 K/uL, and her serum albumin level was 2.9 mg/dL. The patient was admitted to the intensive care unit on the same date. Eight units of packed red blood cells and other blood components were infused, but she still passed away on October 24, 2011 (Day 6) because of refractory shock. Her serum was positive for NS1, IgG and PCR of DF infection.

Commentary: The patient had active bleeding, but her hematocrit level stayed within normal limit initially. Active bleeding might have masked the pivotal sign of plasma leakage and hemoconcentration. The relative low level of albumin was also in favor of the presence of plasma leakage. The clinical picture was compatible with DHF according to the diagnostic criteria.

D . Case 4

The patient was a 69-year-old male living in Kaohsiung, with history of diabetes, liver cirrhosis, and hypertension. He sought for medical care because of fever for 3 days, accompanied with poor appetite and tarry stool passage on November 5, 2011. At ED, his body temperature was 36.9 ^{o} C, heart rate was 103 beats per minute, respiratory rate was 20 times per minute, and blood pressure was 161/103 mmHg. On laboratory examination, his white blood cell count was 5.6 K/uL, hematocrit level was 49.4%, and platelet count was 44 K/uL. The patient visited ED again on the next day, November 6, 2011 (Day 4), because of general malaise. On arrival, his body temperature was 36.8 ^{o} C, heart rate was 137 beats per minute, respiratory rate was 20 times per minute, and blood pressure was 92/65 mmHg. On laboratory examination, his white blood cell count was 6.1 K/uL, hematocrit level was 43.4%, and platelet count was 16 K/uL initially, while his platelet count was 17 K/uL and hematocrit level dropped to 32.2% in the morning on the next day. Packed red blood cells, platelet and fresh frozen plasma were infused, but the patient had sudden collapse which had no response to emergency resuscitation. He passed away that day. The patient’s serum was positive for IgG and PCR but not for IgM and NS1.

Commentary: The patient had abnormal higher level of hematocrit, accompanied with some dangerous signs visiting ED for the first time. By the time he was sent to ED the second time, he already had shock and decreasing level of hematocrit, which could be due to active bleeding in stool. The patient clinically was compatible with normal picture of DHF.

Discussion

Clinical presentations of Dengue virus infection could be categorized into asymptomatic infection, undifferentiated fever, DF, and DHF / Dengue shock syndrome (DSS). Some unusual presentations have been reported in recent years, so some experts have proposed to use expanded Dengue syndrome / isolated organopathy to incorporate these uncommon clinical symptoms (Figure 1) [8]. Because these uncommon clinical presentations, such as hepatorenal failure and encephalopathy, are usually found to be associated with patients' underlying medical conditions or other concurrent infections, not the direct consequence of Dengue virus infection, further evaluations on the casual relationship should be done once they are present [9].

Traditionally, DHF is a specific presentation of Dengue virus infection and only with the presence of plasma leakage can a case be defined as DHF. DF and DHF were therefore two different clinical manifestations. Strictly speaking, DHF is not severe dengue fever. Not every case with DHF is critically ill, and DHF is not an continuum of DF because there is no plasma leakage in DF. We used to take "Dengue fever" as a generalized term to describe all disease patterns caused by Dengue virus infection, while a true DF patient should have specific clinical presentations such as severe retroorbital pain, muscle ache, or bone pain. To correctly categorize the patients, a clear case definition is required. For examples, we had 1,543 Dengue cases, rather than DF cases, in 2011. Twenty cases of the Dengue cases, not DF cases, had DHF. DF and DHF should be two distinct, mutual exclusive traits of Dengue infections. The same definitions are also applied in the database of Dengue surveillance system done by World Health Organization.

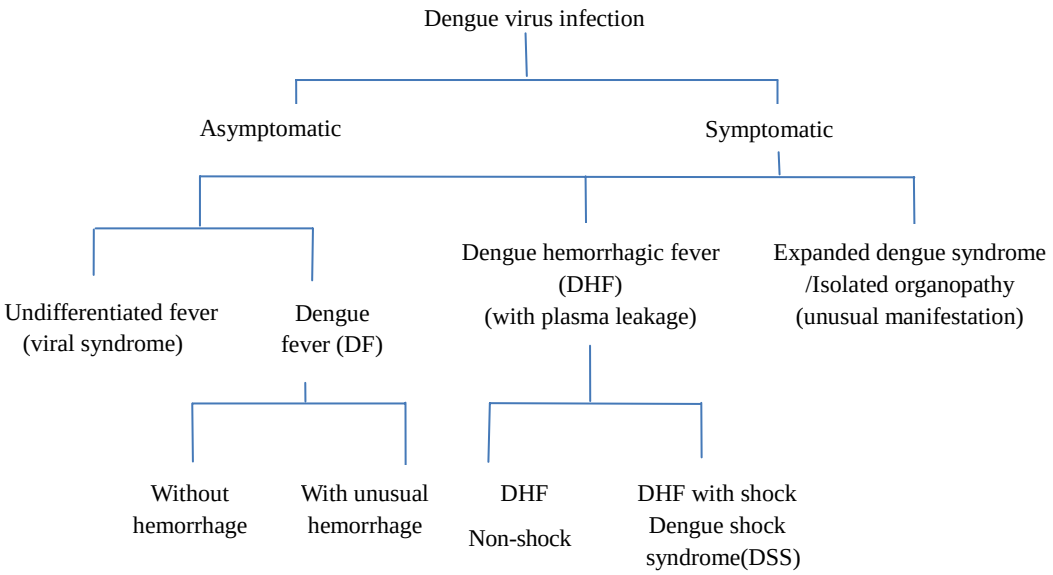

Figure 1. Clinical presentations of Dengue infection

The pivotal diagnostic criterion of DHF is plasma leakage not hemorrhage, so we should not emphasize the term “hemorrhagic fever” to avoid misunderstanding in clinicians and general population [5]. For example, when a Dengue patient does not present with hemorrhage, both doctors and the patient may take it as a simple DF instead of DHF, overlook the signs of plasma leakage, and miss the timing for early intervention and fluid resuscitation. Some problems have been reported in literature when applying the diagnostic criteria for DHF in reality. Take 20% increases in hematocrit level for example; it could easily be masked by fluid challenge or hemorrhage. So when a patient had hypotension and minor increase in hematocrit level, it would be difficult to make a diagnosis since the presentation of DF with bleeding was similar to that of DHF with minimal hematocrit change obscured by hemorrhage. Although it takes time for hemorrhage to affect the hematocrit level, a minor increase in hematocrit level cannot be used to rule out plasma leakage accompanied with major bleeding, because the actual timing of bleeding can hardly be identified. Some image studies or examinations could be helpful in identifying the presence of ascites and pleural effusion, confirming plasma leakage, and diagnosis of DHF. Because whether a patient has plasma leakage can still be difficult to tell, the classification and differentiation of DF and DHF is still a difficult task in clinical practice [5-7].

Because the clinical manifestations of Dengue virus infection are difficult to predict, and some specific sings indicating a more severe pattern of disease can sometimes difficult to identify, physicians have encountered some problems in application of the traditional classification of Dengue virus infection. Therefore, a new classification system has been developed by WHO, indicating Dengue virus infection is an “one disease entity” with different clinical presentations, unpredictable progression pattern and outcomes (Figure 2) [7]. Using

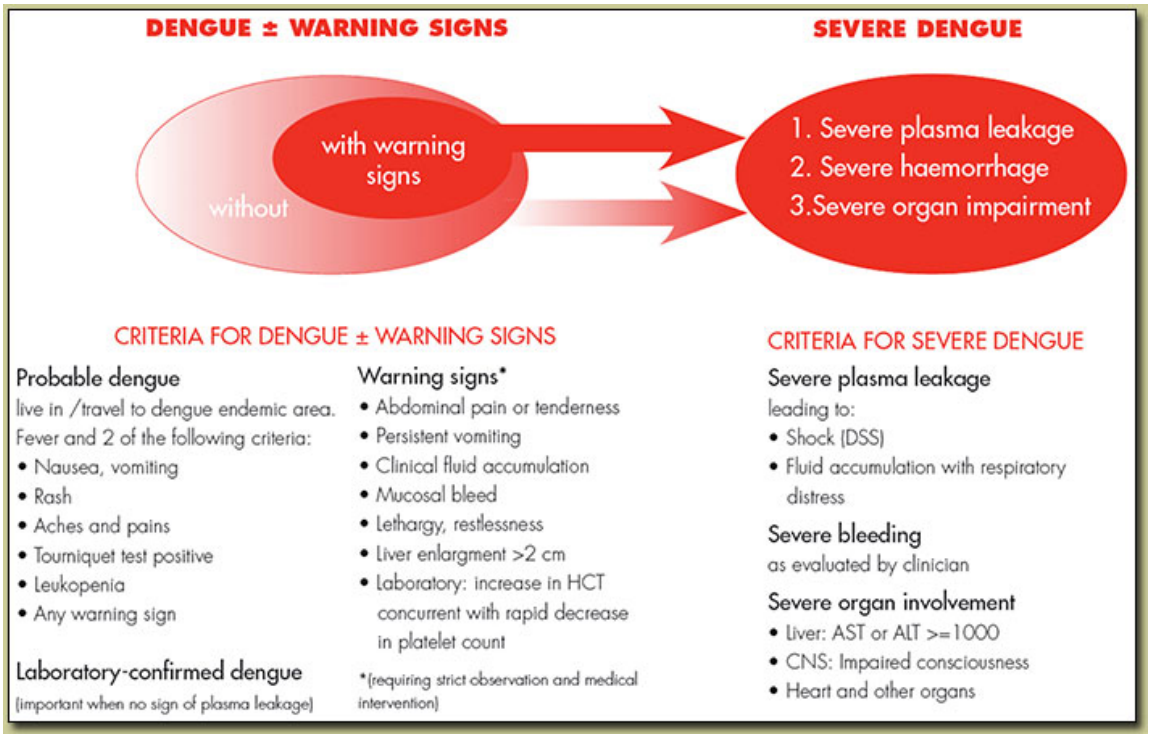

Figure 2. Classification of Dengue virus infection and stratification

the new classification, we stop focusing on diagnosing DHF according to the criteria, but stratify the disease into three patterns: Dengue infection without warning signs, Dengue infection with warning signs, and severe Dengue. Clinicians should treat patients according to the stratification and decide whether the patient should be admitted or sent home. The new classification system is more applicable in clinical practice. It can be helpful in identifying patients who need more aggressive medical treatment that may therefore decrease the mortality, and organizing the descriptions of clinical manifestations of Dengue virus infection [5]. On the other hand, because too many different pathogenic mechanisms have been included in this classification method, the new definition could make the virology and immunology studies more difficult [5].

The pathogenesis of DHF remains unclear, but re-infection was thought to play an important role [10]. However, only 0.5-4% of patients with Dengue virus infection had DHF despite re-infection was not uncommon in endemic area, indicating presence of other contributing factors [11-12]. Underlying chronic medical conditions, such as diabetes, hypertension, allergy, and asthma, were found to increase the risk of becoming DHF [13-15]. Three of four mortality cases had diabetes and hypertension in our case series. Although we were unable to prove the casual relationships, clinicians should be more vigilant on Dengue patients with the aforementioned underlying diseases.

The mechanism of bleeding caused by Dengue virus infection also remains undetermined [16]. Most patients had minor bleeding; those who had severe or lethal bleeding had history of profound or prolonged shock [7, 17]. Peptic ulcer diseases and use of aspirin or other non-steroid anti-inflammatory drugs (NSAID) have been found to be associated with increased risk of bleeding [7, 20]. Although all four patients had gastrointestinal bleeding and no documented peptic ulcer history could be found in their medical records, occult peptic ulcer diseases still could not be ruled out [19]. In addition, some patients with cardiovascular disease need regular use of aspirin and sometimes keep using until admission. Use of NSAID should also be considered as a predisposing factor of bleeding. For example, ketoprofen had been prescribed to Case 1 because of fever and bone pain. Although the complete drug-using records were not available, and no definitive association between use of NSAID or aspirin and the bleeding or death of patients could be confirmed, clinicians should be very cautious on using NSAID for patients with pain and fever of undetermined cause in dengue epidemic seasons since all the contemporary guidelines recommend not to use NSAID or aspirin in Dengue patients [7]. For confirmed Dengue patients, the necessity of using NSAID or aspirin should be carefully re-evaluated, especially for patients with cardiovascular diseases.

Based on this case series, we also found that recognition and management of shock symptoms in Dengue patients are important. When a patient has a normal systolic blood pressure, but with a narrow pulse pressure (<20 mmHg) or a 40 mmHg decrease in systolic blood pressure, presence of shock should be considered. Other clinical presentations, such as

change of consciousness, differences in pulsation, and prolonged capillary refill time (> 2 sec), should be evaluated to confirm if a patient has shock. For patients whose vital signs were unstable, we should check hematocrit level as soon as possible and give fluid challenge. Hematocrit level should be followed up regularly as an indicator to decide whether to keep infusion and the infusion rate. If the patient's vital signs remain unstable and his hematocrit level remained high after initial fluid resuscitation, we should continue aggressive intravenous fluid infusion. If the patient's hematocrit level decreased, early transfusion with whole blood or concentrated packed red blood cells should be given while solely infusion of platelet or fluid should be avoided. If the unstable blood pressure of a Dengue patient comes from plasma leakage, the hematocrit level should be high (>50% in men and >45% in women) [7]. If the hematocrit level was normal or below the normal limit, the patient might already have active bleeding and need transfusion. Usually we prescribe blood transfusion to critically ill patients when their hematocrit level drops to <30%, but it was not the case when it comes to severe Dengue virus infection [21]. A correct and reliable interpretation on the change of hematocrit is important [7].

There are some limitations of this case series. We described the fatal cases, but could not identify the risk factors or causes of bleeding and death. Besides, we reviewed the medical charts. Records on how clinical judgments have been made could hardly be completed, so the actual effects of clinical managements might be under-estimated. In a retrospective study, the information about presence or absence of important clinical signs, warning signs, the timing of symptom onset, and past medical or drug history might not be available. Despite the aforementioned limitations, this case series addressed some important issues. First, interpretation of the change in hematocrit level and the adequate response to it are critical. Second, aspirin and NSAID should be used very carefully in patients with probable Dengue virus infection. Third, warning signs should be known and recognizable.

Based on the currently available information, we have two recommendations on how to reduce the Dengue virus infection associated mortality. First, we have to provide education material (Table) to clinicians so that they can inform the notified patients and to public health professionals so that they can reinforce their knowledge when doing case investigation [7]. Second, we should provide information to clinicians so that they know how to manage patients based on the new version of Dengue virus infection, especially strengthen the ability to recognize warning signs and to treat critically ill patients, including how to interpret hematocrit level, when to give fluid resuscitation and transfusion. For probable cases, whether a patient is using aspirin or NSAID should be reviewed and closely monitored; risk of bleeding should be informed if these drugs are unavoidable. For Dengue patients with underlying chronic medical conditions such as diabetes or hypertension, DHF should always be considered. Although some controversies concerning about how the new classification system, without the category of "Dengue hemorrhagic fever", will affect the current reporting system [22-23], WHO has not decided to change current reporting criteria. Therefore, we will launch campaigns to make the

Table Education sheet about Dengue virus infection

What you should do - • Sufficient bed rest • Sufficient fluid intake: Milk, juice, and isotonic saline are recommended, except in diabetes patients who should be cautious about drinking juice. Plain water alone could result in electrolytes imbalance. • Looking for mosquitos' habitats in your neighborhood
What you should not do - • Take antipyretics (drugs to reduce fever) or analgesics (pain killers) without physicians' prescription
Warning signs - once notice any one of the following, go to see a doctor. • Bleeding - red spots or petechiae - nasal or gum bleeding - hematemesis - tarry stool passage - menorrhagia or vaginal bleeding • Frequent vomiting • Severe abdominal pain • Drowsiness, mental confusion , or convulsion • Pale, cold or clammy hands and feet • Difficult breathing

new classification system and warning signs well-known, but will not change the reporting system in Taiwan, just like in other countries [24].

In conclusion, to reduce Dengue associated mortality, we not only need to keep eliminate the mosquito habitats to reduce the risk of infection, but also need to well educate the health care professionals on how to treat patients who already got Dengue infection, especially when DHF and severe Dengue virus infection are both more common in southern Taiwan.

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Outbreak Investigation Express

A Food Poisoning Outbreak in a Primary School, Taitung County, 2012 May

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A reported of over 100 students with diarrhea between May 9th and 10th was received on May 10, 2012. To response, the local Bureau of Health and the Sixth Branch of Taiwan Centers for Disease Control (Taiwan CDC) initiated the epidemiologic investigation, collected specimens from cases of school students, kitchen workers, suspected food items and water. This outbreak affected a total of 164 students and 97.0% of them only had a single diarrhea. The test results showed rectal swabs from two students with *Staphylococcus aureus*, a food item with *Bacillus cereus* and a kitchen cooking water detected *Bacillus cereus*. Therefore we can not infer a single pathogen causing the food poisoning. Recommendations to the school in the future should actively strengthen the prevention education such as "the school lunch supply health", "washing hands as a good habit" and "environmental cleaning and disinfection". Also, the local health centers should intensify epidemiologic investigation techniques, to enable rapid intervention when a cluster occurs, immediately grasp the correct and detailed information.

Key words: food poisoning outbreak, *Staphylococcus aureus*, *Bacillus cereus*

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