Case Report

Two Pediatric Cases of Dengue Fever Imported from Philippines

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Dengue fever is an important health problem for international travelers to all endemic areas. The steadily increasing numbers of tourists visiting endemic areas raise the risk of exposure, and imported dengue cases are increasingly observed in nonendemic area. Dengue has a wide spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. While most patients recover following a self-limiting, non-severe clinical course, a small proportion progress to severe disease such as dengue hemorrhagic fever or dengue shock syndrome. Therefore, it is important to suspect dengue fever in every febrile patient returning from the tropics. Whenever it is suspected, a quick diagnosis and adequate managements are essential to avoid complications. We report two cases of imported dengue fever in Korean children presenting with fever, headache, nausea, and rash. **(Korean J Pediatr Infect Dis 2013;20:98-104)**

Key Words : Dengue, Korea, Child, Travel

Introduction

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. During the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and an estimated 50 million dengue infections occur annually[1]. Dengue viruses, which is transmitted by *Aedes* mosquitoes[2], belong to the genus *Flavivirus*, family *Flaviviridae*; there are 4 distinct serotypes of dengue viruses, called DENV-1, DENV-2, DENV-3, DENV-4[1]. Clinical manifestations of dengue range from asymptomatic infection, self-limiting dengue fever to dengue hemorrhagic fever with shock syndrome[3]. Dengue fever is endemic in most countries of Southern and Southeast Asia, the Western Pacific regions, Central and South America, the Caribbean and Africa[1]. For the steadily increasing number of tourists visiting endemic area, the disease is an increasingly important problem encountered by international travelers. Dengue is also a major cause of hospitalization in febrile returned travelers[4]. Although various case of dengue fever in international travelers, there was relatively smaller portion of children than adults. In Korea, 20 cases of imported pediatric dengue infection from 2001 to 2008 were reported according to the Korea Centers for Disease Control and Prevention (KCDC)[5]. Since many Korean children visit dengue endemic areas for reasons such as travel, study abroad, and immigration, the imported dengue fever in the infected children is expected to increase further. And children are at a higher risk of severe dengue[6]. Thererfore, awareness about dengue fever of pediatric infectious diseases is important.

Received : 13 March 2013, Revised : 30 April 2013
Accepted : 3 May 2013
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We report two cases of dengue fever which presented with atypical systemic symptoms such as fever, headache, and nausea, developed after travelling in Philippines.

Case Report

1. Case 1

A 13-year-old boy presented with fever, and headache for 5 days; nausea, vomiting, and abdominal discomfort for 2 days. He traveled to the Philippines from July 20, 2012 to July 25, 2012. He presented with a fever after 5 days of his return. He diagnosed with an acute pharyngitis at a primary care clinic and was treated with antipyretics. But the symptoms lasted for 5 days and other symptoms such as nausea, vomiting and epigastric pain were developed. He was referred to our hospital for evaluation. He had a history of asthma, but no other significant past medical history. Physical examination revealed a temperature 39.7℃, pulse rate of 100 beats/min and normal blood pressure and respiration rate. Distinct erythema of the left tympanic membrane was observed. Epigastric tenderness was observed, but there was no hepatomegaly or splenomegaly on abdominal examination.

On admission, the initial laboratory data revealed: hemoglobin (Hb) 12.9 g/dL, hematocrit (Hct) 38.6 %, white blood cell count (WBC) 2,400/mm^3, absolute neutrophil count (ANC) 1,452/mm^3, platelets 195,000/mm^3, total bilirubin (T. bil) 0.16 mg/dL, aspartate aminotransferase (AST) 77 IU/L, alanine aminotransferase (ALT) 84 IU/L, total protein 7.6 g/dL, albumin 4.1 g/dL, blood urea nitrogen (BUN) 11.0 mg/dL, creatinine (Cr) 0.8 mg/dL, sodium (Na) 139 mmol/L, potassium (K) 4.0 mmol/L, chloride 106 mmol/L, serum amylase 37 U/L, serum lipase 24 U/L, C-reactive protein (CRP) <0.50 mg/dL and erythrocyte sedimentation rate (ESR) 48 mm/hr. Urine microscopy, chest X-ray and abdomen X-ray were normal. Viral hepatitis (A, B and C) and Epstein-Barr virus were excluded. Abdominal ultrasonography revealed mild hepatosplenomegaly. Blood and stool examinations were negative for bacteria, parasites and malarial plasmodia. Widal test was negative.

He was given intravenous hydration and treated with empirical antibiotics (intravenous amoxicillin/clavulanic acid 1.2 g/day) under the diagnosis of acute otitis media. On hospital day 3, his fever subsided and gastrointestinal symptoms were improved, but maculopapular skin rash with itching sense was developed on both extremities. We suspected dengue fever based on his symptoms, laboratory values and travel history to endemic area. Enzyme-linked immunosorbent assay (ELISA) and reverse transcriptase-polymerase chain reaction (RT-PCR) were performed. Dengue IgM-caputure ELISA was positive and RT-PCR was negative. On hospital day 4, repeated blood examinations revealed: Hb 13.7 g/dL, Hct 41.5%, WBC 4,800/mm^3, ANC 1,876/mm^3, platelet 147,000/mm^3, AST 94 IU/L, ALT 131 IU/L and ESR 38 mm/hr. Although elevated AST and ALT, his clinical symptoms returned completely normal and he was discharged. On day 17 after discharge, the AST and ALT became normal.

2. Case 2

A 12-year-old boy was admitted with fever, nausea, headache and myalgia for 4 days. He traveled to the Philippines from July 21, 2012 to July 25, 2012. He was presented with a fever after 5 days

of his return. The symptoms lasted for 4 days, and then he was referred to our hospital for evaluation.

He had a history of mycoplasma pneumonia and allergic asthma. His tympanic temperature was 37.0 ℃, pulse rate 92 beats/min, respiratory rate 22 beats/min and throat injection was found on physical examination. Blood examinations revealed: Hb 14.1 g/dL, Hct 42.0%, WBC 3,100/mm^3, ANC 2,005/mm^3, platelets 178,000/mm^3, T. bil 0.80 mg/dL, AST 26 IU/L, ALT 14 IU/L, total protein 6.9 g/dL, albumin 4.3 g/dL, BUN 16.8 mg/dL, Cr 0.8 mg/dL, Na 136 mmol/L, K 4.0 mmol/L, chloride 100 mmol/L, serum amylase 23 U/L, serum lipase 22 U/L, creatine kinase (CPK) 161 IU/L, CRP 2.35 mg/dL and ESR 18 mm/hr. Urine microscopy, chest X-ray and abdomen X-ray were normal. Intravenous hydration was conducted on admission. Myalgia and headache were subsided on the second day of hospitalization and fever subsided on hospital day 4. The rash did not appear during the illness.The next day, repeated blood examinations revealed: Hb 15.8 g/dL, Hct 48.1 %, WBC 3,200/mm^3, ANC 1,830/mm^3, platelet 171,000/mm^3, CPK 667 IU/L and CRP <0.50 mg/dL. Blood culture was negative. Based on his symptoms, laboratory values and travel history to endemic area, we performed dengue specific IgM ELISA and RT-PCR. Dengue IgM-caputure ELISA was positive and RT-PCR was negative. On hospital day 5, he recovered from the illness without significant complications.

Discussion

Among travelers to tropical countries, dengue infection is increasingly reported, and it is also a major cause of hospitalization of febrile returned travelers[7].

Dengue viruses are transmitted by mosquitoes *Aedes aegypti* and *Aedes albopictus*. *A. aegypti* is the principal vector, found worldwide in the tropics and subtropics[8]. The secondary vector *A. albopictus* is widely spread and is also found in Korea. The vector mosquitoes breed in tires, cans and water jars near human dwellings. A study in Puerto Rico showed that water storage containers and discarded tires were important for mosquito producers. They also showed that the population of *A. aegypti* was driven by weather and human activities, and peaks in mosquito density preceded maximum dengue incidence during the rainy season[9]. Halstead reported that warm temperature and high moisture may contribute to increasing adult mosquito[10]. In KCDC report, the dengue fever incidence in returned travelers peaked during summer, from July to August. The peak periods of dengue virus transmission coincide with the rainy season when vector density increases[5].

Dengue fever is a national notifiable infectious disease, group 4 in Korea. After the first case of dengue fever in Korea was reported in 1995[11], the number of reported dengue fever cases has increased in Korea. The KCDC reported 262 cases of dengue from June 1, 2001 to December 20, 2008[5]. It was the most common imported infections identified after malaria (340 cases). Among 262 cases, 20 cases (7.6%, 20/262) were under 20 years of age. The destinations of imported dengue patients were mostly Asian countries except for 5 cases; 1 Africa, 1 South America, 1 North America and 2 unknown. The most common destination where Korean travelers were infected with dengue was the Philippines (31.3 %, 82/262)[5]. Our two cases also had a history of

traveling to the Philippines. There are some cases which have reported dengue infections in Korean travelers who had visited endemic areas[12-14].

Dengue virus infection causes a spectrum of illness ranging from asymptomatic or mild febrile illness to classic dengue fever or severe and fatal hemorrhagic disease[8]. In rare cases, liver failure or central nervous system dysfunction may appear in a patient with acute dengue infection. Unusual neurological manifestations include encephalopathy, seizures, mononeuropathies, and polyneuropathies[15]. After the incubation period of 2-8 days of the infective mosquito bite, the illness begins abruptly and is followed by the three phases; febrile, critical and recovery. Acute febrile phase usually lasts 2-7 days and is accompanied by fever, skin erythema, generalized body ache, myalgia, arthralgia and headache. Anorexia, nausea and vomiting are common[16, 17]. These clinical features are indistinguishable between severe and non-severe dengue cases. Therefore monitoring for warning signs is crucial to recognize progress to the critical phase. In WHO guidelines of 2009, a classification according to severity is outlined: Probable dengue or laboratory-confirmed dengue with and without warning sign, and severe dengue. Several clinical symptoms such as lethargy, abdominal tenderness, mucosal bleeding, liver enlargement, persistent vomiting, increased hemoconcentration with rapidly decreased platelet count were identified as possible predictors of a severe clinical course and defined as warning signs. Severe dengue is defined by one or more of the following: (i) plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress, and/or (ii) severe bleeding, and/or (iii) severe organ impairment[1]. It must be kept in mind that even dengue patients without warning sings may develop severe dengue. In critical phase, when the temperature drops to 37.5-38℃ or less and remains below this level, usually on days 3-7 of illness, an increase in capillary permeability in parallel with increasing hematocrit levels may occur. About 1-2 days after defeverescence, a generalized maculopapular rash appears that spares the palms and soles. It disappears in 1-5 days[18, 19]. Using the WHO guidelines of 2009, case 1 is classified as probable dengue with warning sign due to abdominal tenderness, and case 2 is classified as dengue fever without warning sign.

In Dengue fever, leukopenia, thrombocytopenia or pancytopenia may occur after the 3-4 days of illness. Mild acidosis, hemoconcentration, increased aminotransferase values, and hypoproteinemia may occur during some primary dengue virus infections[20]. Our two patients showed leukopenia and case 1 showed increased serum aminotransferase.

Methods used for the diagnosis of dengue infections include virus isolation, serology such as Dengue specific IgM and IgG ELISA and molecular techniques such as reverse transcriptase-polymerase chain reaction (RT-PCR). We used IgM capture ELISA and multiplex RT-PCR for confirmation of dengue virus infection. Detection of dengue IgM by ELISA was performed according to the Panbio Dengue IgM Capture ELISA (Panbio, Brisbane, Australia). Multiplex RT-PCR was performed using the primer pairs reported by Harris et al[21]. Viral RNA was extracted from serum samples and culture supernatants using the QIAamp viral RNA minikit (Qiagen, Hilden, Germany). The RNA was reverse transcribed and amplified using the Qiagen One Step RT-PCR kit and the Multiplex PCR kit (Qiagen, Hilden, Ger-

many).

Our two patients were suspected of dengue fever based on their symptoms, laboratory values and travel history to the Philippines. And the results of dengue serological tests were positive but RT-PCR was negative. After the onset of illness, the virus can be detected in serum, plasma, circulating blood cells and other tissues for 4-5 days. During the early stages of the disease, virus isolation, nucleic acid or antigen detection can be used to diagnose the infection. At the end of the acute phase of infection, serology such as Dengue specific IgM and IgG ELISA is the method of choice for diagnosis[1]. PCR-based diagnosis is also useful since it is positive early in the course of the disease and becomes negative towards the end of the febrile period when IgM becomes positive[22]. Since we performed serological and molecular test after 8 days of their illness, PCR-based diagnosis may become negative and IgM may become positive. Although the dengue IgM serology was positive, it does not necessarily indicate a recent exposure to dengue virus infection, as the dengue IgM level can remain elevated for up to several months after exposure[1]. Considering that the travel history is not long in our cases, positive serology results can reflect recent dengue virus infection.

Serological cross-reactivity across the *Flavivirus* group is frequently observed: dengue virus types 1, 2, 3 and 4, Japanese encephalitis, Yellow fever and West Nile viruses[23]. During a secondary dengue infection (a dengue infection in a host that has previously been infected by a dengue virus, or sometimes after non-dengue *Flavivirus* vaccination or infection), IgM antibodies are either absent or lower than in primary infection, with high levels of dengue IgG antibodies in the early course of the disease. To distinguish primary and secondary dengue infetions, IgM/IgG ratios are now more commonly used than the hemagglutination-inhibition test[1, 23]. Our patients had no history of infection with other *Flaviviruses*. Since they had been vaccinated against Japanese encephalitis virus, a possible influence of the vaccination could not be denied. Moreover, we performed only dengue-specific IgM ELISA. From this viewpoint, despite a travel history to endemic area, our cases can be considered probable dengue virus infections.

There is no specific antiviral therapeutic drug licensed for treatment of dengue, and prevention relies on mosquito control. Classical dengue fever is treated with supportive care; antipyretic agents, fluid replacement and bed rest. Prompt and adequate fluid replacement is thought to reduce mortality rates in dengue hemorrhagic fever and dengue shock syndrome[24]. Mortality of dengue hemorrhagic fever can be as high as 10-20% (over 40% if shock occurs) without early appropriate treatment, but it is as low as 0.2% in hospitals with staff experienced in the disease[8]. And the most effective measure of dengue prevention for travelers to endemic areas is taking precautions to avoid mosquito bites, such as using mosquito repellents, protective clothing, and insecticides.

The steadily increasing number of tourists visiting endemic areas has raised the risk of dengue virus exposure for large number of travelers. It can be inferred that travelers have the potential to acquire and spread dengue virus infection. But it is difficult that pediatricians in non-endemic areas establish the correct diagnosis, since dengue fever shows atypical symptoms and is not familiar.

In conclusion, there is a need for pediatricians in non-endemic areas to understand the clinical feature, epidemiology, diagnosis and prevention of dengue fever among travelers. Also, it is important to suspect dengue fever in every febrile children returning from the endemic areas, particularly if thrombocytopenia, leukopenia, elevate serum aminotransferase and/or rash are present.

한 글 요 약

필리핀에서 유입된 소아 뎅기열 2례

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뎅기열은 아시아, 남태평양 지역, 아프리카, 아메리카 대륙의 열대지방에 걸쳐 널리 발생하며, 이러한 유행지역으로부터 돌아온 여행자들에게 중요한 감염 질환의 하나로 부각되고 있다. 풍토지역을 방문하는 여행자의 점차적인 증가로 뎅기 바이러스에 대한 노출의 위험도가 증가하고 있으며, 이로 인해 해외에서 유입되는 뎅기 감염 사례가 증가하고 있다. 뎅기열은 다양한 임상 양상을 나타내며, 종종 예측할 수 없는 임상 증상과 결과를 초래하기도 한다. 대부분의 감염자들은 저절로 회복되거나 경한 증상을 보이지만, 일부에서는 뎅기 출혈열이나 뎅기 쇼크와 같은 심각한 경과를 보이기도 한다. 따라서 뎅기열 유행지역 방문자가 발열을 보이는 경우 뎅기열을 의심하는 것은 중요하며, 일단 의심이 되면 신속한 진단과 적절한 치료를 통해 합병증을 예방하는 것이 중요하다. 저자들은 뎅기열 유행지역을 여행한 소아에서 발열, 두통, 구역, 발진 등이 발생하여 시행한 혈청검사에서 뎅기열로 진단된 2례를 경험하였기에 보고하는 바이다.

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