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A Case of Dengue Meningitis Manifested as a Part of Expanded Dengue Syndrome

Gomes RR*

Associate Professor, Medicine, Ad-din Women's Medical College Hospital, Bangladesh

***Corresponding author:** Richmond Ronald Gomes, Associate Professor, Medicine, Ad-din Women's Medical College Hospital, Bangladesh, Tel: 8801819289499; Email: rrichi.dmc.k56@gmail.com

Case Report

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Abstract

Dengue is a prevalent arthropod-borne viral disease in tropical and subtropical areas of the globe. Dengue clinical manifestations include asymptomatic infections; undifferentiated fever; dengue fever, which is characterized by fever, headache, retro orbital pain, myalgia, and arthralgia; and a severe form of the disease denominated dengue hemorrhagic fever/dengue shock syndrome, characterized by hemoconcentration, thrombocytopenia, and bleeding tendency. However, atypical manifestations, such as liver, central nervous system, and cardiac involvement, have been increasingly reported called expanded dengue syndrome. We report a 35 years old lady with atypical and rare presentation of dengue disease marked by meningitis. Condition improved after conservative treatment. Neurological complications in dengue are now increasingly observed with the most common case is aseptic meningitis. Dengue meningitis is self-limiting in almost all cases. Hepatic failure rarely dominates the clinical picture in adults. The main mechanism of dengue meningitis is still unknown though both direct viral infection and immune mediated damage have been suggested to be the cause. To avoid otherwise preventable morbidity and mortality, physicians should have a high index of suspicion for neurological complications in patients with dengue illness and should manage this accordingly.

Keywords: Meningitis; Thrombocytopenia; Expanded Dengue Syndrome; Dengue Fever

Introduction

Dengue, an arthropod-borne viral infection of humans, is endemic to tropical and subtropical regions of the world and represents an important public health problem. Dengue viruses are transmitted by the bite of the *Aedes aegypti* mosquito infected by the one of the four dengue virus serotypes: dengue-1, -2, -3, and -4. More recently, dengue disease has spread geographically to many previously unaffected areas and, as travelling around the world has become more accessible, physicians in temperate areas are more likely to see returning travelers with dengue infection [1,2].

World Health Organization (WHO) classification of symptomatic dengue infection, continuously evolved, first in 1997 it divided into dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). In 2009 it improved into dengue with or without warning signs and severe dengue [3].

However, in 2011, WHO Regional Office for South East Asia (SEARO) revised and further improving the classification, divided into DF, DHF without shock or with shock (DSS) characterized by increased vascular permeability, thrombocytopenia (platelets <100,000), bleeding tendency, and, in a small percentage of patients, circulatory shock and

expanded dengue syndrome [4-8].

Expanded dengue syndrome is a new entity added to the classification system to incorporate a wide spectrum of unusual manifestations of dengue infection affecting various organ systems that had been reported including gastrointestinal, hepatic, neurological, cardiac, pulmonary and renal systems [8].

Unlike other viral infections, meningitis determined by dengue infection is a rare complication [9]. We describe a 35 years old Bangladeshi lady diagnosed with meningitis caused by oligosymptomatic dengue infection.

Case Report

A 35 years old lady, service holder, not known to have any diabetes mellitus, hypertension, coronary artery disease or bronchial asthma presented to us with the history of high grade, intermittent fever, severe headache, bodyache and retro orbital pain for 5 days, vomiting for several times for the same duration and severe prostration for 1 day. She denied any altered consciousness, convulsion, cough, chest pain, palpitation, shortness of breath, abdominal pain or distension, burning micturition, joint pain. She had no recent history of travel of late. She lives in 1stfloor of her apartment and have hobby of gardening. His husband just recovered from dengue 1 week prior her illness. On examination, she was toxic, conscious, oriented febrile (temperature 104^{o}F), with pulse 120 beats/min, with normal rhythm and volume, blood pressure was 100/70 mm of Hg. There was diffuse blanching erythema, more prominent over trunk. Neurological examination showed the presence of nuchal rigidity, with positive Kernig's sign and Brudzinski sign. Fundoscopy was normal. Other systematic examination revealed no abnormalities (Table 1).

Test Names (Reference Range)	Day 1	Day 2	Day 3	Day 4	Day 5
Hb (12-16 gm/dl)	12	12.8	13.6	11.8	11.9
TC WBC (3500-11000/mm^3)	3700	3150	2320	4600	5100
Platelet(150000-450000/mm^3)	130000	92000	23000	67000	178000
PCV (35-47%)	37.1	40	48	44	36.5
SGOT (10-45 U/L)	315	404	458		96
SGPT (10-50 U/L)	218	387	412		69
Blood urea (15-40 mg/dl)	21	40	26.5		28
S. Creatinine (0.6-1.2 mg/dl)	1.1	0.8	1.1		1
S. Sodium (135-145 mmol/L)	130	141	136		140
S. Potassium (3.555mmol/L)	4.2	4.1	3.7		4.3
S. Calcium (8.5-10.5 mg/dl)			8.8		9.1
S. Albumin (3.5-5.0 g/dl)			3.3		3.8
Blood glucose (<7.8 mmol/L)	7	5.7	6.9		5.9
Non fasting cholesterol(mg/dl)			96		
C-reactive protein (<6 mg/L)		18	28		5
S. LDH (140-280U/L)		210			
ICT for malaria	Negative				
Blood film for malarial parasite	Negative				
Blood Culture	No growth				
Dengue NS1 antigen	Positive				

Table 1: Day count is as per hospital stay.

She was started treatment conservatively with intravenous fluids, anti-emetics and anti-pyretic. On the following day, she became afebrile but intensity of vomiting, headache and bodyache remain unchanged. As repeat complete blood count showed progressive leucopenia and thrombocytopenia she was monitored closely for evidence of dengue hemorrhagic fever. Repeat abdominal examination showed epigastric tenderness and ascites as evidenced by presence of shifting dullness without hepatomegaly. There was also evidence of bilateral pleural effusion.

There was no active bleeding from any site but narrowing of pulse pressure (100/90 mm of Hg) with rapid thread low volume pulse (120 /min) was observed. So clinical diagnosis of dengue hemorrhagic fever was established. Considering her persisting neurological symptoms brain computed tomography was done which failed to reveal any abnormalities. Cerebrospinal fluid (CSF) analysis showed white blood cell count of 82 cells/mm^3 (lymphocytes 92%), no red blood cells, CSF glucose 88 mg/dL (blood glucose 106 mg/dL) and CSF protein 87 mg/ dL(nomal 15-45mg/dL). CSF gram stain and fungal stains and bacterial cultures were negative. CSF analysis for herpes simplex virus, Japanese encephalitis virus and dengue virus was not done due to unavailability. She was started short course intravenous dexamethasone and continued for 3 days. With conservative management she showed dramatic improvement in following 3 days with reduced headache, vomiting and improving general well being. Serial complete blood count was done which showed progressive improvement of her white cell and platelet counts. She was discharged on the tenth day of illness with complete recovery and was found to be well on follow-up.

Discussion

Dengue is a worldwide public health problem and causes innumerous deaths. More than 40% of the world's population lives in dengue endemic areas, and the World Health Organization estimates that about 2.5 billion people in 100 countries are at risk of infection and that as many as 100 million people are infected by dengue viruses every year. In the majority of infected people, dengue is an auto-limited disease that resolves in 5–7 days. However, approximately 500,000 people develop a severe form, leading to about 20,000 deaths annually. Consequently, approximately 0.5% of dengue patients develops a severe form and requires a specialized treatment [2,10].

Dengue virus infection is a disease that found in children and adults with the main symptoms of fever, muscle and joint pain that usually worsens after the first three days. This disease is an acute febrile illness accompanied by bleeding manifestations with potential shocking and can lead to death in children<15 years, but not likely to attack adults [11]. Signs of this disease are sudden high fever 2 to 7 days with no obvious cause, weakness, lethargy, anxiety, heartburn, accompanied by signs of bleeding in the skin (petechiae), bruising (ecchymosis) or rash (purpura).Sometimes there are other spontaneous bleeding manifestations such as nosebleeds, bleeding gums to dysentery. Severe symptoms can lead to decreased awareness or shock [12].

Laboratory results in dengue fever are found in thrombocytopenia (20% of the baseline on dengue hemorrhagic fever is a sign of plasma. Serological tests results in dengue are influenced by the type of dengue infection, whether it is the primary/first, or secondary/reinfection. IgM antibodies are detectable by days 3–5 after the onset of illness, rise quickly in two weeks and decline to undetectable levels after 2–3 months, because this late appearance, the first five days of clinical illness are usually negative of IgM. In dengue secondary infection, the rises of IgM are not as high as primary infection, and sometimes absent/undetectable completely [13].

IgG antibodies in primary infection, evolves relatively slow, with low titres 8-10 days after fever onset, increase subsequently and remain for many years, whereas in secondary infection it evolves rapidly, with high titres soon after fever onset and persist to a lifelong period. Hence, a ratio of IgM/IgG is commonly used to differentiate between primary and secondary dengue infections. Ratio of IgM/IgG titre less than 1.2 is considered a secondary dengue infection. But to be noted, titre ratio only could be validly use as a data if the IgG/IgM serological test is using pure quantitative means, not by qualitative or semi-quantitative [14].

NS1 antigen detection is widely used and cost-effective, NS1 could be detected from day 1-8 of fever onset, unaffected by a primary or secondary dengue infection. In conclusion, by combining the serological (IgG and IgM) and NS1 tests, clinicians could rapidly assess the dengue diagnosis with its types (primary or secondary infection) and applies the best treatment [15].

In 2011, based on many reports of cases with dengue-related unusual manifestations and organ complications, WHO-SEARO further improved and revised 2009 WHO guidelines by adding a new entity, that is expanded dengue syndrome (unusual/atypical manifestation of dengue), these include neurological, hepatic, renal, cardiac and other isolated organ involvement, that could be explained as complications of severe, profound shock or associated with underlying host conditions/diseases or co infections [8].

Uncomplicated dengue infections very rarely presents with meningitis as the initial symptom. The reported time of onset of neurological symptoms is three to seven days from the start of fever [16]. Immuno suppression caused by dengue infection, increases the chances of organisms to invade the body and cause widespread viral and bacterial infection. Drowsiness and nuchal rigidity are the main clinical signs noted in dengue meningitis or meningoencephalitis [17]. Meningitis is seen in around 3-4% of dengue cases [18].

Our case had the typical clinical features of dengue infection. The main symptoms were high-grade fever with severe generalized bodyache and headache, which

was refractory to analgesics. Headache is a very common symptom in patients with dengue fever, and severe or very severe headache is reported in 79% of patients with dengue fever [19]. As CSF analysis is not done routinely to differentiate 'non-specific dengue headache from dengue meningitis, a number of patients with dengue meningitis may remain undiagnosed [20]. However, in addition to headache, presence of neck stiffness with a positive Kernig's sign in our patient pointed toward the clinical diagnosis of meningitis.

A number of neurological manifestations, such as meningoencephalitis, acute disseminated encephalomyelitis, transverse myelitis and Guillain–Barre´ syndrome, have been reported in association with dengue infection [17,21,22]. Encephalitis, the most common neurological manifestation, is thought to occur in up to 6.2% of patients with dengue hemorrhagic fever but is rare in uncomplicated dengue fever [16]. Meningitis is a rare manifestation of dengue fever, and only few such cases have been reported in the literature [20,23,24].

The exact mechanisms by which dengue virus causes central nerve system involvement are unclear, but experimental evidence suggests direct tissue lesion caused by the virus because of its neurotropicity, capillary hemorrhage, disseminated intravascular coagulation and metabolic disorders, which might play a role [25].

Dengue is a rare cause of viral meningitis [9]. Encephalitis is a more recognized feature. In a prospective study by Soares *et al*. from Brazil, dengue emerged as the leading cause of encephalitis with normal CSF cellularity (75%). On the other hand, dengue was found in only a minority of patients presenting mainly with meningitis [20]. A Jamaican study found 13.5% of dengue patients presenting with neurological symptoms or signs with encephalitis as the leading feature. Meningitis due to dengue was present in only 4% (18 out of 401) of patients [26].

Time of onset of neurological symptoms in dengue has been reported to range from three to seven days on an average from the start of fever [16]. In our case, headache and neck pain occurred simultaneously with fever onset.

In our case, the diagnosis was suspected after demonstration of thrombocytopenia which was most prominent on the sixth day of fever. This observation is in good agreement with a large Brazilian study that included 543 dengue patients and found a decrease in platelet count from the third day of fever in uncomplicated cases, while thrombocytopenia started from one and two days in dengue hemorrhagic fever. In both groups the lowest platelet count occurred around the seventh day of fever [27]. Our case recovered completely from the ailments and she was followed up for one month without any residual neurodeficit. Misra *et al*. found that recovery was complicated with three out of 11 dying patients and another three with residual neurodeficit [28]. On the other hand Kankirawatana, et al., Solomon, et al., and Kularatne, et al. have shown a more benign outcome [29-31].

In most cases, diagnosis depends on detection of the virus itself (by culture, polymerase chain reaction or dengue NS1 antigen) or detection of host immune reaction (IgM antibody) in the serum. All these methods, which are validated for serum, with suitable modifications, have been used for CSF with a high specificity [32,33]. The gold-standard method for viral detection has traditionally been viral culture, although it is difficult and time-consuming. PCR assays are quicker, allow discrimination between viral serotypes, and have been shown to be highly specific within the first five days of fever. PCR assays have recently been utilized in a recent report by Soares, et al. [34] in the presentation of a case of pure oligosymtomatic dengue meningitis in 2010, in which type 3 dengue virus was isolated as the pathogen [20]. Dussart, et al. has achieved a sensitivity of 89% with an assay for NS1 antigen [35]. This test is rapid, reliable and less costly than PCR. In a recent study in fatal dengue meningoencephalitis cases, a kit for detection of the NS1 antigen in CSF gave sensitivity of 50% and specificity of 100%. When used in combination with IgM, the detection rate rose to 92.3% [32]. Another recent study by Puccioni-Sohler evaluated CSF and serum dengue IgM and IgG in dengue patients with neurological manifestations; their results showed that 7 out of 10 of their patients had evidence of intrathecal production of IgM in response to dengue infection [33]. This observation also lays support to test for dengue specific IgM in CSF in patients with neurological manifestations in the background of dengue infection [33].

MAC ELISA measures dengue-specific IgM. One time presence of anti-dengue antibodies vouches for recent infection (within 24 weeks). A rising titre in two serum samples can confirm acute infection. Singh, et al. reported the sensitivity of MAC-ELISA at 69%, rising to 90% with repeat convalescent testing. Specificity was 80% [36]. It is generally recommended to use PCR or NS1 antigen detection in patients with fever for fewer than five days, and MAC ELISA in patients with fever for more than five days [16]. In the clinical spectrum of viral meningoencephalitis, especially when dengue is a possibility, other flaviviruses such as Japanese encephalitis should be excluded.

Studies have shown that dengue meningitis usually has a benign outcome. Mortality rates reported in cases of dengue patients with neurological manifestation ranged from 5% to 8.35% [17,22]. However dengue meningitis has a benign outcome similar to other types of viral meningitis.

Conclusion

In conclusion, our report demonstrates that meningitis with or without encephalitis can be the first manifestation of dengue infection. In endemic areas, dengue infection should always be considered as a probable etiological agent of meningitis. Regular monitoring of platelet count can be an invaluable diagnostic screening tool. Dengue NS_1 antigen and IgM anti dengue antibody detection in both serum and CSF may help in reaching the correct diagnosis.

Conflict of interest: None declared.

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