

Atypical Dengue Meningitis in Makkah, Saudi Arabia with Slow Resolving, Prominent Migraine like Headache, Phobia, and Arrhythmia

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ABSTRACT

Although dengue meningitis is a rare presentation of dengue infection, our aim is to focus on atypical presentation of dengue meningitis that may appear in dengue endemic area like the Makkah region. We report two cases of clinical meningitis with positive dengue virus (DENV) IgM in cerebrospinal fluid, followed for minimal 3 months for their prominent attacks of migraine like headache, phobia, and arrhythmia. With special consideration to attack time, type, severity, and respond to classical therapy, using regular ECG monitoring, visual analog pain score and neuropsychological assessments were done. Both cases showed resistant migraine like headaches to classic anti-migraine therapy except for strong NSAID and narcotics with tendency to have severe to extreme severe daily migraine like headache on early to late afternoon time, associated with non-fatal arrhythmias and extreme death phobia, that resolve slowly in a minimal 3 month period. In conclusion, dengue meningitis in the endemic area may present atypically.

Key words: Abnormal behavior, Atypical, Arrhythmia, Dengue meningitis, Makkah, Migraine like headache, Phobia, Slow resolving

INTRODUCTION

Dengue is one of the world's major re-emerging infections.^[1,2] The disease is endemic in more than 100 countries and around 2500 million people are at risk.^[3] WHO estimates that there may be 50 million cases of dengue infection worldwide every year.^[4] Dengue virus belongs to the genus *Flavivirus*, family *Flaviviridae*. It is composed of single-stranded RNA and has four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4).^[5,6] It is transmitted by the bite of *Aedes aegypti* mosquito. According to WHO, dengue virus can cause classic dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS).^[7] Makkah province of Saudi Arabia since 1994 became the dengue endemic area.^[8] Several dengue epidemic have been reported after 2001 in the Makkah region.^[9] Neurological manifestations occur in 4-5% of dengue infection, and unlike other viral infections, meningitis determined by dengue infection

is a rare complication accounting for 4-5% of dengue neurological manifestation.^[10] We describe two cases of dengue meningitis with aim to document that rare dengue meningitis in dengue endemic area may present with extremely painful migraines like headache, terrifying phobia, and arrhythmia that may need several months to resolve completely.

CASE REPORTS

Case 1

A 27-year-old Saudi female, living in Makkah, was referred from ophthalmology clinic, with severe retro-orbital headache and neck pain started 3 days before admission. There was no myalgia, arthralgia, bleeding manifestation, cutaneous rash, or any similar or significant past medical history. On examination, she was in pain, febrile with a temperature of 38.3°C, respiratory rate of 20/min, heart rate of 112/min, and blood pressure 116/63 mmHg. Her chest, cardiovascular, abdomen, and neurological examinations including fundus were unremarkable, except of mild neck rigidity. She was admitted with professional diagnosis of acute meningitis and started on intravenous

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dexamethasone, vancomycin, ceftriaxone, and acyclovir with good hydration. Brain CT scan was normal. CSF was normal except of pleocytosis (85% lymphocytes). The complete blood count was as follows: WBC 4.5 cell/mm³, 60% lymphocytic, Hb 12.1 gm/dL, platelets count 135/mm³. The blood tests for malaria, brucella, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), and swine flu virus (H1N1) in the blood were negative. Dengue serology sent to Makkah central laboratory due to relative low platelets and low grade fever. Upon these result dexamethasone, vancomycin, and ceftriaxone were stopped on the next day and the patient was kept on intravenous acyclovir only. Throughout the 7 days admission period, the patient was almost afebrile but showed bizarre headache appearing as persistent diffuse headache with attacks of severe retro-orbital pain, eye tearing, and blurring vision mainly on left eye that respond only to pethidine intravenous injection in spite of trial of multi analgesic and neuropathic medication including amitriptyline, topiramate, pregabalin, and tramadol. The headache attacks predominantly appeared between 3 and 11 pm, associated with anxiety and fear of death in addition to episodes of arrhythmia range between bradycardia down to 45/min and supraventricular tachycardia up to 180/min, that required many cardiology and psychiatry on call review. On 4th day of admission, serum dengue IgM reported to be positive. To further strengthen the diagnosis, we repeated the CSF test for dengue IgM. On the 7th day, the patient was so much upset and asked discharge against medical advice to seek abroad management. 20 days later, the patient was seen in neurology out-patient clinic complaining of persistence migraine like headache and the CSF test for dengue IgM was found to be positive. Over several months later, the patient was on amitriptyline and tramadol on need. Then gradually and slowly, headache attacks diminished in frequency and severity, resolving almost completely 4 months after onset.

Case 2

A 48-year-old Egyptian obese woman, not known to have any medical illness before, was referred by ENT specialist as possible central dizziness with history of severe dizziness, nausea, and vomiting associated with blurring of vision and headache 1 day before. On examination, she was looking ill, with a temperature of 38.4°C, respiratory rate of 21/min, heart rate of 124/min, and blood pressure of 167/93 mmHg. Her chest, cardiovascular, abdomen, and neurological examination were unremarkable, except of mild early bilateral papilledema, neck rigidity, and ataxic gait. A CT scan of brain done with/without contrast in emergency department showed possible left sigmoid sinus partial

occlusion. She was admitted and started on heparin infusion and ceftriaxone with good hydration plus amitriptyline, betahistine, cinnarizine, and heparin 5000 IU 6 hourly sc injections. Next day, MRI/MRV of brain was done and reported to be normal, but the platelet count dropped to 109/mm³, and GPT raised to 87 compared to normal result on baseline admission result; this supports stopping heparin therapy. On the third day afternoon, she was suffering from severe diffuse burning quality headache mainly on right temporo-occipital with severe central scalp scratching and pressing like pain last several hours and aborted only on pethidine intravenous injection. On the 4th day, lumbar puncture was done and the CSF was normal. The blood tests for CV, EBV, HIV, and H1N1 were also negative but serum dengue IgM was positive. A CSF sample for dengue IgM sent to private lab reported as positive. Throughout the 23 days admission period, the patient was almost afebrile but showed significant fatigue with bizarre headache appearing as persistent diffuse pressure like headache with attacks of severe bilateral temporo-parietal burning and central scratching pain associated with nausea, vomiting, dizziness, phonophobia, photophobia, anxiety, and near death phobia and bradycardia (40/60) that required many cardiology and psychiatry on call review. On the 22nd day, the patient was discharged after showing reduction of headache attacks severity and frequency with normal blood count and liver enzymes. Then patient was on weekly out-patient neurology clinic follow up for several months using amitriptyline, respridone, and tramadol on need. Then gradually and slowly, headache attacks diminished in frequency and severity, resolving completely about 3 months after onset.

DISCUSSION

Millions of Muslims living in dengue hyper-endemic areas come yearly to Makkah for Hajj, with the possibility of introduction of dengue viruses.^[11] Since 1994, Makkah province became a dengue endemic area with high rate of dengue infection during spring and early summer.^[12,13] The dengue infection in both cases was suspected on appearance of fever, headache, and low platelets count in dengue endemic area, which was strong evidence in large Brazilian study.^[14] Meningitis suspected and CSF study done in both cases due to the appearance of headache, fever, and neck rigidity. The dengue meningitis in both cases was confirmed by finding positive CSF IgM. Normal CSF cellularity in one case was not exclusion of meningitis as most dengue meningoencephalitis reported in large Brazilian study showed normal CSF cellularity.^[15] Both cases had low grade fever which resolved within several days without purpura, rash, or bleeding, suggesting associated DF syndrome rather

than dengue hemorrhagic one. Both cases had moderate to extremely painful migraine like headache with VAS score ranging between 6 and 10 [Figure 1]; first case showed headache similar to cluster headache with retroorbital pain, eye tearing, and blurring vision, while the second case showed similar to classic migraine with severe unilateral to bilateral temporo-parietal burning and central scratching pain associated with nausea, vomiting, dizziness, phonophobia, and photophobia. It was the initial and the most prominent symptom in both cases.^[16] Both cases showed unique relation to day time with terrifying sense of near death associated with crying, weeping, and fluctuating bouts of significant bradycardia and supraventricular tachycardia that was not reported before. The afternoon time (between 1 pm and 11 pm) was the time of extreme severe pain, phobia, and arrhythmia [Figure 2]. Both cases had normal cardiac enzymes and echocardiography that rule out rare reported dengue myocarditis.^[17] Both cases showed no to little respond to classic anti-migraine therapy with good respond to narcotic. Tramadol and NSAID were partially effective. Classic migraine abortive therapy like ergotamine and triptan was the worse therapy [Table 1]. This analgesic resistance was evident in few reported cases.^[18,19] Both cases prolonged course and associated severe headache, phobia, and arrhythmias may explain by what reported that dengue virus positive CSF may have higher risk for development of severe forms of dengue infection.^[20-22] Both cases recovered completely over several months without any residual neurological deficit [Table 2]. This benign course was shown on rarely reported dengue viral meningitis.^[23]

CONCLUSION

Our report demonstrates that in endemic areas meningitis can be the first manifestation of dengue infection. Dengue infection should be considered as a probable etiological agent of meningitis even in the absence of typical picture of the infection. Dengue meningitis

may present with migraine like headache that could not respond to classic anti-migraine therapy and may have poor respond to common analgesic. Dengue meningitis

Table 1: The effect of common anti-migraine therapy

Anti-migraine therapy	Case 1	Case 2
Narcotic	+++	+++
NSAID	+	++
Tramadol	++	+
Ergotamine	—	—
Triptan	—	—
Botulinum toxin	+	+
Tricyclic antidepressants	+	+
SSRI	-	-
Pregabalin	-	-
Topiramate	-	-
Beta blockers	—	-
Calcium blockers	—	-

+++ Good effect, ++ Some effect, + Little effect, - No effect, - Bad effect

Table 2: Characteristic clinical picture of each case

Clinical picture	Case 1	Case 2
Fever	+	+
Neck stiffness	+	+
Rash	-	-
Bleeding	-	-
Fatigue	-	+
Arthralgia / myalgia	+	++
Headache	+++	+++
Migraine like headache	+	+++
Cluster like headache	+++	+
Death phobia	++	+++
Anxiety	+	++
Depression	++	+
Supraventricular tachycardia	+++	+
Sinus bradycardia	+	+++
Slow recovery	+++	+++

+++ Severe, ++ Moderate, + Mild, - No

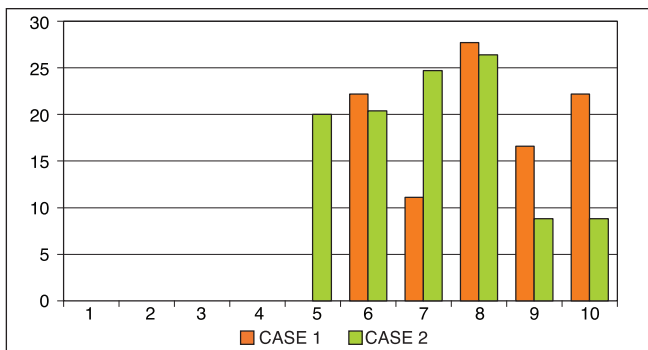


Figure 1: Headache was moderate to extremely painful (VAS score 6-10)

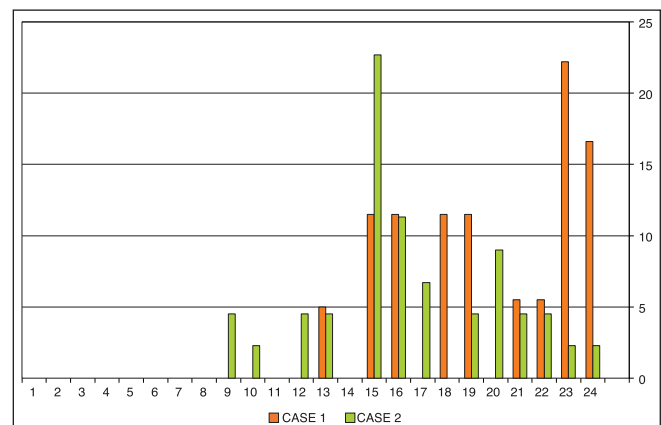


Figure 2: After noon time was the time of extreme severe pain, phobia, and arrhythmia

may be associated with behavior change, extreme anxiety, fear, and arrhythmia. Normal CSF cellularity should not exclude dengue meningitis. In appropriate clinical settings, detection of dengue IgM in serum and CSF may lead to correct diagnosis. CSF IgM positive cases may have a atypical, severe, and prolonged course.

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