Unusual presentation of more common disease/injury

Subdural haematoma and axonal polyneuropathy complicating dengue fever

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Correspondence to Dr Madhukar Mittal, mittalspace@gmail.com**Summary**

The authors report a case of dengue fever presenting with aseptic meningoencephalitis and developing subdural haematoma and pure motor quadriparesis due to axonal polyneuropathy. This 27-year-old female patient presented to us during the latter part of the dengue epidemic in India in 2010. She had mild thrombocytopaenia and subtle signs of capillary leak. Dengue-specific IgM antibody was positive. She presented initially with recurrent seizures. Initial CT scan of brain was normal with cerebrospinal fluid showing albuminocytologic dissociation. After 6 days, the patient developed quadriparesis with areflexia. MRI showed bilateral subdural haematoma with no evidence of spinal nerve root compression. The nerve conduction study showed evidence of axonal neuropathy. The patient's quadriparesis improved such that she was able to walk with support after 4 weeks with conservative management. This case report highlights a possible association between dengue and motor axonal neuropathy subtype of Guillain-Barré syndrome.

BACKGROUND

Worldwide, 50–100 million cases of dengue infection occur each year.^{1 2} Dengue fever occurs in tropical and subtropical areas of the world. According to the estimates by WHO, dengue alone costs India almost \$30 million every year² and is part of several western travel advisories on India. Cyclic epidemics are seen in India and cases of dengue generally start to increase from August onwards, which is the postmonsoon season and decrease as winter sets in.

Dengue is transmitted by the bite of the *Aedes* mosquito infected with any one of the four dengue virus serotypes. Infection by different serotypes offers no cross protection and epidemics caused by multiple serotypes can occur. Infection can be asymptomatic or present with symptoms ranging from fever, headache, retro-orbital pain, myalgias, arthralgias and rash to the potentially fatal form of dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). The spectrum of neurological disease in dengue is not very well elucidated. We present here a case of dengue fever with neurological involvement as the predominant manifestation.

CASE PRESENTATION

A 27-year-old woman was admitted in an unconscious state following multiple episodes of generalised tonic-clonic seizures over past 10 h. There was preceding history of high-grade fever with backache and myalgias for 7 days. Purpuric rashes or any other bleeding manifestations were absent. On examination, the patient was febrile and comatose with a Glasgow coma score (GCS) of 10. There were no signs of meningeal irritation. No cranial nerve involvement was seen. Cardiovascular and respiratory system examination did not reveal any abnormality.

Laboratory investigations showed a normal total leucocyte count and low platelet count (8200/mm³ and

100 000/mm³, respectively). Both smear and card test for antigen were negative for malaria. Serology for herpes simplex virus 1 and 2, Japanese encephalitis, *Salmonella typhi* and *S paratyphi* were all negative. However, dengue-specific IgM antibody by commercial micro-well enzyme immunoassay kit (IVD Research Inc, Carlsbad, California, USA) was positive. Blood sugar and serum electrolytes were normal. Serum aminotransferases were raised; however, prothrombin time and partial thromboplastin time were normal. Ultrasonography showed mild peritoneal and pleural fluid collection. Fundus examination and CT scan brain were normal. Total cell count of 10/mm³ (all lymphocytes) and protein content of 173.7 mg/dl were present on cerebrospinal fluid (CSF) examination.

Antiepileptic management was instituted in the form of intravenous infusion of phenytoin sodium followed by regular maintenance doses. Over a hospital stay of 3 days, the patient's consciousness improved and her GCS became 14. The patient was soon able to take oral feeds. However, she developed weakness of both lower limbs on day 6 which progressed to involve the upper limbs over next 24 h. Neurological examination revealed a power of 2/5 and 1/5 on Medical Research Council scale in upper and lower limbs, respectively. Weakness was accompanied with hypotonia, areflexia and non-elicitable plantar reflexes. Sensory system, cranial nerves and autonomic system function examination were all normal. The patient developed hypokalemia (table 1) which was corrected by giving oral potassium chloride; however, her quadriparesis persisted. We repeated her brain imaging (MRI brain including spine) which showed bilateral subdural haematoma not limited by suture lines over both cerebral hemispheres with focal petechial haemorrhage in left parietal region in subcortical white matter (figure 1). No significant compression over cord and nerve roots in

Figure 1 (A) Normal CT scan brain, (B) bilateral extra-axial concavo convex lesion, displaying hypointense on T1W image (arrow), (C) coronal section T2W FLAIR image showing focal haemorrhage in left parietal region subcortical white matter (arrow).

Figure 2 Normal MRI cervical spine.

cervical region was seen (figure 2). Neurosurgical opinion was taken and conservative management was advised. Nerve conduction study (NCS) included normal latencies, sensory nerve action potential and velocity in sensory NCS when checked in bilateral median, ulnar and sural nerve. Normal latencies, low compound muscle action potential and normal velocities were seen in the motor NCS (table 2); features suggestive of acute motor axonal polyneuropathy (AMAN).

Conservative management and general supportive care of the patient was continued. We could not offer plasma exchange to the patient, as the facility was not available in

our hospital and cost was a constraint for giving intravenous immunoglobulin. Corticosteroid therapy is of uncertain benefit for patients of Guillain-Barré syndrome (GBS) and was not given. No ventilatory support was required during the course of her illness. The patient showed a slow but gradual improvement in power (3/5 in upper limbs and 2/5 in lower limbs) over several days and was discharged on day 17. Weekly review of the patient on follow-up showed further improvement, with a power of 4/5 in upper limbs and 3/5 in lower limbs after 2 weeks and gradually the patient was able to walk with support over another 2 weeks.

INVESTIGATIONS

Table 1 Laboratory parameters

Parameters (Reference ranges)		Date: November 2010								
		11	12	14	16	17	21	22	23	24
Haematocrit (35–44% for female)		24.3			26.2					
Total WBC count (4000–11 500 cells/mm ³)		11 400			7790		7500			
Platelet count (1.5–4.5 lacs/mm ³)		1.0			0.59	1.56	2.98			
Random blood sugar (mg/dl)		121		60			156	136		152
S. Sodium (135–148 meq/l)		142	153	137			162	165	157	138
S. Potassium (3.5–5 meq/l)		3.4	2.9	4.8			2.6	2.7	4.3	5.1
S. Urea (15–43 mg %)		162		64						
S. Creatinine (0.6–1.2 mg %)		1.94		1.4						
PT (12–16 s)		14								
INR (0.8–1.2)		1.0								
aPTT (25–36 s)		30								
S. Bilirubin (0.5–1.2 mg/dl)			1.5	0.5						
SGPT (9–45 IU/l)			651	202						
CSF	Cells (<5/mm ³)	10								
	Protein (15–60 mg/dl)	173.2								
	Sugar (50–80 mg/dl)	162								
	ADA (<10U/l)	9.13								

ADA, adenosine deaminase; aPTT, activated partial thromboplastin time; CSF, cerebrospinal fluid; INR, International Normalised Ratio; PT, prothrombin time; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cell.

Table 2 Nerve conduction and EMG study with reference ranges

Nerves		Latencies (ms)		Peak amplitude (μV)		Velocities (m/s)			
		Patient	Reference	Patient	Reference	Patient	Reference		
Sensory NCV	Left median	3.1	<3.5	15.6	15	52.5	>50		
	Right median	3.2		17.2		55.1			
	Left ulnar	3.1		17.9	17	51			
	Right ulnar	3.4		20.9		62.3			
	Right sural	3.1		19.2		64.2			
Motor NCV	Left median	4.15	<4.4	3.6	≥4	46.3	≥44		
	Right median	3.65		3.9		48.2			
	Left ulnar	2.9	<3.3	2.9	≥6	42.8	≥45		
	Right ulnar	3.5		2.6		41.3			
	Left common peroneal	3.5	<6.5	3.5	≥2	38.3	≥40		
	Left tibial	4.75	<5.8	2.4	≥4	40.1	≥40		
EMG		Summary table							
	Spontaneous					MUAP			Recruitment
	IA	Fib	PSW	Fasc	HF	Amp	Dur	PPP	Pattern
L. Quadriceps	N	None	None	None	None	N	1+	1+	Reduced
L. Tib. Ant.	N	None	None	None	None	N	N	1+	Reduced
R. Brachioradialis	N	None	None	None	None	N	N	N	Reduced
Impression	Neuropathic pattern								

Amp, amplitude; Dur, duration; EMG, Electromyography; Fib, fibrillation; HF, high frequency potentials for myotonia and paramyotonia; IA, insertional activity; MUAP, motor unit action potential; NCV, nerve conduction velocity; PPP, poly phasic potential; PSW, positive sharp waves.

TREATMENT

Conservative management and general supportive care of the patient was continued. We could not offer plasma exchange to the patient as the facility was not available in our hospital and cost was a constraint for giving intravenous immunoglobulin. Corticosteroid therapy is of uncertain benefit for patients of GBS and was not given.

OUTCOME AND FOLLOW-UP

No ventilatory support was required during the course of her illness. The patient showed a slow but gradual

improvement in power (3/5 in upper limbs and 2/5 in lower limbs) over several days and was discharged on day 17. Weekly review of the patient on follow-up showed further improvement, with a power of 4/5 in upper limbs and 3/5 in lower limbs after 2 weeks and gradually the patient was able to walk with support over another 2 weeks.

DISCUSSION

Neurological manifestations were first reported in 1976 as atypical manifestations in dengue infection.³ The frequency of central nervous system involvement in dengue fever remains largely unknown. So far, the incidence of

neurological manifestations in patients with dengue fever has been reported to vary from 3% to 25% in different studies.⁴

A wide array of neurological manifestations such as headache, seizures, altered sensorium and behavioural disturbances as part of encephalitis or aseptic meningitis, in patients with dengue infection have been described. The CSF picture in our patient had elevated protein with normal sugar levels. She presented with seizures which responded to first-line antiepileptic treatment.

Isolated cases of mononeuropathy,⁵ polyneuropathy including GBS,^{6 7} myelitis,⁸ intracranial thrombosis and haemorrhage^{9 10} have been reported. Electrophysiologically, demyelinating, axonal and mixed forms of GBS are known with demyelinating pattern as the most common form. Besides GBS, other causes reported for quadriparesis in dengue fever patients are myositis¹¹ and hypokalemia.¹² Bleeding into segmental nerves can lead to manifestations; however, our patient had symmetrical quadriparesis and MRI spine focussing on cervical segment was normal.

Our patient presented with fever, seizures and loss of consciousness followed by axonal polyneuropathy (possibly AMAN type of GBS as suggested by NCS) and quadriparesis. Since the patient was residing in a dengue endemic area and her clinical presentation and lab investigations (mild thrombocytopaenia and evidence of capillary leakage in the form of small peritoneal and pleural fluid collection and subdural haematoma) suggested a clinical picture of dengue fever, the patient's blood was tested for IgM antibodies against dengue virus. A positive serology confirmed infection by dengue virus. We could not perform quantitative testing for the dengue antibody titres. Screening MRI for whole spine with particularly focus on cervical segment was normal. Collective features such as acute onset, areflexic, ascending and symmetric pattern of paralysis without bladder, bowel and sensory involvement suggested GBS. AMAN subgroup was distinguished by electrodiagnostic study results that are consistent with a pure motor axonopathy. However, antibodies to gangliosides (like anti-GM1 antibodies) were not done.

The most severe well known forms of dengue infection are DHF and DSS. Prior infection with heterogeneous serotypes and production of non-protective antiviral antibodies that bind to Fc receptor of macrophages and monocytes may have an antibody dependent enhancement phenomenon.¹³ It results in increased cytokine production and activation of complement system, leading to increased vascular permeability, capillary fragility and thrombocytopenia and ultimately contributes to mortality. However, neurological manifestations of dengue entail greater morbidity. Whether neurological disease in dengue now being increasingly recognised is because of increased awareness for the disease or is part of new virological strains is a matter of speculation and further research. Dengue serotype

3 was the predominant serotype in a report from India in 2005.¹⁴

In this report, we describe a patient of dengue fever with mild thrombocytopaenia and involvement of both central as well as peripheral nervous system as the predominant presentation for the disease. Axonal polyneuropathy could possibly be associated with dengue as in this case. A high index of suspicion needs to be maintained in patients with short duration of febrile illness with atypical neurological manifestations especially in areas of endemicity for the disease.

Learning points

- Aseptic meningoencephalitis as a presentation for dengue fever.
- Subtle manifestations of capillary leak (small peritoneal and pleural fluid collection with or without subdural haematoma) as a pointer towards dengue.
- Quadriparesis in dengue due to motor axonal neuropathy type of GBS.

Competing interests None.

Patient consent Obtained.

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