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IMAGING HIGHLIGHT

Dengue haemorrhagic encephalitis: Report of a child from Myanmar with bilateral thalamic involvement

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INTRODUCTION

Dengue viruses are single-stranded RNA viruses of the *Flavivirus* genus. It is a common viral infection worldwide, especially in tropical regions. Various neurological manifestations such as encephalitis, encephalopathy, meningitis, acute disseminated encephalomyelitis (ADEM) acute viral myositis, Guillain–Barré syndrome and others are increasingly reported. However, acute haemorrhagic encephalitis is a very rare presentation. Currently, there are only few previous case reports.[1-4]

CASE REPORT

This was a 11 year old girl who presented with five days fever and altered sensorium for two days. She had a few episodes of generalized clonic seizures occurred on the fifth day. On presentation, she was drowsy with language difficulty but attempted to say few words which were slurred. The eyes opened to command and there was withdrawal response to pain stimuli. Pupils were equal and reactive to light with no opthalmoplegia. Apart from mild facial diplegia with swallowing difficulties, there was no other cranial nerves abnormalities and no meningism. She was tetraparetic. Liver was palpable at 2cm below the right costal margin. No other systemic manifestations were seen, with some petechial rash over trunk and limbs. She was initially treated as meningoencephalitis, and was given antibiotics and other supportive management. Her conscious level deteriorated to Glasgow Coma Scale score of 3/15 on third day of admission and was intubated for 17 days for respiratory support.

Full blood count showed thrombocytopenia, lowest at 37x 10^9/L on the admission at fifth day of fever, and leucopenia (WBC 2.6 x10^9/L with neutrophil of 32% and lymphocyte 47%), which started to improve on day-7 of illness (Table 1). C-reactive protein, electrolytes, and liver function tests were within normal limit. Coagulation profile were slightly deranged (PT 34 seconds and INR 3) on Day 2 admission and back to normal on Day 4 after receiving few units of blood products. Dengue non-structural protein 1(NS1) antigen test was positive in serum on admission. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis (lymphocytes 58 cells/cmm) with elevated protein (260 mg/dl) and normal sugar (63mg/dl). Serum IgG/IgM antibodies and CSF PCR for dengue virus were positive.

There was no evidence of systemic causes of encephalopathy such as acute liver failure, hypovolemic shock, and metabolic derangements. CSF and blood PCR for herpes simplex, varicella zoster and Japanese B encephalitis were negative. Tests for malarial parasites, Salmonella and leptospira were also negative.

CT scan of the brain on day 5 of illness (Figure 1) showed ill-defined symmetrical non-enhancing hypodensities in both thalami and pons. Magnetic resonance imaging (MRI) on 4th week of illness (Figure 2, 3) showed findings similar to the initial CT. The lesions in bilateral thalami and pons were hyperintense on T1WI, hyperintense with hypointense rim on T2WI and FLAIR images. On SWI images, the lesions

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Table 1. Investigations of the patient

	Day 2	Day 5 fever (On admission)	Day 7	Day 11	Day 15	Day 22
Hb(g/L)	12.5	13.5	10.6	11.5	11.9	12.6
WBC(10^9/L)	4.7	2.6	3.5	5.5	6.7	9.5
Platelets(10^9/L)	95	37	66	83	90	132
CRP	8	10	6		6.5	
Urea(mmol/L)		5.1		5.8		
Creatinine(mmol/L)		56		55		
ALT(mmol/L)		43	45		38	
PT(sec)			34	10		
INR			3	1.2		
Na(mmol/L)		135	138	137		140
K(mmol/L)		4	3.8	3.7		4,4

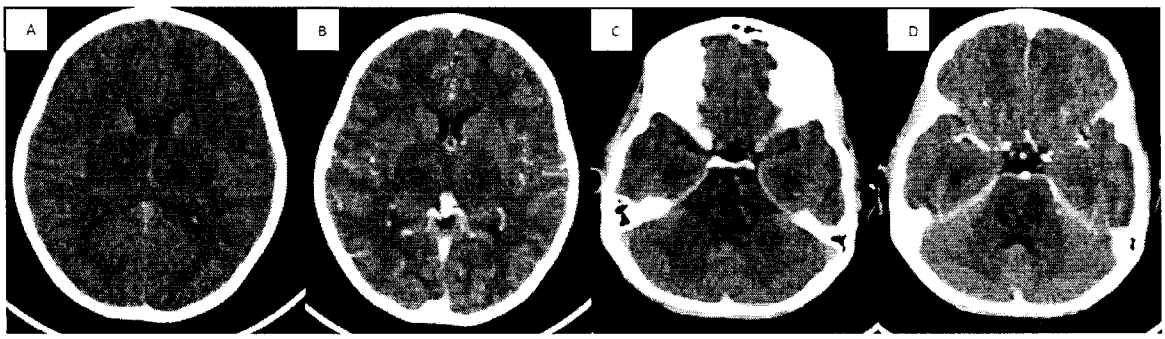

Figure 1. CT on Day 5th of illness showed ill-defined symmetrical non-enhancing hypodensities in both thalami and pons (A, B, C and D)

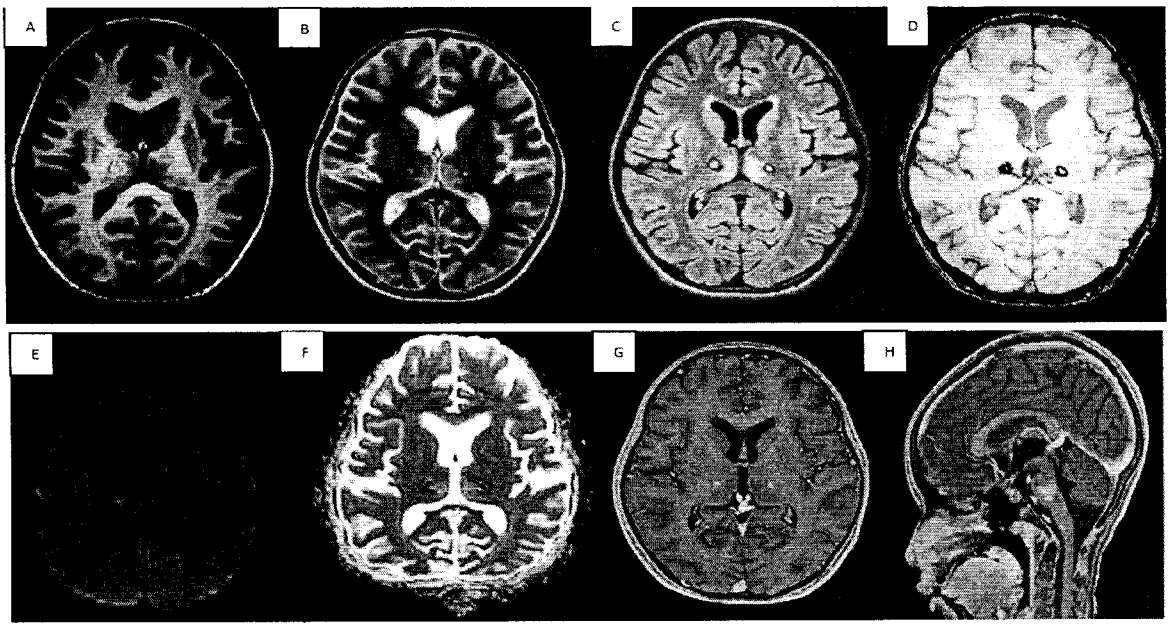

Figure 2. Contrast enhanced MRI brain performed at 4th week of illness (A, B, C,D) showed lesions in both thalami which were hyperintense on T1WI (A), hyperintense lesion with hypointense rim on T2WI(B) and FLAIR(C) . SWI image (D) demonstrated signal drop due to blooming effect, suggestive of hemorrhage. Intense restricted diffusion was seen on DWI and ADC map (E,F). T1 contrast showed no evidence of cerebral venous sinus thrombosis (G,H)

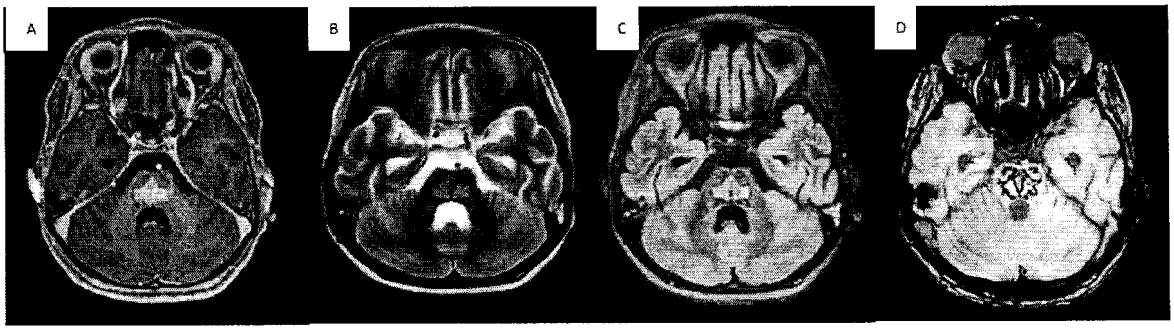

Figure 3. Contrast enhanced MRI brain performed at 4th week of illness showed hyperintense pontine lesion in Axial T1, T2, FLAIR images (A,B,C), signal drop with blooming effect on SWI images (D) .

demonstrated signal drop with blooming effect in keeping with haemorrhage in both thalami and pons. The centre of the lesions showed intense diffusion restriction on DWI and ADC map. T1 contrast images showed no evidence of cerebral venous sinus thrombosis.

Her conscious level gradually improved with supportive treatment over the next two weeks. However; there were some neurological sequelae with limb muscle weakness (GMC grade 3/5), dystonia, tremors and slurred speech. After 3 months, the dystonia and tremors reduced significantly; she spoke more clearly and could walk with support.

DISCUSSION

We believe that our patient has dengue encephalitis. She had an acute febrile illness with hepatomegaly, petechial rash, thrombocytopenia, leucopenia, positive dengue IgG and IgM, NS1 antigen and PCR in the serum all indicating a systemic dengue infection. There was signs of acute cerebral involvement with altered consciousness or personality and seizures, supported by abnormalities of CT and MRI brain. The positive dengue PCR in CSF provide a direct evidence of viral invasion of central nervous system. We could not find any other causes of encephalitis and encephalopathy.

Among the 4 dengue viruses, neurological manifestations are mainly associated with dengue virus type - 2 or 3.[5] Incidence of neurological manifestations occurs in 0.5-6.2% of patients and pathogenesis is still poorly understood. [6]

MRI brain in dengue encephalitis may be normal or show non-specific cerebral oedema.[7] Some cases of dengue encephalitis show features similar to Japanese encephalitis in the form of common involvement of thalami, basal ganglia and brainstem. Similar findings were also reported in other viral encephalitis like influenza A or west nile virus encephalitis.[8,9] Bhoi *et al.* found 9/21 (43%) dengue cases with MRI abnormalities, one third of whom (three patients) had bilateral thalamic lesions.[3] Bilateral thalamic changes were also reported in other dengue case reports.[1,4,10-12] Our case is similar to that by Basir Ahmad *et al.*[1] and Borawake *et el.*[10] , for the bilateral hemorrhagic thalamic involvement.

There were three other paediatric case reports of dengue haemorrhagic encephalitis from India.[13,14] The clinical presentations are quite similar, however; our case has more extensive brain involvement with extensive haemorrhage. Dengue related endothelial dysfunction, thrombocytopenia, platelet dysfunction, and mild coagulopathy may contribute to haemorrhages in the encephalitis.

This is the report of a dengue hemorrhagic encephalitis, highlighting the involvement of both thalamus.

DISCLOSURE

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Conflicts of interest: None

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Poster #93

Etiology and clinical profiles of pediatric encephalitis in Myanmar: A prospective study

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Introduction

- Encephalitis is a clinical syndrome of brain parenchyma inflammation with neurologic dysfunction, which can cause significant long-term morbidity and mortality [1,2].
- Epidemiological studies suggest that 3.2-10.5 pediatric hospitalizations per 100,000 are due to encephalitis [1,3,4].
- A conclusive etiology has remained unidentified for many patients with encephalitis [4-6].
- Non-infectious encephalitis can present with signs and symptoms similar to infectious etiologies with predominant psychiatric, cognitive, and movement disorder symptoms [7,8].
- Encephalitis is most prevalent in South Asia and Southeast Asia, however, there are very few prospective studies of encephalitis performed in Southeast Asian (SEA) countries [9-13].
- Objectives: (1) Prospectively identify presumed infectious and autoimmune encephalitis using clinical criteria in a resource-limited setting; (2) Evaluate impact of advanced technology (FilmArray multiplex PCR, cell-based autoantibody testing) on diagnosis and prognosis; (3) Identify co-prevalence of NMDA-receptor-positive status and viral infection in patients with encephalitis.

Methods

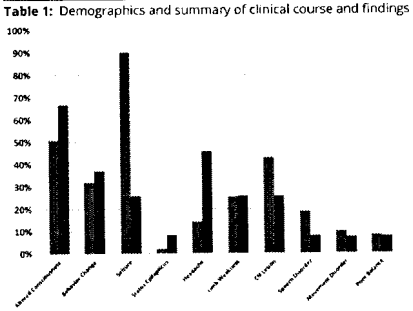
- Prospectively recruited pediatric patients with meningoencephalitis from September 2016 to December 2017 who were admitted to a tertiary care pediatric hospital in Yangon Myanmar, using 2013 International Encephalitis Consortium Consensus criteria [2].
- Defined Tuberculosis meningoencephalitis according to the 2010 International Tuberculous Meningitis Workshop Consensus Case Definition [14] in children who also fulfilled the criteria for encephalitis.
- Cases of autoimmune encephalitis were defined solely by criteria established by Graus, et al, in 2016 [15]. Antibody testing was performed by Euroimmun.
- A second cohort of patients was recruited from late December 2017 through August 2018 using the above criteria, with addition of BioFire FilmArray PCR to testing regimen to assist with identification of pathogen.
- Cases of autoimmune encephalitis were identified as above, with additional criteria of negative viral multiplex PCR (or in two cases, negative targted JE virus PCR).

Results

- Of 97 patients with encephalitis, 24 cases were excluded because of the overlapping clinical data with South East Asian Encephalitis project.
- Diagnoses were classified into probable (43), and possible (15) encephalitis.
- Only 12 (22%) cases had likely etiology, including Japanese encephalitis (2), tuberculosis (8), varicella zoster (1), herpes simplex (1).
- Head CT studies were performed in 47 patients, of which 30 were abnormal.
- Probable encephalitis was associated with higher rates of morbidity (modified Rankin scale average 1.7 vs. 1.3) and mortality (11% vs. 0%) compared to possible encephalitis but the results were not statistically significant.
- CSF autoimmune encephalitis panel was performed in 11 children from the first cohort presenting with psychiatric symptoms, seizures or movement disorders and 5 (45%) had positive NMDAR antibodies (Table 2). Of these, two patients had co-infection with JE virus.
- Of the 11 children evaluated for autoimmune encephalitis, 10 patients were treated with either IV methylprednisolone, IV immunoglobulin, or both, with all treatment regimens leading to clinical improvement (Table 3).
- Availability of multiplex PCR increased diagnostic yield of presumed infectious cases (3% vs. 25%, p 0.0005). There was no similar improvement noted in diagnostic yield of presumed autoimmune cases (44% vs. 42%).
- Rates of antibody detection for autoimmune encephalitis cases were similar to rates in American populations (48%), however NMDA-R antibodies were more prevalent in our series [16]
- Pathogenic etiologies identified with FilmArray included HSV, Enterovirus, H. influenzae, and CMV.

	Probable Encephalitis	Possible Encephalitis	Difference	P-value
Demographics				
Male	21(49%)	8(53%)	4%	0.76
Age, median months (range)	0.8 (0.2-9)	2.6 (0.4-12)		
Clinical Data				
Delay to Presentation, Median Days (Range)	7 (1-56)	7 (1-19)		
ICU admission	9(20.9%)	2 (13.3%)	7.6%	0.52
Concurrent Symptoms				
Fever	40 (93%)	11 (73.3%)	19.7%	0.04
Diarrhea	6(14%)	4 (26.7%)	12.7%	0.26
Rash	3 (7.0%)	0 (0%)	7%	0.56
Seizure	40 (93%)	5 (33.3%)	59.7%	< 0.0001
Initial neuroimaging abnormal	26 (72.2%)	4 (36.4%)	35.8%	0.03
Death	5 (11.6%)	0 (0%)	11.6%	0.167
Modified Rankin Score, Average (Range)	1.7 (0-5)	1.3 (0-3)	0.4	0.49

Table 1: Demographics and summary of clinical course and findings of initial patient cohort.



Key Point, Table 1: In a cohort of patients evaluated without availability of viral multiplex PCR, fever, seizure, and abnormal initial imaging are significantly more prominent in patients diagnosed with probable encephalitis than in those diagnosed with possible encephalitis.

Key Point, Figure 1: Seizure is the most useful clinical sign for differentiating cases of probable from possible encephalitis. Status epilepticus, CN lesions, movement disorders, and poor balance also trended toward being more prominent in probable encephalitis.

Figure 1: Clinical profiles between probable and possible encephalitis

Key Point, Table 2: Patients evaluated for autoimmune encephalitis frequently had psychiatric symptoms, behavioral symptoms, speech disorders, and movement disorders. Nearly half of all patients selected for this testing were positive for anti-NMDAR antibodies.

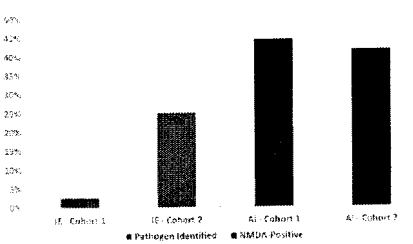
Characteristics	Distribution	
Sex	Male (9, 81.8%)	Female (2, 18.2%)
Age, Median (Range)	8(2 - 12)	
Seizure	Yes (6, 54.5%)	No (5, 45.5 %)
Psychiatric symptom	Yes (11, 100%)	No (0)
Behavior symptom	Yes(10, 90.9%)	No (1,9.1)
Altered consciousness	Yes (11, 100%)	No (0)
Visual symptom	Yes(0)	No (11, 100%)
Speech disorder	Yes (11, 100%)	No (0)
Movement disorder	Yes (9, 81.8%)	No (2, 18.2 %)
Fever	Yes (6, 54.5%)	No (5, 45.5%)
CN lesion	Yes (1, 9.1%)	No (10, 90.9%)
Weakness	Yes (5, 45.5%)	No(6, 54.5%)
Abnormal Reflexes	Yes (7, 63.6%)	No (4, 36.4%)
Status epilepticus	Yes (4, 36.4%)	No (7, 63.6%)
Mortality	Yes (1, 9.1%)	No (10, 90.9%)
CT (n=11)	Normal (7, 63.6%)	Abnormal (4, 36.4%)
MRI(n=4)	Normal (1, 25%)	Abnormal (3, 75%)
Anti-NMDAR Antibody (n=9)	Positive (4, 44.4%)	Negative (55.6%)

Table 2: Demographics, clinical course, and findings for patients evaluated for autoimmune encephalitis.

Key Point, Table 3: Both IVMP and IVIG provided successful outcomes among patients with clinically-suspected autoimmune encephalitis.

	Steroid	IVIG	Steroid+IVIG
Treatment	16	2	3
Outcome	15 (93.8%) Improved	2 (100%) Improved	0 (0%) Improved

Table 3. Comparison of treatment modalities among patients evaluated for autoimmune encephalitis (cohort 1 and cohort 2).



Key Point, Figure 2: Percentage of cases of presumed infectious encephalitis with identified pathogen increased significantly with addition of viral multiplex PCR. Known absence of pathogenic agent (negative FilmArray) did not improve detection of autoimmune cases over clinical criteria alone.

Figure 2: Comparison of diagnostic yield between cohort 1 (no viral multiplex available) and cohort 2 (viral multiplex available) in cases of presumed infectious encephalitis (IE) and autoimmune encephalitis (AI).

Conclusions

- Encephalitis is very common in Myanmar.
- Etiology is identified in only a small percentage of the cases.
- Clinical characteristics may help guide management in resource-limited nations.
- NMDAR encephalitis is positive in almost 50% of tested cases. Inclusion of advanced testing to evaluate for pathogenic etiologies did not improve antibody detection rate over clinical acumen alone.
- Viral Infection, specifically JE virus, may be a pathologic trigger for NMDAR encephalitis.
- Comprehensive testing using advanced research techniques to identify pathogen and antibodies may increase our understanding of interaction between viruses and host immune system.

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