Acute Necrotizing Encephalopathy (ANE) is a distinct clinicoradiological syndrome in Dengue virus encephalitis

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INTRODUCTION

- Reports of dengue virus encephalitis describe a febrile encephalopathy with bilateral haemorrhagic thalamic and brainstem involvement on neuroimaging, closely resembling the clinicoradiological syndrome of acute necrotizing encephalopathy (ANE). [1]
- The bilaminar haemorrhagic thalamic lesions have been variously termed a “double doughnut” sign or ring lesions. [1,2]
- Dengue virus infections are characterized by high fever with rash and lethargy, followed by a sudden deterioration with multiorgan involvement (often with encephalopathy) on days 4-5 of illness. This deterioration involves a cytokine storm. [1,3]
- ANE is characterized by a rapid deterioration with encephalopathy and multiorgan failure occurring early in a febrile viral illness (typically from respiratory viruses, e.g. influenza virus). ANE has a complex pathobiology and a cytokine storm is a key feature. [4,5]

METHODS

- Systematic review of paediatric and adult literature on dengue encephalitis was curated for clinical, laboratory, radiological and outcome data.
- ANE diagnostic criteria was applied: Acute febrile encephalopathy, characteristic neuroimaging, elevated cerebrospinal fluid protein, no evidence of an alternative diagnosis. [4]
- Dengue encephalitis diagnosis was based on established criteria. [6]
- “Classical” ANE neuroimaging were bilateral thalamus + pons/cerebellum involvement +/- cerebral white matter lesions, with haemorrhage. [5]
- *Forme fruste* patterns were deemed “ANE Compatible”, but bilateral thalamic lesions were a mandatory requirement
- ANE severity scoring (ANE-ss) [7] was applied and compared against outcomes.

RESULTS

- Data on 127 patients (median age 21 (range 0.4-85 years)) met inclusion criteria and were extracted from 81 articles; 53 (42%) were children ≤18 years.
- Demographics, clinical features and cerebrospinal fluid (CSF) parameters were generally similar between ANE and other encephalitis syndromes. Key clinical features were fever (94%), thrombocytopenia (69%), seizures (46%) and abnormal motor signs (49%).
- Patients with ANE were notable for an early onset of disease (Figure 1) and for poorer outcomes: 42% death/moderate-severe disability in ANE versus 13% in other encephalitis (p<0.01) (Figure 2).
- In ANE, median CSF white blood cells was 12/mm^3 (0-300) and 20 (43%) had Dengue virus IgM or PCR positivity in CSF.
- “Classic“ ANE neuroimaging was seen in 26 (57%) of ANE. “ANE Compatible” patients had lower ANE severity score (ANE-ss) and were more likely to have meningism or seizures, as compared to Classic ANE (Table 1).
- A Higher ANE-ss correlated well with poor outcome. (Table 2)

Figure 2: Outcomes in Dengue virus Clinicoradiological Encephalitis Syndromes

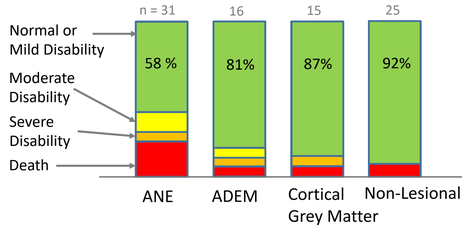

Table 2. ANE-ss and Outcomes in Dengue virus ANE

	Low risk (0-1)	Moderate risk (2-4)	High risk (5-9)	Unable to score ANE-ss
n	-	10	25	11
Normal outcome, or mild disability	-	7 (70%)	9 (36%)	2 (18%)
Moderate disability	-	2 (20%)	2 (8%)	
Severe disability or death	-	0	8 (32%)	1 (9%)
No follow up	-	1 (10%)	6	8 (72%)

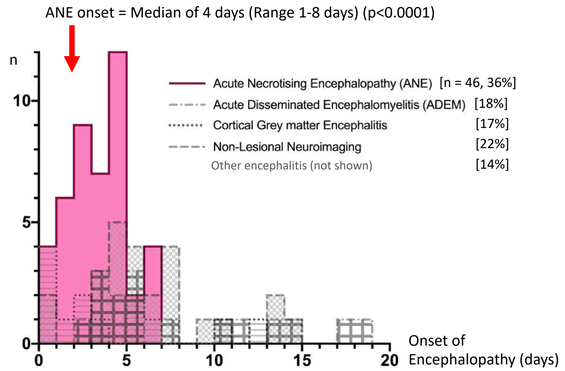

Figure 1: Clinicoradiological Syndromes in Dengue Virus Encephalitis

Table 1. Patients with “Classic” ANE and “ANE Compatible” Neuroimaging.

	“Classical” ANE	ANE Compatible	p value	OR (95% CI)
n	26	20		
Median Age, years (Range)	22 (2.5 - 58)	18 (5 -55)	NS	NS = not significant
Male: Female ratio	1: 0.73	1: 0.67	NS	
Clinical Features				
Median ANE-ss	6 (3-9)	4 (2-7)	0.0047	
Median Days, Onset of encephalopathy (Range)	5 (1-7)	3 (1-8)	NS	
Low Platelets (<100,000/mm^3)	21	14	NS	
Hypotension	3	5	NS	
Elevated liver enzymes	15	8	NS	
Meningism	1	6	0.0326	10.71 (1.36 - 126.9)
Seizures	9	16	0.003	7.56 (1.79 - 24.52)
Status epilepticus	2	3	NS	
Pyramidal signs	11	10	NS	
Extrapyramidal signs	1	5	NS	
Cranial nerve or brainstem signs	6	3	NS	
Ataxia	5	2	NS	
Imaging and Laboratory data				
Pons involvement	21	7	0.0016	9.75 (2.52 - 32.58)
CSF white cell count	14 (0-113)	10 (0-300)	NS	
CSF protein level	0.81 (0.22-4.8)	0.80 (0.3- 2.65)	NS	
CSF Dengue positivity	12	8	NS	
Treatment and Outcome				
Immunotherapy	3	3	NS	
Moderate to Severe Disability, or Death	9 of 17 (53%)	4 of 14 (29%)	NS	

SIGNIFICANCE OF FINDINGS

- We confirm that the clinicoradiological syndrome of ANE is present in Dengue virus infection.
- The pathobiology of Dengue virus ANE appears to be different to respiratory virus-related ANE (typically a cytokine storm induced encephalopathy) as there is clear evidence of an Encephalitis process.
- The majority of Dengue virus ANE patients have CSF pleocytosis and the demonstration of Dengue virus in the CSF.
- ANE-ss mirrored outcome prediction in respiratory virus-related ANE: 78% with a normal or a mild disability outcome in Medium-risk patients whilst all deaths (100%) were only seen in patients with High-risk scores.
- ANE with CSF pleocytosis should be recognized as a distinct form of ANE.
- The role of Immunotherapy (IV steroids, tocilizumab) or Therapeutic Hypothermia (common treatment strategies in respiratory virus-related ANE) has not been evaluated in Dengue virus ANE.

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