VOLUME - 11, ISSUE - 04, APRIL - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Paediatrics

ACUTE NECROTISING ENCEPHALOPATHY OF CHILDHOOD ASSOCIATED WITH DENGUE: A CASE REPORT IN A TERTIARY CARE CENTRE, KOLKATA, INDIA.

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ABSTRACT Acute Necrotising Encephalopathy of Childhood (ANEC) is a rare clinico-radiological entity leading to acute onset febrile encephalopathy with rapid progression, caused by para-infectious trigger, mainly viruses including influenza, human herpes virus-6, parainfluenza etc. It is associated with poor outcome. Dengue is a common arboviral infection classically presenting with fever, arthralgia, headache, rash, bleeding manifestations and features of capillary leak. Expanded dengue can involve almost all the systems. Neurological complications are uncommon in dengue, encephalopathy being the most common. ANEC due to Dengue is extremely rare. The rarity of ANEC in association with dengue and relatively good neurological recovery with supportive treatment made us to report this case. This case also aim to raise awareness about this fatal complication of dengue infection as dengue is a global health care problem.

KEYWORDS : Acute necrotizing encephalopathy of childhood (ANEC), Dengue, Acute necrotizing encephalopathy (ANE)

The Case:-

A previously healthy 14 year old girl child presented to the emergency department of a tertiary care centre, Kolkata, with history of fever for last 5 days along with altered sensorium and one episode of convulsion 12 hours back.She was having respiratory distress with copious secretion and dribbling of saliva and two episodes of haematemesis before admission.On arrival, the child was drowsy, encephalopathic with Glasgow Coma Score of 7/15 (E2,V1,M4), with respiratory rate 24 breadth per minute, pulse rate 94 beats per minute, blood pressure 96/60 mmHg.Rest of the examination was unremarkable.She was already diagnosed positive for Dengue NS1 before admission.

On admission child was started on IV fluids, inj Levetiracitam, inj Pantoprazole, inj Ceftriaxone, inj Acyclovir and inj 3% NaCl at 25 ml/hr. She was ventilated as she was not maintaining her airways and intensive neuro-protection was started. Routine blood reports were unremarkable except slightly raised liver enzymes and low albumin. Inflammatory markers were not raised.

CT scan brain done outside showed features of raised intracranial tension with hypoechoeic areas seen around midbrain and brainstem with bilateral thalamic involvement suggesting features of encephalitis (Figure1). MRI brain showed bilateral symmetrical areas of extensive edema and swelling showing abnormal signal intensity in both thalami, midbrain, pons, dentate nuclei, bilateral cerebellar hemisphere, bilateral internal/external capsule, bilateral centrum semiovale and periventricular white matter suggestive of acute necrotising encephalopathy(ANE).The lesions showed diffusion restriction and no contrast enhancement. There was also foci of blooming in the T1 hyperintense center of thalami, pons and right frontal white matter, GRE sequence – consistent with sub-acute haemorrhage. There was also evidence of mild tonsilar herniation compressing the medulla implying impending conning (Figure 2). Intensive neuro-protection was continued. She was also treated with IVIG 2gm/kg and Dexamethasone. A repeat CT scan brain done 4 days later showed some improvement of the oedema and tonsilar herniation. We could not do a lumbar puncture because of the extremely raised ICT. EEG on Day 5 showed background slowing suggestive of encephalopathy but no epileptic activity. Sedation was tapered gradually and she started waking up. However, there were significant motor deficits and she remained somewhat drowsy. She was finally extubated on Day13. Her neurological status continued to slowly improve. On the day of discharge, she could protrude her tongue on command, eyes follow and track the hand movements, mild muscle flickering movements were present on left foot, and in the right side. She was maintaining stable vitals, having few lip-smacking like involuntary movements. Cough & gag reflexes were intact.

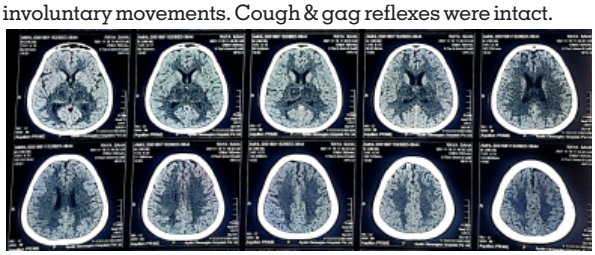

Fig 1:- NCCT brain showing hypoechoic areas around midbrain & brainstem

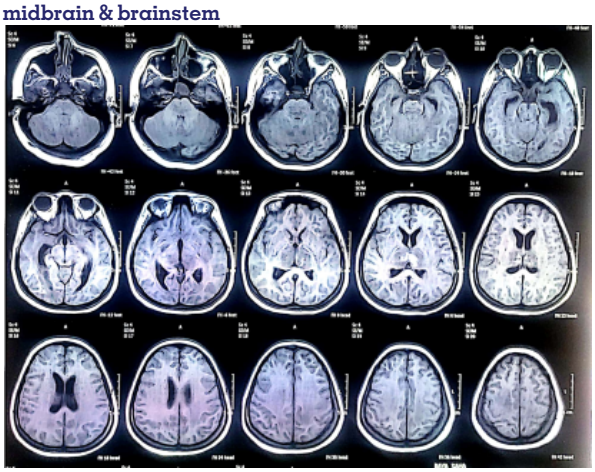

Fig 2:-T1 hyperintense centre in thalami, pons & right frontal lobe

The child had two episodes of significant gastro-intestinal bleed which was managed successfully with pantoprazole infusion, sucralfate and cold saline lavage. Due to persistent non tolerance of nasogastric feeds, child was started on nasojejunal feed with nasojejunal Frekka tube which was

inserted under fluoroscopic guidance. Subsequently, she did tolerate full nasogastric feeds. She had one episode of sepsis with Klebsiella grown from both blood and endotracheal tube which was treated successfully. Her blood Beta D Glucan was strongly positive for which she was treated with Amphotericin B lipid complex in view of persistent fever, although she never grew any fungus.

We subsequently checked her Dengue antibody which was positive for IgM, confirming the diagnosis of Dengue. Her lowest Platelet count was 66000/μL of blood which improved subsequently. She never manifested any sign of fluid leak.

On her last follow up,she was able to move all her limbs, she obeys simple commands and started speaking. However, she remains chair bound.

DISCUSSION:-

Acute necrotizing encephalopathy of childhood (ANEC) was first described by Mizuguchi *et al*. in 1995.A rare clinico-radiological entity with rapid progression and poor outcome, predominantly seen in children. Imaging finding usually shows bilateral, symmetrical necrotic lesion of thalami and other brain regions.[1] Globally more common in East Asian countries including Japan and Taiwan.[2]However sporadic cases have been reported from all around the world. It is triggered by various prodromal viral infections, most common being influenza, parainfluenza, human herpes virus-6.[3]Along with radiological findings, most common clinical presentations are fever, rapid alteration in the level of consciousness, seizures. The diagnosis of ANEC was determined by specific diagnostic criteria as described by Mizuguchi[4] which consist of (a) Encephalopathy preceded by viral febrile illness with rapid deterioration in the level of consciousness and convulsions. (b) Absent cerebrospinal fluid (CSF) pleocytosis. (c) Symmetric multifocal brain lesions. (d) Elevation in serum aminotransferase levels. (e) Exclusion of similar diseases.[4]

Dengue, an arboviral disease, is the second most common mosquito-borne illness affecting humans.[5] It can affect multiple organ systems. However, neurological complications are rare and include dengue encephalopathy, encephalitis, immune complex-mediated syndromes, and dengue muscle dysfunction. [6,7] Although CNS involvement with dengue infection has been well described, the types of brain lesions we observed in our patient is very rare.

Literature on ANEC in association with dengue is extremely limited. A case was reported in Pakistan in September 2017 who developed ANEC secondary to Dengue with classical clinico-radiological findings and unfortunately did not survive.[8]

In India, another case was reported from PGIMER Chandigarh in September 2020, where a 6 year old male child was diagnosed as a case of ANEC associated with Dengue infection who recovered with good prognosis.[9] Besides these two, we could not find any other similar case report.

The exact etiology of ANEC is yet to be determined. The most commonly accepted hypothesis regarding it's pathogenesis is hypercytokinemia with elevated level of TNFα, INFγ, IL1, IL2, IL6, IL8, IL10, IL13, IL18, TGFβ, C3a, C4b, C5a, MCP1, CCL2, VEGF, NO.[10] This hypercytokinemia ("cytokine storm") can eventually lead to multi-organ dysfunction as observed in our patient.

The treatment of ANEC is not well-established and remains controversial. The commonly used modalities include steroids, intravenous immunoglobulins (IVIG) and plasmapheresis.[9] Some studies have shown the beneficial role of antiviral agents such as Amantadine and Oseltamivir along with methylprednisolone pulse doses and IVIG.[11] We managed the case with IVIG and Inj Dexamethasone. Okumura et al in their study demonstrated that administration of steroids within 24 hr of onset of encephalopathy was associated with better outcomes in children with ANEC without brainstem lesions.[11]

The outcome of ANEC is generally poor with high mortality (30% - 40%) and survivors usually have moderate to severe disability and complete recovery is seen in < 10% of children.[9] We observed a good recovery may be due to aggressive intensive and supportive care and neuroprotective strategies.

Dengue usually presented as high grade fever with maculopapular rash, headache, generalised bodyache. Dengue is well known for two major complications – namely thrombocytopenia leading to bleeding and capillary leakage leading to shock – the later being the more serious. Our patient never showed any feature of capillary leak whatsoever. Her lowest platelet count was 66000/μl at presentation. Thereafter, it kept on increasing. Although she did have two major episodes of GI bleed but none were related to thrombocy topenia and happened much later in the course of the disease. So, our patient did not have either of the two major and common complications of Dengue. Notably, the other two reported cases of Dengue with ANEC also did not mention anything about either thrombocytopenia or capillary leak.

Dengue affects a major and densely populated part of the globe. So, it is important to be aware of even a rare complication of Dengue. It is even more so for two reasons. Firstly, although we have very limited experience, but it seems that these patients usually do not develop the standard major complications of Dengue. So, unless it is tested in a patient with ANEC, it may be missed. Secondly and more importantly, treatment of Dengue with ANEC is IVIG, steroids or Plasmapheresis none of which forms a part of standard Dengue management and hence will not be provided unless it is recognised.

CONCLUSION:-

Dengue is a common endemic illness in many parts of the world. ANEC is a devastating illness with poor prognosis but some established treatment. This case report along with two others highlight the importance of considering ANEC in a Dengue patient with severe neurological symptoms.MRI is the most important investigation in establishing the diagnosis. Therapy involves IVIG, steroids or Plasmapheresis.

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