

CASE REPORT

Acute Leukoencephalopathy with Restricted Diffusion in an Infant with Severe COVID-19 and Dengue Coinfection Progressing to West Syndrome

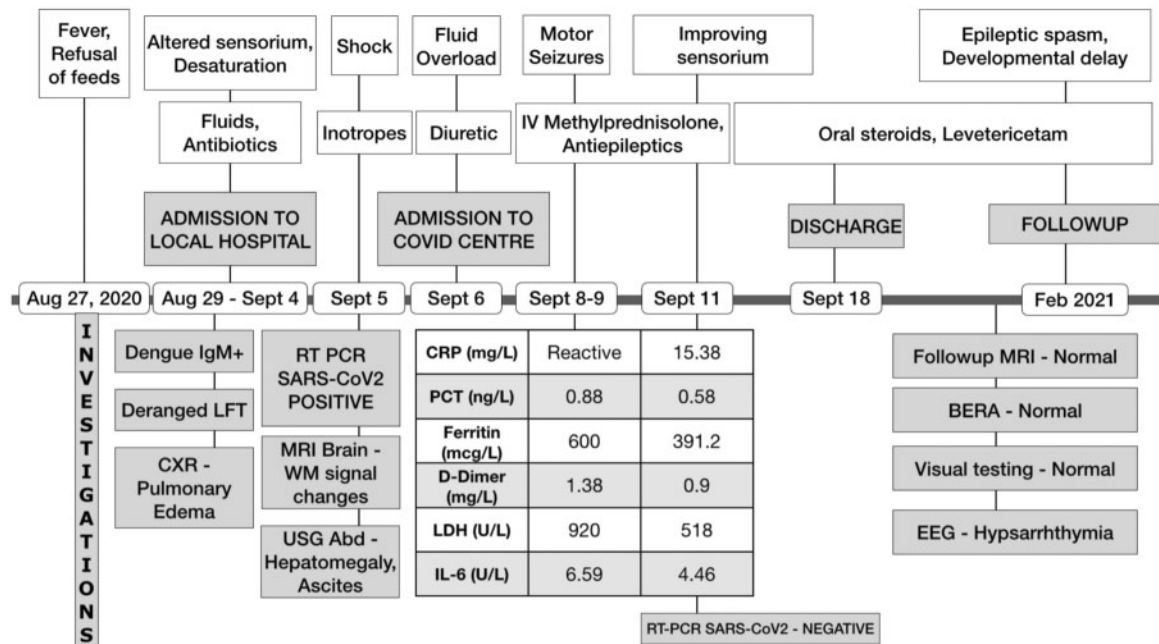
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ABSTRACT

COVID-19 pandemic is increasingly being recognized in infants and some develop cytokine storm mediated tissue damage. We report 5-month-old infant presenting with fever, refusal of feeds, developing altered sensorium and convulsions during the hospital course, tested positive for SARS-CoV2 RT-PCR in second week of illness. Her serology was also Dengue positive. She had features of cytokine storm and her MRI Brain suggested acute demyelinating encephalomyelitis (ADEM). She was treated with high-dose methylprednisolone followed oral prednisolone, under antibiotics cover. Infant improved gradually over 3 weeks duration following a stormy hospital course. On follow-up, infant showed delayed motor milestones with epileptic spasms and hypsarrhythmia on EEG, progressing to develop secondary West syndrome. Features of acute encephalopathy, hypercytokinemia and restricted diffusion on DWI–MRI, with post-encephalopathic epilepsy, pointed to a differential of ADEM—acute leukoencephalopathy with restricted diffusion (ALERD) as the primary diagnosis; establishing ALERD as a possible neurological complication of COVID-19 infection in infants.

GRAPHICAL ABSTRACT



Timeline of events. There is a demonstrable fall in the inflammatory markers with clinical improvement following the start of intravenous methylprednisolone. Epileptic spasms and developmental delay with hypsarrhythmia noted on follow-up, suggestive of secondary West syndrome.

KEYWORDS: COVID19, SARS-CoV2, ALERD, infantile dengue, West Syndrome, ADEM

INTRODUCTION

Coronavirus Disease - 2019 (COVID-19) in children accounts only for a small portion of those with symptomatic illness. Neurological complications have rarely been documented in medical literature. Cytokine storm induced by the virus leads to widespread tissue damage, is being reported on an increasing trend in children [1]. Acute leukoencephalopathy with restricted diffusion (ALERD) is a newly identified clinico-radiological diagnosis of infection-associated encephalopathy syndrome in childhood and its association with COVID-19 is presently unknown. This case report is that of a COVID-19 positive infant with Dengue coinfection, presenting with cytokine storm and features of ALERD, which was initially managed as ADEM, progressing to West syndrome over the course of few months.

CASE REPORT

Five-month-old female infant presented with high-grade fever lasting for 5 days, altered sensorium and refusal of feeds on day 3 of illness. Infant was treated for severe dengue with shock, supported by positive Immunoglobulin M (IgM) dengue serology Enzyme linked immunosorbent assay (ELISA) on day 5 of illness. Chest X-ray revealed bilateral hilar infiltrates suggestive of pulmonary oedema and ultrasound abdomen showed evidence of hepatomegaly with altered echotexture and ascites. On day 10 of illness, Real Time Polymerase Chain Reaction (RT-PCR) performed on nasopharyngeal and oropharyngeal swabs tested positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) infection. In view of altered sensorium, Magnetic Resonance Imaging (MRI) brain (Fig. 1) was done revealing

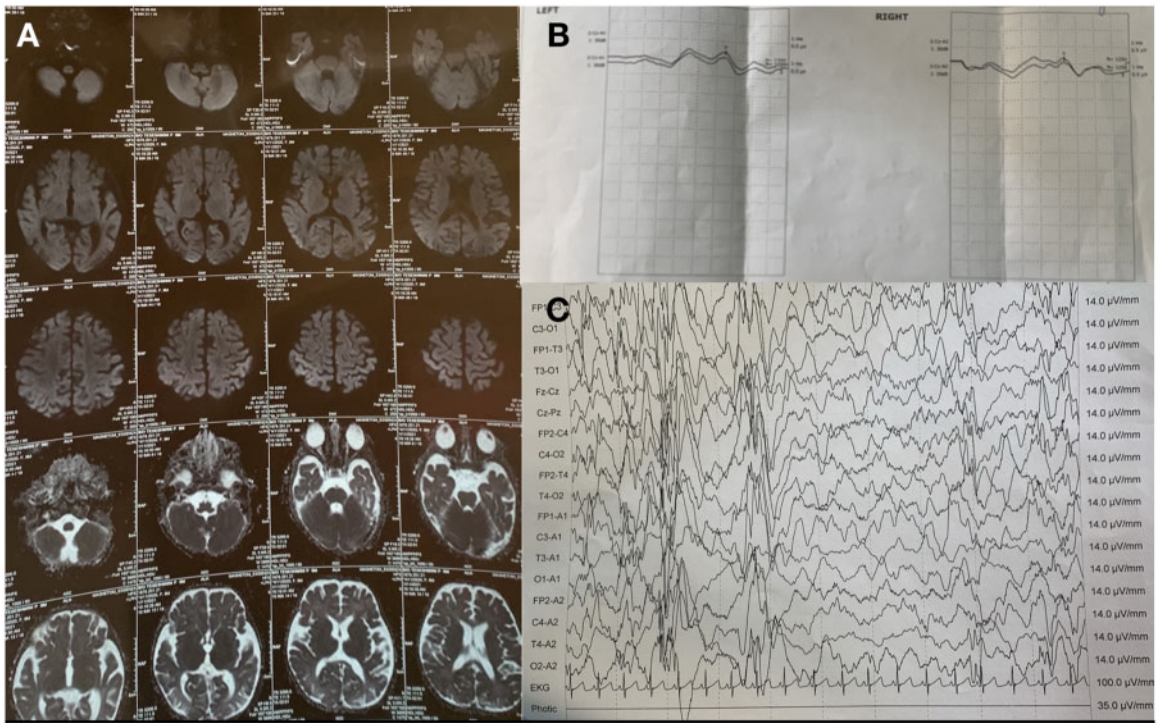


Fig. 1. MRI brain. Restricted diffusion in subcortical white matter in DWI sequences suggestive of ALERD.

restricted diffusion and oedematous changes in subcortical whitematter, suspected acute demyelinating encephalomyelitis (ADEM). The infant was shifted to our designated COVID Centre for further treatment. Encephalopathy features (GCS—E2V2M4) with decreased consciousness, movement of all extremities and perception of pain was noted in the baby. Baby had generalized oedema with reduced urine output, but maintained mean arterial pressure in the normal range. Diuretic was added to tackle fluid overload. Repeat workup revealed anaemia (7.8 g/dl), thrombocytopenia (65 000 cells/mcl), deranged liver enzymes (Aspartate aminotransferase (AST)—869 U/l, Alanine aminotransferase (ALT)—486 U/l) with raised inflammatory markers, C- Reactive Protein (CRP)—reactive and procalcitonin—0.88 ng/ml (normal <0.5 ng/ml). Cytokine storm criteria were met with elevated serum ferritin—600 µg/l (>300 µg/l), serum LDH—920 U/l (S.Ferritin+S.LDH >600), IL-6 levels—6.59 (>3 times upper limit) and elevated D-Dimer—1.38 mg/l (Normal—<0.3 mg/l). Cerebrospinal fluid (CSF) analysis was within normal limits.

Intravenous methylprednisolone 20 mg/kg/day was added for 5 days under the cover of antibiotics pending culture reports as to tackle dual dilemma of suspected ADEM and Cytokine storm. On day 12 of illness, infant threw an afebrile motor seizure and phenytoin was loaded to terminate the episode. She continued to have three more such episodes, which were finally terminated with levetiracetam. By day 15 of illness, baby's sensorium improved and was started on nasogastric feeds. Repeat chest X-ray revealed clearing of the infiltrates. Following 5-day therapy with IV steroids, inflammatory markers registered a downward trend and oral prednisolone 2 mg/kg/day was initiated for 14 days, followed by tapering dose. Repeat testing was done for COVID-19 on day 16 of illness and found to be negative. Persistent neurological deficits were noted in the power of bilateral lower limbs, even after improvement in general sensorium. Baby started taking direct breastfeeds on demand by day 20 of illness. Baby was discharged with oral steroids and levetiracetam. Repeat MRI showed clearing of all previous lesions, but baby persisted to have delayed motor development, with loss of

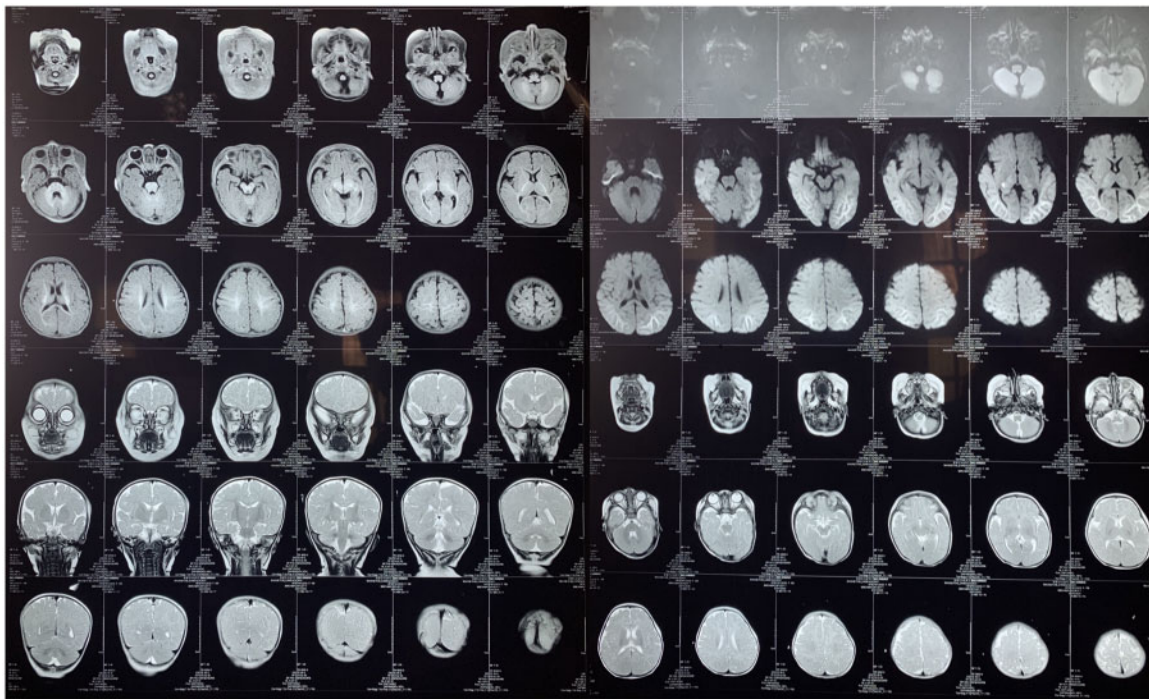


Fig. 2. Follow-up showing MRI resolution, normal BERA and hypsarrhythmia on EEG.

previously attained milestones. Her Brainstem evoked response audiometry (BERA) and Visual Evoked Potential (VEP) were normal for age. Over the course of next 5 months, she developed repeated episodes of epileptic spasms with Electroencephalogram (EEG) features of hypsarrhythmia (Fig. 2) Diagnosis of West syndrome post-encephalopathy was made in her, and is presently continuing oral steroids with levetiracetam, with partially controlled symptoms and is under consideration for Adrenocorticotrophic hormone (ACTH) therapy. Reviewing the course of illness, hypercytokinemia, typical MRI features of bright tree appearance on Diffusion weighted image (DWI) and follow-up MRI resolution, with post-encephalopathic sequelae of West syndrome, ADEM was superseded by its differential—ALERD as the primary diagnosis in this child.

DISCUSSION

Acute encephalopathy usually complicates viral infections and ALERD is a newly emerging clinical–radiological syndrome seen in childhood with higher

incidence of neurological sequelae. Known causative pathogens are usually viruses like HHV6, Adenovirus, Rotavirus, Enterovirus or toxins. Its presents as febrile encephalopathy with varying degrees of altered sensorium and seizures. Hypercytokinemia defined by elevated IL6, IL8 and IL10 leading to excitotoxic injury and neuronal death is hypothesized as possible mechanism. Unlike ADEM, no autoantibodies are identified and diffusion abnormalities are a result of glutamate induced astrocytic swelling and oedema. MRI demonstrates markedly restricted diffusion and oedematous changes in cortical and subcortical areas on DWI images, dubbed as ‘bright tree appearance’ which revert on Apparent Diffusion Coefficient (ADC) images. Follow-up imaging maybe normal with resolution of white matter restriction on DWI over 2–4 weeks. ADEM is a close differential with multifocal restriction more pronounced in T2 weighted (T2W) images than DWI unlike in ALERD [2].

SARS-CoV2 infection in infants is usually asymptomatic or mild illness. Severe COVID-19 infection is rare and is accompanied by an aberrant, aggressive

inflammatory response, correlated directly with lung injury, multi-organ failure and unfavourable prognosis. Early recognition and prompt treatment of cytokine storm can lead to better outcomes [1]. Baseline investigations and inflammatory markers like CRP, procalcitonin, Ferritin, IL-6, Lactate Dehydrogenase (LDH) and D-dimer are necessary in diagnosing cytokine storm.

Neurological manifestations of COVID-19 can be secondary to direct effects of virus, para and post-infectious immune-mediated disease. Encephalitis, encephalopathy, cerebrovascular accidents, Guillain-Barré syndrome (GBS), stroke and neuropathies are reported in increasing accounts in COVID-infected individuals. In case of parainfectious presentation of encephalopathy with SARS-CoV2 antigen still detectable, as in our case, clinicians need to be extra cautious with treatment as it may blunt patient's immune response to virus [3].

In dengue endemic countries like India, coinfection with SARS-CoV2 poses a challenge in diagnosis and treatment as initial symptoms overlap with nearly identical lab parameters [4]. Encephalopathy is known to complicate dengue infection, either in the acute phase or in the post-infectious phase, secondary to immune mediated attacks by cytokine overproduction triggered by Dengue Virus (DENV). Dengue and COVID-19 coinfection surmounted a massive cytokine storm in our infant leading to ALERD, an immune mediated encephalopathy.

Treatment of ALERD includes supportive and immunomodulatory therapy, similar to ADEM. High-dose intravenous methylprednisolone and intravenous immunoglobulin are the first line modalities of treatment. Intravenous methyl prednisolone (10–30 mg/kg/day, up to a maximum of 1 g/day) for 3–5 days followed by oral corticosteroid treatment continued with gradual tapering over 6 weeks to reduce the risk of relapses. In the background of

COVID19 cytokine storm, steroids with heightened monitoring, seems the logical approach to treat the patient.

CONCLUSION

All cases of documented dengue fever with presenting with shock and/or altered sensorium need to be tested for COVID-19, especially in this time of pandemic. Markers of cytokine storm need to be evaluated if there is multi-organ involvement and altered sensorium validates need for neuroimaging, as early and optimal dose of steroids can drastically improve survival and reduce morbidity. ALERD is a newly emerging post-infectious encephalopathy, needs to be differentiated from ADEM, and maybe a neurological complication of COVID-19 infection in children, both of which cause hypercytokinemia. Such children also need follow-up post-discharge, due to ALERD's infamous associations with long term neurological sequelae, compromising child's quality of life.

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