Acute Encephalopathy Following Measles Vaccination: A Novel Entity

Dear Editor,

Acute encephalopathy with biphasic seizures and late diffusion restriction (AESD) is a newly proposed radiological syndrome primarily associated with viral infections in children of Asian descent. Initial neurological symptom of prolonged febrile seizure followed by a seizure free interlude and recurrence of seizures with deteriorating sensorium by day 4 to 6 of illness adorns the clinical picture.[1] We report a 10-month-old Indian girl with clinical and radiological features consistent with mild form of AESD associated with a recent vaccination.

Case

A 10-month-old previously healthy girl was referred with concerns of repetitive focal clonic seizures of left upper limb. She was apparently asymptomatic 5 days prior to admission when she received her first dose of Measles Rubella vaccine. Following vaccination, she mounted fever within 24 h and had her first episode of left focal seizure of 3 min duration. The seizure was self-limiting, but she was drowsy with poor response to mother's commands and was evaluated in a local hospital. Her sensorium improved within 4 h of hospital stay and was afebrile and seizure free for 36 h with clear mentation. However, on day 3 of hospital stay, child developed two episodes of left clonic seizures lasting for 5 min with no return of sensorium between these episodes and hence was referred to our hospital. History of vomiting, irritable cry, ear discharge, and exanthemata was not forthcoming. Her development was appropriate for age and was able to crawl and stand alone, point fingers at things, play peek-a-boo and says mamma, dadda with a developmental quotient of 89 by Developmental Assessment Scale for Indian Infants. Her family history was uninformative. At admission, child was febrile and general examination revealed head circumference of 44 cm (0 to 1 Z); no neurocutaneous markers and flat anterior fontanelle. She was lethargic with incomprehensible sounds and poor motor response. On focused neurological examination, the paucity of movement of the left upper and lower limb and left facial palsy was striking. Hypotonia with poor antigravity movements and brisk muscle stretch reflexes were noted in the left side. Bilateral Babinski sign was positive. Rest of the systemic examination was unremarkable. Given the staggered clinical course and recent history of vaccination, acute demyelinating disorder was strongly considered. Investigations revealed neutrophilic leukocytosis (15126/mL^3[79%]) with no dyselectrolytemia or liver dysfunction. Sepsis screen including C-reactive protein and blood culture was negative. Electroencephalogram was suggestive of diffuse encephalopathy with no evidence of nonconvulsive status epilepticus. Brain Magnetic resonance imaging on day 5 revealed intense subcortical diffusion restriction in the right hemisphere with no appreciable changes in T1 and T2 imaging [Figure 1]. Cerebrospinal fluid (CSF) analysis was acellular with elevated protein (76 mg%) and normal glucose (60 mg%). CSF polymerase chain reaction (PCR) viral panel (Herpes/Enterovirus/Japanese Encephalitis/Scrub typhus/Chikungunya/Influenza/Parvovirus/Human Herpes Virus 6) was unsupportive. Nasopharyngeal swab for Influenza A and B by PCR was negative. Based on the neuroimaging, a diagnosis of acute encephalopathy with biphasic seizures and late diffusion restriction was arrived at. She received a 5-day course of methylprednisolone therapy and physical rehabilitation. At the time of discharge, she was seizure free with residual left hemiparesis. In the follow-up assessment at 2 years of age, she was able to walk upstairs, say two-word sentences, and play besides other children (DQ 91) with complete seizure remission and no lingering motor deficits. Parental consent was obtained for this manuscript.

Discussion

Acute encephalopathy with biphasic seizures and late diffusion restriction is defined by convulsions within 24 h from the onset of fever, subsequent improvement in consciousness followed by recurrence of seizures (clusters of partial seizures) on fourth to sixth day of illness with impaired consciousness and high signal intensity lesions in cerebral subcortical white matter on diffusion imaging on 3rd to 9th day of illness.[2] Clinical delineation from complex febrile seizure is difficult in the early phase as febrile status epilepticus followed by transient recovery of consciousness is common. However, the biphasic course with drop in sensorium and new onset seizure clusters and distinctive neuroimaging heralds the diagnosis

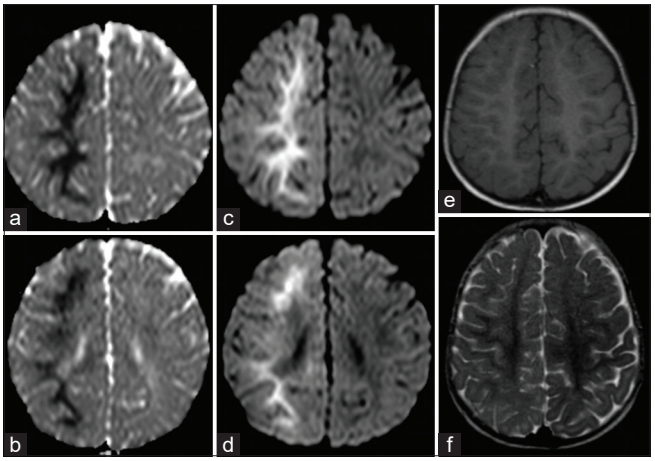

Figure 1: Axial diffusion weighted (a and b), apparent diffusion coefficient (c and d), T1 (e) and T2 (f) weighted images showing right hemispheric white matter diffusion restriction with no appreciable changes on T1 and T2 weighted imaging

of AESD. It is commonly associated with various viral infections including Influenza A, Influenza B, Rotavirus, Scrub typhus, Human Herpes Virus 6, Human Herpes Virus 7, and Hepatitis A.[1] The diagnosis is strictly radiological, and two distinguishing patterns of diffusion restriction have emerged. Widespread restriction in bilateral frontal and parieto-occipital regions (diffuse pattern) and reduced diffusivity with sparing of bilateral sylvian fissures (central sparing pattern) are often described.[3] The exact pathogenesis of AESD remains elusive and possible role of noninflammatory excitotoxic neuronal damage has been suggested. Post-mortem neuropathology in a Japanese boy with AESD revealed a decrease in myelinated axons with a remarkable increase in gemistocytic astrocytes with no neuronal loss.[4] This early stage of astrocytosis may account for reduced diffusion in AESD. Our index child deserves special mention for host of reasons. First, the imaging pattern is distinctive with novel hemispheric pattern of diffusion restriction. Literature search on the hemispheric pattern of restriction is limited with an isolated correspondence by Saini *et al*. in a 3-year-old north Indian girl with Hepatitis A infection.[5] Isolated subcortical diffusion restriction without any transient FLAIR or T2 gyral changes in frontal, temporal, or hippocampus differentiate AESD from post ictal changes of status epilepticus. Second, AESD has usually been described as an infection associated encephalopathy syndrome. The temporal association between Measles Rubella immunization and clinical course in our index child points toward the probable role of vaccines as a trigger for excitotoxic injury. Traul *et al*. reported AESD following Diphtheria, Acellular Pertussis, Tetanus administration in a child of Japanese descent in the United States.[6] The clinical spectrum is heterogeneous with cognitive difficulty, cortical visual impairment, epilepsy, focal motor deficits, and cerebral atrophy as the reported sequelae and mortality of <5%. A retrospective analysis by Ito *et al*. in 44 children with AESD recognized post encephalopathic epilepsy in 23% of patients over 3-year follow-up. Focal clonic seizures and epileptic spasms were the commonest semiology.[7] The 1-year seizure remission in our index child with no focal motor impediments highlights the milder course with full recovery.

In conclusion, we would like to highlight the association of acute encephalopathy with biphasic seizures and late diffusion restriction with Measles Rubella vaccine. Akin to viral infections, it is likely that vaccines are a part of spectrum of triggers that share a common pathological process resulting in excitotoxic injury in children and AESD.

Declaration of patient consent

An informed consent form was signed by the parents of the patient to approve the use of patient information or material for scientific purposes. The patient identity has not been disclosed anywhere in the manuscript and does not contain any identifiable images.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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