Early-Onset Subacute Sclerosing Panencephalitis: Report of Two Cases and Review of Literature

Sir,

Measles-related neurological syndromes encompass primary measles encephalitis, acute postmeasles encephalitis, measles inclusion-body encephalitis, and subacute sclerosing panencephalitis (SSPE).\(^1\) SSPE is a catastrophic consequence of the defective wild-type measles virus with an estimated risk of 4–11/100,000 cases worldwide. Effective vaccination campaigns have eliminated measles from the developed countries, unlike, developing countries like India where the current reported incidence rate is 21 cases per million population.\(^2\) This is possibly related to the reported risk factors such as younger age at measles (16 times greater risk), poverty, rural area, overcrowding, higher birth order, and higher number of siblings.\(^3\) The clinical presentation of SSPE can be quite variable, but in general, is characterized by progressive cognitive decline, periodic slow myoclonus, and extrapyramidal motor dysfunction. The classic age at presentation is 8–11 years and usually occurring after a latent period of 6 years. We describe two toddlers with early-onset SSPE and a review of the previously published cases of early-onset SSPE. For the purpose of the is review, citations were identified through PubMed searches limited to the past 30 years (1988–2017) using the search terms (including variations), “subacute sclerosing panencephalitis (SSPE),” “SSPE AND infant,” “SSPE AND toddler,” combined with study filters for case reports, case series, cohort studies, and original research. Additional articles were identified from the reference lists of identified papers. Only papers published in English were reviewed.

**Case 1**

A 26-month-old, previously healthy boy was admitted with a 4-week history of recurrent head drops. Prior to this illness, he was well and achieving age-appropriate milestones. Three episodes of generalized seizures heralded the onset of illness, 3 months back, following which he had progressive decline in developmental milestones. He had a history of measles-like illness at the age of 1 year, despite receiving measles vaccine at 9 months of age. On examination, he was in a minimally conscious state. There were repetitive periodic myoclonic jerks at a regular frequency of 6-8 s. Motor examination revealed generalized central hypotonia. On investigation, electroencephalography (EEG) revealed periodic generalized complexes [Figure 1]. Magnetic resonance imaging (MRI) showed periventricular white matter changes [Figure 2]. The diagnosis of SSPE was confirmed with elevated (1:625) titers of cerebrospinal fluid (CSF) and serum anti-measles antibody (immunoglobulin G). The child was initiated on Isoprinosine and antiepileptic medications. At 2-months of follow-up, the child was in vegetative state.

**Case 2**

A 27-month-old unimmunized girl presented with developmental regression and recurrent head drops for the past 1 month. She had language predominant global delay with a current developmental age of 15–18 months. Her perinatal period was uneventful. There was no past history of exanthematous illness. The child had repetitive myoclonic jerks every 9 s. Neurological examination revealed a normal
fundus with central hypotonia and bipyramidal signs. The EEG and MRI were suggestive of SSPE which was confirmed by elevated anti-measles antibody titers in CSF. At 4-week follow-up, the child was in vegetative state.

SSPE is frequently misdiagnosed or not suspected because of the variable presentation. Given the heterogeneous expression, accurate initial diagnosis of SSPE was made in only 21% cases presenting to a tertiary care center in South India. The first child in our report is exceptional for the early onset of SSPE and also for the short latent period of 14 months. The two cases highlight the fulminant nature of such an early presentation typified by a vegetative state within 3 months of onset.

The earliest description of SSPE in infancy and toddlerhood dates back to the late 1960s by Dayan et al. with histological and immunologically confirmed cases of 5-month and 15-month-old children at necropsy. Review of English literature identified 13 comparable cases in the past 30 years highlighting the rarity of this atypical presentation. Perinatally acquired measles were reported in 5 of the 13 cases [Supplementary Table 1]. Several important observations emerge on review of these children. First, the clinical course is atypical and does not follow the classic four stages of the Jabbour Classification. Second, the typical clinical picture of subacute mental deterioration with stereotyped generalized myoclonus is often preceded by a premorbid developmental delay with or without seizures in all five children as in our second child. On the other hand, in the primary measles group of 8 children, fulminant course of the disease is characterized by progression to a vegetative state within 3 months or fatal outcome within 6 months was the norm. The median latency in this group was 12.5 months with the shortest latency of 2 months. The exact reason behind this short latency and fulminant course is yet to be ascertained.

Genetically determined immune dysfunction in the first 2 years of life preventing a successful cell-mediated immune clearance of measles virus has been implicated in the susceptibility to SSPE. Genetic polymorphisms of programmed cell death-1, Toll-like receptor 3, MxA, interleukin-4, and interferon-1 genes have also been hypothesized but not proven. Besides, the role of phylogenetic spectrum of the wild-type measles virus in the etiopathogenesis has to be considered. The wild-type measles D3 and D6 are the most prevalent genotypes identified in SSPE on nucleotide sequence analysis. However, D7 genotype with hypermutation in the M gene has been isolated in an adult with fulminant SSPE from autopsy in South India and its association is still speculative.

The other early presentations of SSPE include visual complaints, Balint’s syndrome, dystonia, and ataxia. The diagnosis is usually established by Dyken’s criteria with periodic electroencephalographic complexes and raised CSF measles antibody titers (100% sensitivity and positive predictive value). SSPE is essentially an incurable disease with limited treatment options inclusive of Isoprinosine, interferon, ribavirin, and flupirtine. Given the poor eventual outcome of the therapeutic strategies, prevention through vaccination is the only way to eradicate the disease. Hence, there is a need for intensification of the primary immunization and measles eradication program in India.

Meanwhile, atypical presentation of SSPE should be considered in the differential diagnosis of any unexplained neurological illness irrespective of age, especially in endemic countries. A knowledge of the measles-like illness (also in the mother during the antenatal period), focused visual examination, and predominant white matter changes in MRI supplemented by an elevated CSF antibody titers are essential for an early diagnosis of this devastating condition.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other

Figure 1: Electroencephalogram. An awake electroencephalogram (international 10–20 system, average montage, sensitivity – 20 &mu;V/mm and sweep speed – 30 mm/s, low frequency filter – 1 Hz and high frequency filter – 70 Hz) revealed periodic generalized complexes consisting of bilaterally symmetrical, high-voltage (>400 &mu;V) bursts of polymorphic delta-waves with sharps and background slowing and recurring every 4–8 s.
Letters to the Editor

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Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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DOI: 10.4103/aiian.AIAN_443_18

Figure 2: Magnetic resonance images of the brain. T2-weighted (a) and fluid-attenuated inversion recovery (b) axial sections illustrating bilateral symmetrical hyperintensities in the periventricular white matter region in a child with SSPE.

Clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
### Supplementary Table 1: Prior studies with early-onset subacute sclerosing panencephalitis in infants and toddlers

| Case reports          | Country  | Age at onset in months | Age at diagnosis in months | Primary measles | Perinatal measles | Latency in months | Fulminant course | MRI brain white matter changes | Treatment | Outcome in months |
|-----------------------|----------|------------------------|----------------------------|-----------------|-------------------|-------------------|------------------|-----------------------------|-----------|-------------------|
| Zwiauer et al., 1995  | Austria  | 4                      | 11                         | -               | Yes               | -                 | No               | -                           | Supportive | Death at 16       |
| Bancher et al., 1996  | Austria  | 4                      | 4                          | -               | Yes               | -                 | Yes              | -                           | Supportive | Death at 16       |
| Cruzado et al., 2002  | Switzerland | 17                   | 18                         | -               | Yes               | -                 | Yes              | Diffuse                     | Isoprinosine | Death at 28       |
| Dasopoulou et al., 2004 | Greece  | 5                      | 14                         | -               | Yes               | -                 | No               | Multifocal                  | Isoprinosine intraventricular interferon | Death at 36 |
| Simsek et al., 2005   | Turkey   | -                      | 13                         | -               | Yes               | -                 | -                | Parieto-occipital           | Isoprinosine intraventricular interferon | -          |
| Primary measles       |          |                        |                             |                 |                   |                   |                  |                             |           |                   |
| Baram et al., 1994    | USA      | 22                     | 24                         | Yes             | -                 | 21                | Yes              | Corona radiata            | Supportive | Death at 25       |
| Lackmann et al., 2000 | Germany  | 23                     | 25                         | Yes             | -                 | 5                 | Yes              | Occipital                  | Supportive | Death at 29       |
| Serdaglou et al., 2003 | Turkey  | 23                     | 24                         | Yes             | -                 | 17                | -                | -                          | Supportive | Death at 25       |
| Kamate et al., 2012   | India    | 30                     | 34                         | -               | -                 | 4                 | Yes              | -                          | Supportive | Death at 40       |
| Saurabh et al., 2012  | India    | 10                     | 11                         | Yes             | -                 | 2                 | Yes              | Frontal                    | Isoprinosine | Vegetable state   |
| Aulakh et al., 2013   | India    | 23                     | 30                         | Yes             | -                 | 12                | No               | Frontal                    | Supportive | Withdrawal of treatment |
| Vijayalakshmi et al., 2014 | India  | 24                     | 27                         | Yes             | -                 | 18                | Yes              | -                          | Supportive | Withdrawal of treatment |
| Dhawan et al., 2016   | India    | 25                     | 27                         | Yes             | -                 | 13                | Yes              | Peritrigonal               | Supportive | Vegetative state  |
| Holt et al., 2016     | USA      | 36                     | 39                         | Yes             | -                 | 31                | Yes              | Diffuse                    | Isoprinosine | Vegetative at 46   |

MRI = Magnetic resonance imaging