Case Report

Early-onset subacute sclerosing panencephalitis and its rapid clinical course of progression to vegetative state: An atypical presentation

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ABSTRACT

Subacute sclerosing panencephalitis (SSPE) is a recognized neurodegenerative illness, known to be caused by the persistence of mutated measles virus in neurons and oligodendrocytes. The typical SSPE picture involves behavioral issues followed by myoclonic jerks, progressive intellectual and cognitive decline, bedriddenness, and an incontinent (vegetative) state leading to death. Considering atypicality, ataxia, tremors, dystonia, and hemiparkinsonian features are documented. Very few cases of early-onset SSPE have been reported to date. This report describes one such case with a review of published cases on early-onset SSPE in infants and toddlers in Indian settings. We present the case of a toddler with a positive history of measles at 11 months of age, despite measles vaccination at 9 months, who presented to us 29 months later with repeated head-drops, sudden atonic falls, and recurrent myoclonic jerks. Her brain magnetic resonance imaging and electroencephalography indicated SSPE, which was confirmed by positive antibody titers for measles. The toddler received isoprinosine, anti-seizure medications, and the ketogenic diet, to which she responded well initially. Later, as a consequence, the patient's clinical condition deteriorated rapidly, and thereby, she attained a complete vegetative state at 3-month follow-up.

Key words: Early onset, Measles, Subacute sclerosing panencephalitis, Vegetative state

Primary measles encephalitis, acute post-measles encephalitis, measles inclusion-body encephalitis, and subacute sclerosing panencephalitis (SSPE) are the neurological ailments associated with measles [1]. SSPE is a catastrophic consequence of the wild-type measles virus, with an estimated global risk of 4–11/100,000 infections. Developed countries have eliminated measles through effective vaccination campaigns; however, underdeveloped countries such as India have a current reported incidence rate of 21 cases per million people [2]. This could be related to the documented risk factors for measles, such as younger age (16 times higher risk), poverty, rural regions, overcrowding, and higher birth order. SSPE is characterized by myoclonic jerks, progressive cognitive decline, and typical electroencephalography (EEG) findings, with death typically occurring within 4–5 years of symptom onset [3]. The clinical picture of SSPE involves behavioral issues followed by myoclonic jerks, progressive intellectual- and cognitive decline, bedriddenness, and an incontinent (vegetative) state leading to death. In addition, cases have been reported with atypical features, such as ataxia, tremors, dystonia, and hemiparkinsonian features [4]. The classic age of presentation is reported to be 8–11 years (usually occurs after a latent period of 6 years). Recently, a series of two cases was documented as having early-onset SSPE [5].

This report describes a case of a toddler who had early-onset SSPE, tested positive for measles 2 months after receiving the first dose of the measles vaccine, and then presented to a tertiary-care university hospital with classic SSPE symptoms 29 months later. We also discuss previously published cases of early-onset SSPE in infants and toddlers in Indian settings.

CASE PRESENTATION

A 40-month-old girl child, born of non-consanguinity with normal birth weight and development, was evaluated in the emergency department of a tertiary-care hospital because of recurrent head-drops, sudden atonic falls due to abnormal jerky movements (myoclonus) while sitting mostly forward with no pre-monitory signs, and a complaint of urinary incontinence. The parents noted these symptoms 15–20 days ago, where myoclonus

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spontaneously recovered within a few seconds while getting up from the sitting position. Myoclonic jerks involved axial body parts, which gradually progressed in frequency and intensity with multiple episodes per day for the past 5–6 days before medical attention. She also had gait instability and sudden falls after walking a few steps on her own, a history of irrelevant talks with concurrent slowing and slurring of speech, and some amount of comprehension deficit intermittently. Before this illness, she was doing well and achieving age-appropriate milestones. Parents revealed that she tested positive for measles at the age of 11 months, despite receiving the first dose of measles vaccine at 9 months. There was no history of seizures, limb weakness, behavioral problems, or altered sensorium. Her perinatal period was uneventful. The family history was unremarkable. She was fully immunized until 18 months of age, including measles, mumps, and rubella (MMR-II), as per the government schedule.

On examination, she was afebrile, conscious, and partially disoriented, irritable but consolable, and spontaneously moving her eyes in all directions. Comprehension was impaired. Her vitals were within normal limits. Examinations of the cardiovascular, respiratory, and gastrointestinal systems were unremarkable. Neurological examination showed mild-to-moderate mental retardation. The pupils were of normal size, and a consensual light reflex was present. Bilateral lateral rectus palsy was present; except for this, on examination, the other cranial nerves were intact. A motor system examination showed normal tone and power. Deep tendon reflexes were brisk with an extensor plantar response. She could not fixate her gaze on objects, and the menace reflex was absent. The gag reflex was hypoactive. Her fundus examination was normal. Moderate-grade limb rigidity (R>L), neck rigidity, and intermittent dystonic posturing in the right upper and lower limbs were noted. Cerebellar examinations were normal. There were repetitive, periodic myoclonic jerks at a regular frequency of 5–6 s. As such, no resting tremors were present. Based on this clinical presentation, the possibility of SSPE was considered, and the patient was investigated on these grounds.

The patient's blood glucose and electrolytes were normal, as were the complete blood count with differential count and the results of tests of thyroid function, kidney function, liver function, and coagulation. Plasma lactate, vitamin B12, and homocysteine levels were also within normal limits. Cerebrospinal fluid (CSF) studies showed acellularity, an opening pressure of 20 cm H_2O (normal: 4–12), glucose of 63 mg/dL (normal: 50–80), and proteins of 22 mg/dL (normal: 15–40). The CSF gram stain, Ziehl–Neelsen stain, India ink, and culture for pyogenic, tubercular, and fungal organisms were negative, as were the CSF polymerase chain reaction for *Mycobacterium tuberculosis*. Serum and CSF measles immunoglobulin-G antibodies were positive in high titers (1:461 and 1:16). Screening for hepatitis B and C, HIV, and neurosyphilis was found to be negative. Imaging studies were obtained. On the day of admission, magnetic resonance imaging (MRI) of the brain was performed (Fig. 1) which revealed mild cerebral atrophy and bilateral symmetrical confluent subcortical white matter hyperintensities involving both cerebral hemispheres fronto-parieto-temporal regions on T2-fluid-attenuated inversion recovery imaging (Panels a, b, and c) with no diffusion restrictions (Panel d), and signal changes were also recorded in the basal ganglia and internal capsule regions (Panel e). The interictal EEG records were grossly abnormal in view of intermittent slowing of awake and sleep background activities, myoclonic jerks with typical fairly stereotyped and

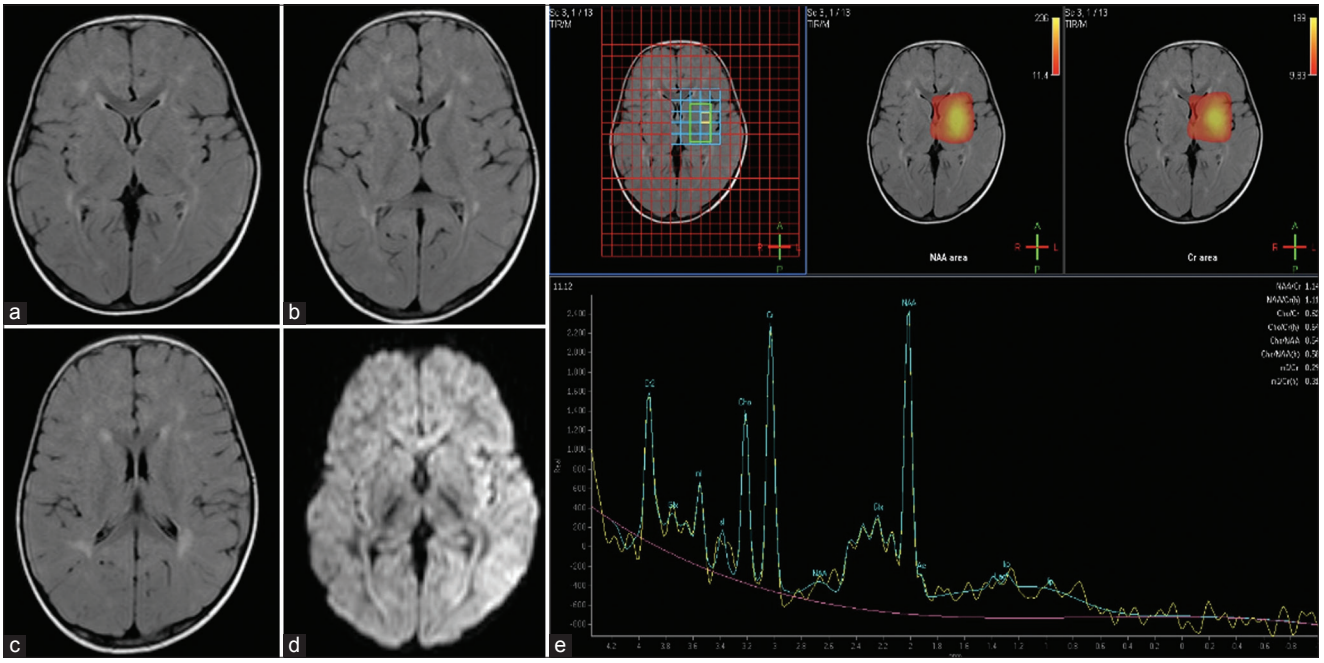

Figure 1: Magnetic resonance imaging of the brain showing axial sections; (panel a-c) illustrating mild cerebral atrophy and bilateral symmetrical confluent subcortical white matter hyperintensities involving both cerebral hemispheres fronto-parieto-temporal regions on T2-fluid-attenuated inversion recovery imaging. As such, there were no diffusion restrictions (panel d). White matter signal changes were recorded in the basal ganglia and internal capsular regions (panel e)

Table 1: Clinical characteristics from the previous Indian studies on early-onset subacute sclerosing panencephalitis in infants and toddlers

Citations	Sex	Age at measles onset (months)	Vaccination before measles disease	Age at SSPE diagnosis (months)	Cognitive/motor deficit before SSPE diagnosis	Electroencephalography	Measles antibody (CSF)	Radio imaging	Treatment received	Outcome
Sharma *et al*. (2008)	M	48	No	68	Myoclonic jerk, cognitive decline	Typical periodic/ rademacher complexes	Positive	-	-	His disease progressed rapidly and the child died at the age of 6 years.
Kamate *et al*. (2012) [10]	M	30	No	34	Myoclonic jerk, reduced speech output, choreoathetosis and hyperreflexia	Pseudo-periodic generalized epileptiform discharges	Positive	CT picture was normal	Anti-seizure	Died after 6 months of diagnosis.
Raut *et al*. (2012) [11]	F	-	No	36	Quadriparesis, hypotonia, neck instability, hypoactive deep tendon reflexes with extensor plantar, multifocal and generalized myoclonic-jerks involving limbs and trunks	Periodic high-amplitude sharp-and-slow wave discharge of duration 0.5–1 s every 4–5 s	Positive	White matter changes, ill-defined T2 hyperintense signal changes extending from C2 to C6	Sodium valproate, interferon	No further improvement in myoclonic jerks.
Saurabh *et al*. (2013) [12]	M	10	No	11	Myoclonic jerk, reduced speech output, altered sensorium	Periodic generalized complexes consisting of bilaterally symmetrical, high voltage bursts of sharp waves and delta waves which repeat at interval of 3–20 s with a slow background	Positive	Hyperintense signal in the cortex and subcortical white matter of frontal lobe, diffuse cerebral atrophy	Isoprinosine, sodium valproate, clonazepam	After 3 months, child did not show any improvement in cognitive function.
Aulakh and Tiwari (2013) [13]	M	23	No	30	Cognitive decline, myoclonic jerks, rigidity with brisk reflexes and extensor plantar, visual deterioration	Periodic bursts of high-amplitude, slow-wave complexes every 3–5 s	Positive	Hypointense small focal lesion in the left frontal lobe, ill-defined patchy areas of hyperintense signal in bilateral peritrigonal and paraventricular parietal white matter	Isoprinosine, sodium valproate, and clonazepam	Frequency of myoclonic spasms reduced significantly. Parents decided to discontinue further therapy and took child home.
Vijaylakshmi and Pushpalatha (2014) [14]	M	24	No	27	Myoclonic jerk, cognitive decline, decreasing vision	Diffuse high amplitude bursts of periodic slow complexes	Positive	Normal	Sodium valproate and levetiracetam	Difficulty swallowing, vision decreased, vegetative state.
Dhawan *et al*. (2017) [15]	M	25	Yes	27	Periodic myoclonic jerks, cognitive decline, involuntary choreiform movements	Periodic large amplitude slow wave complexes	Positive	Bilateral T2/ FLAIR white matter hyperintensities in bilateral deep peritrigonal areas	Sodium valproate and clonazepam	6 months after discharge child was in vegetative state.

(*Contd*...)

Table 1: (*Continued*)

Citations	Sex	Age at measles onset (months)	Vaccination before measles disease	Age at SSPE diagnosis (months)	Cognitive/motor deficit before SSPE diagnosis	Electroencephalography	Measles antibody (CSF)	Radio imaging	Treatment received	Outcome
Kasinathan *et al*. (2019) [5]	M	12	Yes	26	Developmental delay, periodic myoclonic jerks at regular intervals of 6-8 sec	Periodic generalized complexes of bilaterally symmetrical, high-voltage bursts of polymorphic delta waves every 4-8 sec	Positive	Bilateral symmetrical hyperintensities in periventricular white matter region	Isoprinosine and antiseizures	After 2 months child was in vegetative-state.
Kasinathan *et al*. (2019) [5]	F	-	No	27	Myoclonic jerks every 9 s, language-predominant global delay, and seizures	Stereotyped and periodic generalized high amplitude and slow wave complexes	Positive	Hyperintensities in periventricular white matter region	-	After 1 month child was in a vegetative state.
Nathan *et al*. (2019) [16]	M	24	No	48	Myoclonic jerks and repeated falls	Abnormal: stereotyped and periodic generalized high amplitude and slow wave complexes	Positive	Hyperintensity in the corona radiata extending to the periventricular region with diffuse cerebral atrophy and dilation of lateral and third ventricles	Isoprinosine, ribavirin, lamivudine, anti-seizure, and ketogenic diet	At 11 months, myoclonic jerks subsided, After 36 months, cognition and physical ability vastly improved in the child.
Kamate and Detroja (2019) [17]	F	-	Yes	144	Frequent myoclonic jerks, frequent falls, reduced speech output, forgetfulness, and sudden extension of the head	Generalized periodic complexes with asymmetrical background activity	Positive	Unilateral and isolated basal ganglia involvement. Isolated hyperintensities in left lentiform nuclei on T2-weighted/ fluid-attenuated inversion recovery sequences	-	-
Panda and Sharawat (2020) [18]	M	11	No	22	Recurrent head drops, generalized dystonia, intermittent choreoathetosis, repetitive myoclonic jerks	Generalized periodic epileptiform discharges, with bursts comprising of high amplitude spike and slow-wave complexes	Positive	Patchy periventricular white matter signal changes	Isoprinosine, antiepileptics	Myoclonic jerks subsided; however, he was in a vegetative state and had persistent extrapyramidal features.

SSPE: Subacute sclerosing panencephalitis, CSF: Cerebrospinal fluid , FLAIR: Fluid-attenuated inversion recovery, CT: Computed tomography

periodic, generalized, high-amplitude, sharp and slow wave complexes with frontal dominance, and relative attenuation of background with exaggerations mainly in sleep, diagnostic of SSPE. Based on Dyken's diagnostic criteria for SSPE, the patient fulfilled 4 of 5 criterias, thus becoming a definitive case of SSPE.

The child was initiated on isoprinosine 100 mg/kg/d in 3-divided-doses, amantadine 100 mg/d in 2-divided-doses, intravenous levetiracetam 20 mg/kg/d, intravenous valproate 10 mg/kg/d, and clonazepam 0.125 mg/d. A ketogenic diet was advised. At 4 weeks, the child had a reduction in the frequency of myoclonic jerks but her condition worsened subsequently and she attained a complete vegetative state at 3 months of follow-up.

DISCUSSION

SSPE was clinically defined originally in 1933 as "Subacute Inclusion Encephalitis" when inclusion bodies were detected in the brain biopsies; the same was referred to by the eponymous "Dawson's encephalitis" [6]. Today, SSPE is recognized as a neurodegenerative illness caused by the persistence of the mutated measles virus in neurons and oligodendrocytes [7]. It is reported to occur in the age group of 2–10 years after the primary infection with measles. Children with SSPE seem to be naturally infected with the measles virus at a young age, half before the age of 2 years, suggesting that persistent brain infection occurs in this age group before the immune system matures fully. Dayan *et al*. [8] first described SSPE in infancy and toddlerhood in the late 1960s, using histological and immunologically confirmed cases of 5- and 15-month-old children at necropsy. Immunization against measles can minimize the risk of both the infection and SSPE. Since infants and toddlers are specifically vulnerable to measles and SSPE, vaccination and hearing immunity are the most vital. Although the first dose of the MMR vaccine is typically recommended at age 9–15 months in India, the Centers for Disease Control and Prevention in the USA recommends infants aged 6–11 months receive the first dose of MMR vaccine, and children aged ≥12 months should receive a second dose. The neurological ailments of measles infection often appear 5–14 days following a rash. Measles inclusion-body encephalitis develops in immunocompromised individuals following a measles infection and has a latency of 3–6 months.

Considering its diverse presentation, SSPE remains commonly undiagnosed or sometimes even misdiagnosed. Given the varied manifestations, only 21% of cases presenting to a South Indian tertiary-care hospital received a precise initial diagnosis of SSPE [9]. A review of English-language literature identified 12 comparable cases, highlighting the scarcity of this atypical presentation in Indian settings (Table 1) [5,10-18]. Males in 9/12 (75%) were predominant. The median (interquartile range) age (months) at measles onset and SSPE onset was 24 (11–27) and 28 (26–42), respectively. Of the 12 cases, only 3 cases reported measles vaccination as per schedule. The current dual-dose measles immunization method provides 98% protection against illness. Vaccination provides proven protection; however, SSPE remains prevalent in low-income regions due to a lack of universal coverage. In countries that have adopted efficient measles immunization programs, the incidence stays significantly low. Upon reviewing these cases, several key observations arose. For instance, in 8 of 12 children and our patient, the usual clinical picture of subacute mental decline with stereotyped generalized myoclonus is frequently preceded by a premorbid developmental delay with or without seizures. We also observed that the clinical course deviates from the standard four stages of the Jabbour classification in most of the reported cases, including ours.

In the context of the fulminant course of disease (i.e., progression to a vegetative state or death within months), we observed 7 of 12 such cases, and ours is the new addition. The median latency in this group was 14 months, with the shortest being 2 months, as reported by Saurabh *et al*. [12]. The true explanation for this short latency and fulminant course has yet to be determined. Other early signs of SSPE include visual problems, Balint's syndrome, dystonia, and ataxia. Dyken's criteria are typically used to form the diagnosis, which includes periodic electroencephalographic complexes and elevated CSF measles antibody titers (100% sensitivity and positive predictive value). SSPE is predominantly an incurable condition with limited therapy choices, including isoprinosine, interferon-alfa, ribavirin, flupirtine, plasmapheresis, and a ketogenic diet [7]. Isoprinosine, ribavirin, interferon-alfa, and lamivudine combined have shown some therapeutic promise so far. However, more efforts are required to study their benefits in pediatrics.Corticosteroids (if at all considered for the management) should be used judiciously in SSPE patients. As the disease resembles autoimmune encephalitis in terms of its clinical presentation with rapid cognitive decline and seizures, the use of corticosteroids is not recommended, or at least should be limited, considering its possible relationship with the development of fulminant SSPE [7].

CONCLUSION

The atypical presentation of SSPE should be evaluated in the differential diagnosis of any unexplained neurological condition, regardless of age, particularly in endemic areas. Recognizing measles-like disease, focused neurological examination, and prominent white matter abnormalities in MRI, supported by elevated CSF antibody titers, are essential for timely diagnosis and management of this deadly condition.

ETHICAL APPROVAL

Not applicable.

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AUTHOR'S CONTRIBUTION

VRS and VK were involved in the management of the case and conceived the idea for reporting. VRS, AHA, PT, and GA were involved in case follow-ups and data collection. VRS, AHA, and PT performed the literature review and drafted the first version of the manuscript. All authors reviewed and approved the final draft of the manuscript.

CONSENT

Verbal and written informed consent was obtained from the patient's family for the publication of this case report.

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