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EARLY ONSET SUBACUTE SCLEROSING PANENCEPHALITIS IN INDIAN CHILDREN: A CASE SERIES HIGHLIGHTING AN ALARMING TREND AND THE NEED TO RE-ASSESS THE CURRENT VACCINATION STRATEGIES

Pediatrics

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ABSTRACT

Subacute Sclerosing Panencephalitis (SSPE) is a very rare and deadly complication of measles infection, with its incidence being significantly higher in developing countries. Our retrospective analysis of four patients highlights another ominous trend of this deadly disease, i.e, early age at onset leading to a rapid progress of symptoms. Four patients, presenting to the pediatrics department of a tertiary care hospital of eastern India, from February 2020 To December 2020, diagnosed as SSPE, by the modified Dyken's criterion, were analyzed. Paired CSF and serum samples were taken from all the patients and were analyzed for measles-specific IgG in serum (dilution 1:404) & CSF (dilution 1:2) using measles specific IgG ELISA (Enzyme-linked immunosorbent assay) kit. All the patients were under 6 years of age with a mean latency period of 2.5 years. All had contracted measles infection before receiving the scheduled first dose of vaccine at 9 months of age. Treatment was initiated according to the institutional protocol, keeping in mind the affordability. However, follow-up of the patients reflected the rapid progression of the disease. High morbidity and mortality is associated with SSPE in developing countries like India, where treatment availability and affordability becomes a major issue. In order to prevent this disease, it is necessary to prevent measles infection. Recent studies have recorded early disappearance of maternal measles-specific antibodies thus pointing towards the need to vaccinate early. Our case series emphasizes the need to revamp the current vaccination strategies in India with particular focus on re-scheduling the first dose to 6 months of age.

KEYWORDS

Pediatric, SSPE, measles vaccine, neuroregression.

INTRODUCTION

Subacute Sclerosing Panencephalitis (SSPE) is a very rare and deadly complication of measles infection with an estimated prevalence of 1 in 100,000 patients [1]. It is a chronic infection of the central nervous system which leads to progressive neurodegeneration. Patients usually present in the age of 8-11 years [2], [3] with symptom onset having a latency period of 2 to 10 years [4], beginning typically with subtle behavioral changes, cognitive decline followed by seizures (usually myoclonic) and finally progressing to complete vegetative state and death. The diagnosis is dependent on high clinical suspicion in the background of prior measles infection and is often delayed due to overlapping of the symptoms with other differentials like progressive myoclonic epilepsy, psychiatric illness, early stages of other viral encephalitis, leukodystrophies, demyelinating diseases of the central nervous system (CNS) and metabolic encephalopathies. Fulfillment of 2 major (typical clinical course, elevated cerebrospinal fluid (CSF) measles antibody titer) and 1 minor criteria (typical electroencephalogram (EEG) findings, increased cerebrospinal fluid (CSF) immunoglobulin G (IgG), brain biopsy, molecular diagnostic test identifying mutated measles virus genome) as proposed by Dyken's, is considered diagnostic. Even with the advent of Isoprinosine and possible therapeutic role of interferon alpha, SSPE remains a fatal disease with death usually occurring within 1-3 years of symptom onset. [5]

The incidence of SSPE in India is estimated to be about 21 per million population [6], which is significantly higher than developed countries. This can be attributed to the fact that in developing countries like India, the risk factors for measles like poor socioeconomic status, lack of proper hygiene and poor vaccine coverage are always present. The latest WHO data (2019) [7] reports that the current measles incidence in India is 29.68 per million population, with the highest incidence (76.4 per million population) reported among infants. Early age at infection aggravates the chances of developing SSPE later on.

In our retrospective analysis of four patients, we highlight another ominous aspect of this deadly disease, i.e, early age at onset and shorter latency period between primary measles infection and SSPE symptoms. Only a handful of studies have reported this alarming trend in recent times.

Patients And Methods

Four patients, presenting to the pediatrics department of a tertiary care center of eastern India (Midnapore Medical College and Hospital), between February 2020 To December 2020, diagnosed as SSPE, by the modified Dyken's criterion, were analyzed retrospectively. Paired CSF and serum samples were taken from all the patients and were analyzed for measles-specific IgG in serum (dilution 1:404) & CSF (dilution 1:2) using measles specific IgG ELISA (Enzyme-linked immunosorbent assay) kit (for which there is no established reference range). The concept, based on nonlinear (hyperbolic) functional relationship, described by Reiber & Lange[7], was used to discriminate between blood-derived and brain-derived proteins in CSF. The CSF/serum quotient reference ratio (CSFQ ref), which is the ratio between CSF/serum measles specific IgG quotient and CSF/serum total IgG quotient, was calculated. A value of more than 1.5 was considered to be indicative of measles specific antibody production in the CNS [7], [8]. All the patients were subjected to Magnetic Resonance Imaging (MRI, 1.5 Tesla) of brain and EEG. Routine CSF analysis for bacterial culture and polymerase chain reaction (PCR) for herpes simplex virus (HSV) and Enterovirus were negative for all patients, thus ruling out any infectious etiology. Neurometabolic screening and routine blood biochemistry, done for all patients, was not suggestive of any metabolic encephalopathy. Both the mothers and their children were found to be negative for HIV I and II.

All patients were started on oral Isoprinosine (100mg/kg/day) and managed symptomatically till discharge. Interferon alpha was considered but affordability became an issue. The parents were advised for regular follow-up and counseled regarding the poor outcome. Informed consent was taken at discharge, for data collection and possible usage in research work.

RESULTS

Clinical reports of the four patients enrolled, are described below and the investigational findings are summarized in Table 1. All the patients were under 6 years of age with a mean latency period of 2.5 years. All had received 2 doses of measles vaccine as per the Extended Program of Immunization (EPI), India. The mothers of all the four patients had received single doses of measles vaccine in their childhood according to the immunization schedule in practice, at that time. All the patients

hailed from rural areas.

Case 1

A 1.5 years old girl was brought with complains of inability to walk and frequent jerky movements of the body, with head drops for the last 10 days. She also had progressive loss of interest in surroundings and increased sleep frequency since last 1 month. She was born out of non-consanguineous marriage, at term, by uncomplicated normal vaginal delivery. The mother developed fever 2 days prior to delivery and exanthematous rash on 4th day postpartum. The girl developed mild exanthem on 6th day postpartum, which subsided within 3 days following which she had an unremarkable infancy with normal development. On examination, the baby had altered sensorium, frequent myoclonic jerks with truncal hypotonia and slight rigidity of the lower limbs. The deep tendon reflexes (DTR) were brisk in both upper and lower limbs along with normal bowel and bladder control. The cranial nerves and fundi examinations were normal. MRI of the brain (Figure 1) revealed patchy sub cortical and periventricular white matter hyperintensities on T2 weighted images. Electroencephalogram (Figure 2) showed periodic bursts of sharp and slow wave complexes coinciding with the myoclonus.

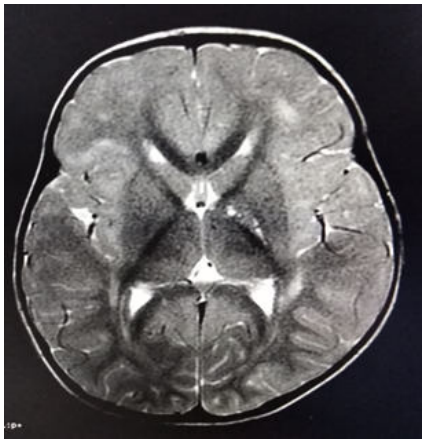

Figure 1: Magnetic Resonance Imaging. Bilateral hyper intensities in periventricular and subcortical white matter in T2 weighted image.

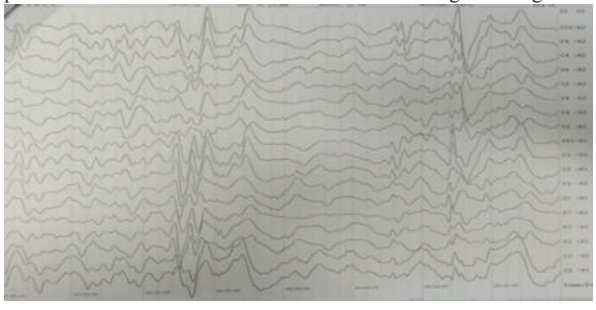

Figure 2: Electroencephalogram. Periodic bursts of sharp and slow wave complexes recurring at intervals of 15 seconds.

Case 2

A 5 years old girl presented with chief complains of frequent falls during walking with progressive loss of ability to communicate about daily needs since the last 2 weeks. The parents also complained that the girl had started having repeated episodes of jerky movements involving bilateral upper limbs for the last 2 days. She was born out of a normal vaginal delivery without any perinatal or postnatal complications.

There was no history of consanguinity and she was developmentally at par with age until the symptom onset. She had a past history of an episode of fever with generalized exanthematous rash at 4 months of age which was diagnosed as measles and treated accordingly. On examination the girl was disoriented and had minimal verbal output. The semiology of the movements described, was found to be myoclonic drop attacks. Tone and DTR were increased in bilateral lower limbs and mild truncal hypotonia was noted. Bowel, bladder control was normal with normal cranial nerves and fundus examination. MRI brain was non-contributory. EEG showed occasional bursts of sharp waves bilaterally with diffuse slowing.

Case 3

A 2.5 years old girl presented with the chief complains of subtle behavioral abnormality in the form of altered sleep pattern and inability to recognize her family members for the last 10 days. The mother also complained of frequent attacks of head drops for the last 5 days. Born out of a non-consanguineous union, the girl was developmentally at par with age. However during the course of illness she was progressively losing the ability to walk properly. The baby had past history of measles infection in the late neonatal period (26 days age). On examination; the baby was disoriented and was having recurrent episodes of myoclonic drop attacks. The CNS examination revealed truncal hypotonia with mildly exaggerated DTR in the lower limbs. Rest of the systemic examination revealed no significant abnormality with normal bowel and bladder control. MRI brain revealed no significant abnormality. EEG however showed typical periodic bursts of sharp and slow waves.

Case 4

A 2 years old boy was brought to us with chief complains of frequent episodes of tripping since the last 12 days. The mother also complained of 2 episodes of scissoring movement of the upper limbs which she noticed during the last 3 days. Born out of a non-consanguineous union, he had an uneventful, normal vaginal delivery. The boy was developmentally at par with age. He contracted measles at the age of 7 months. On examination, the semiology of the scissoring movement described, was deduced as myoclonic jerks. Increased tone with exaggerated DTR was noted in bilateral lower limbs. Rest of the CNS examination was unremarkable with normal bowel and bladder control. MRI of brain showed T2 hyperintensity in the head of the left caudate nucleus [Figure 3]. EEG showed the typical bursts of periodic sharp and slow waves [Figure 4]

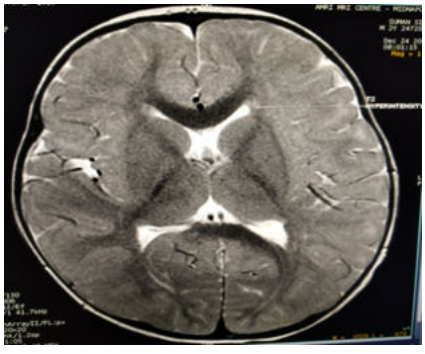

Figure 3: Magnetic Resonance Imaging. Hyper intensity in the head of the left caudate nucleus in T2 weighted image.

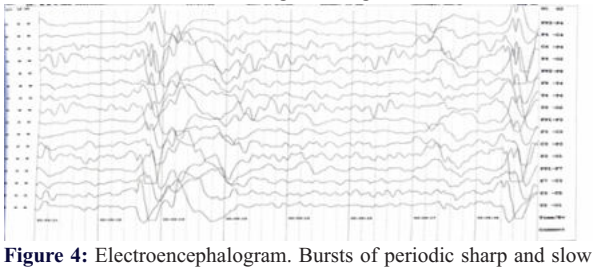

Figure 4: Electroencephalogram. Bursts of periodic sharp and slow waves recurring at intervals of 20 seconds.

Table 1: Patient Profile And Investigational Findings

Sl no.	Age/sex	MRI brain	EEG	Paired CSF and serum analysis	
				Parameter (biological reference interval)	Value
1.	1.5 years F	Patchy sub cortical and periventricular white matter hyperintensities on T2 weighted image.	Periodic bursts of sharp and slow wave complexes coinciding with the myoclonus.	Serum IgG measles	9854 u/ml
				CSF IgG measles	13744.4u/ml
				Serum total IgG (700-1600)	1630 mg/dl
				CSF total IgG (0-3.4)	10.9 mg/dl
				CSFQ ref (>1.5 = positive)	5.57

2.	5 years F	Normal	Occasional bursts of sharp waves bilaterally with diffuse slowing.	Serum IgG measles	10886.5 u/ml
				CSF IgG measles	17407.6 u/ml
				Serum total IgG (700-1600)	2820 mg/dl
				CSF total IgG (0-3.4)	18.93 mg/dl
				CSFQ ref (>1.5 = positive)	5.3
3.	2.5 years F	Normal	Periodic bursts of sharp and slow waves.	Serum IgG measles	4122 u/ml
				CSF IgG measles	4098 u/ml
				Serum total IgG (700-1600)	2870 mg/dl
				CSF total IgG (0-3.4)	1.29 mg/dl
				CSFQ ref (>1.5 = positive)	10.95
4.	2 years M	T2 hyperintensity in the head of the left caudate nucleus.	Bursts of periodic sharp and slow waves.	Serum IgG measles	9763 u/ml
				CSF IgG measles	7999.2 u/ml
				Serum total IgG (700-1600)	1941 mg/dl
				CSF total IgG (0-3.4)	11.24 mg/dl
				CSFQ ref (>1.5 = positive)	4.3

DISCUSSION

The exact pathophysiology of SSPE is still debatable although Cathomen et al [9] and Watanbe et al [10] have postulated that it may be due to the defective M (matrix) and F (fusion) proteins synthesis while interacting with an immature immune system. In fact most cases progressing to SSPE usually have history of measles at a tender age. Usually a long latency period of 6-15 years is observed, however shorter latency periods have been observed in children affected earlier than 2 years and the incidence is 18/100,000 in children younger than 5 years [11]. Factors suggested as a cause for this, apart from the immature immune system, are the co-occurrence of another viral infection and the presence of measles antibodies of maternal origin, which can cause genetic mutations resulting in the defective measles virus [12]. A similarity can be found in immunocompromised children with measles encephalopathy [13].

Follow-up of the four patients reflected the relentless progression of the disease with case 1 having already reached Jabbour stage 3 (at 3 months after discharge). SSPE remains a fatal disease in developing countries like India and in order to prevent this, it is necessary to prevent measles infection.

In our study, all the patients had measles infection before 6 months of age. Considering the fact that, India has introduced the second dose measles vaccine in the NIS in 2010, the mothers of all our patients had received only a single dose in their childhood. A recent study [14] conducted on Indian infants has shown that, the prevalence of anti-measles antibody was only 4.7% at 6 months and 2.7% at 9 months, which depicted the natural decay of maternally derived antibodies. Waning titres can be presumed as a cause for such early infections in cases 2, 3 and 4. Case 1 was diagnosed as congenital measles retrospectively, which is a very rare occurrence in itself. Only four cases [15], [16], [17], [18] of perinatally acquired measles progressing to SSPE have been reported. Measles infection, although rare in pregnancy, can have serious consequences on the fetus like abortion, premature delivery, low birth weight, and congenital cardiac and ocular defects [19]. Measles infection during pregnancy, in this case, further points towards the waning of maternal antibodies.

The mean latency period between measles infection and SSPE noted in our study, is 2.5 years which is significantly lower than usual. The early age at measles infection presumably enhances the natural course of SSPE.

The logic behind the first dose of vaccine at 9 months age is the increased seroconversion after waning of transplacentally derived antibodies. Recent studies [20], [21] from developing countries, however, have noted early disappearance of transplacentally derived antibodies, thus challenging the current practice and pointing towards the need to vaccinate early. Even studies from developed countries like Netherlands [22], have documented early disappearance of maternal antibody (3months). 75% of the children were shown to be susceptible to measles at 6 months in a study [23] conducted in Turkey. A recent study [24] has shown that early vaccination (first dose at 4-6 months) while maternal antibodies are still present, can provide better protection.

A systemic review and meta-analysis study [25] has shown that, early age (before 9 months) at administration of first dose of measles vaccine followed by booster doses, will lead to increased seropositivity and T-cell activity. Higher T-cell stimulation index have been reported [26] in children (age group of 5-10 years, having received 3 doses of measles vaccine) receiving the first dose of vaccine at 6 months age as compared to those receiving the first dose at 9 months age. Concerns have been raised regarding the blunting effects of an early first dose to subsequent booster doses. However in the background of measles endemicity, the benefits seem to outweigh the potential risks.

Furthermore, herd immunity plays a significant role in measles epidemiology. In developing countries like India, the vaccine coverage falls hopelessly below average. A survey has shown that only 30% infants receive vaccine at the age of 9 months [27].

Studies [28], [29] documenting early onset SSPE in recent years, stresses the importance of keeping this deadly disease as a differential diagnosis in endemic countries. Even if there is no history of clinical measles, the differential needs to be kept in mind in an otherwise non-explainable neurological illness, because, the ratio of clinical to subclinical measles infection in Indian infants, was found to be 4:10 in a recent study [14]. This high rate of subclinical infection, again, points towards inadequate vaccine coverage.

CONCLUSION

The four SSPE cases, described in our study, presenting within such short duration (10 months), highlights a menacing trend and emphasizes a need to revamp vaccination strategies in India. Firstly, there is a need to intensify vaccination campaigns so as to reach the desired levels of coverage. Secondly, re-scheduling the first dose to 6 months age followed by a second dose at 12-15 months age and a third one at 4-6 years of age need to be considered. Latest IAP (Indian Academy of Pediatrics) recommendation is MMR (Measles, Mumps, Rubella) vaccine at 9 months, 15-18 months and 4-6 years of age. Thirdly, mass screening for measles antibody titre in women of child bearing age need to undertaken to identify waning titres, and possibly, a booster dose can be considered.

REFERENCES:

1. Johnson RT (1994) Slow infections of the central nervous system caused by conventional viruses. Ann NY Acad Sci 724: 6–13.
2. G. G.Gascon, "Randomized treatment study of inosiplex versus combined inosiplex and intraventricular interferon-alpha in subacute sclerosing panencephalitis (SSPE): international multicenter study," Journal of Child Neurology, vol. 18, pp. 819–827, 2003.
3. L. K. Prashanth, A. B. Taly, V. Ravi, S. Sinha, and S. Rao, "Long term survival in subacute sclerosing panencephalitis: an enigma," Brain and Development, vol. 28, no.7, pp. 447–452, 2006.
4. R. K. Garg, "Subacute sclerosing panencephalitis," Journal of Neurology, vol. 255, no. 12, pp. 1861–1871, 2008.
5. Kliegman, R., Stanton, B., St. Geme, J., Schor, N., Behrman, R. and Nelson, W., n.d. Nelson Textbook of Pediatrics. 21st Ed.
6. Campbell H, Andrews N, Brown KE, Miller E. Review of the effect of measles vaccination on the epidemiology of SSPE. Int J Epidemiol.2007; 36:1334–48.
7. Neuroimmunology: immunoglobulins and the intrathecal polyspecific immune response in acute, subacute and chronic neurological diseases. Prof. H Reiber, IFCC vol 15.
8. Guidelines on cerebrospinal fluid analysis. EFNS task force. F. Deisenhammer et al. European Journal of Neurology 2006.
9. Cathomen T, Mrkic B, Spehner D, Drillien R, Naef R, Pavlovic J, et al. A matrix-less measles virus is infectious and elicits extensive cell fusion: consequences for propagation in the brain. EMBO J 1998; 17: 3899-908
10. Watanabe M, Wang A, Sheng J, Gombart AF, Ayata M, et al. Delayed activation of altered fusion glycoprotein in a chronic measles virus variant that causes subacute sclerosing panencephalitis. J Neurovirol 1995; 1: 177-88.
11. Sharma V, Gupta VB, Eisenhut M. Familial subacute sclerosing panencephalitis associated with short latency. Pediatr Neurol.2008; 38(3):215-217.
12. Kipps A, Dick G, Moodie JW. Measles and the central nervous system. Lancet 1983; 2(8364):1406-10.
13. Aicardi J, Goutieres F, Arsenio-Nunes ML, Lebon P (1977) Acute measles encephalitis in children with immunosuppression. Pediatrics 59: 232–239.
14. Malshe, N., Palkar, S., Kulkarni, R., Lalwani, S., Mishra, A. and Arankalle, V., 2019. Early disappearance of maternal anti-measles, mumps, rubella, and varicella antibodies in Indian infants. *Vaccine,* 37(11), pp.1443-1448.
15. Zwiauer K, Forstenpointner E, Popow-Kraupp T, Hauser E, Jellinger KA (1995) Rapid progressive subacute sclerosing panencephalitis after perinatally acquired measles virus

infection. Lancet 345: 1124.
16. Sawaishi Y, Abe T, Yano T, Ishikawa K, Takada G (1999)SSPE following neonatal measles infection. Pediatr Neurol 20:63–65.
17. Cruzado D, Masserey-Spicher V, Roux L, Delavelle J, Picard F, Haenggeli CA. Early onset and rapidly progressive SSPE. Eur JPediatr 2002; 161:438-41.
18. Dasopoulou M, Covanis A (2004) Subacute sclerosing panencephalitis after intrauterine infection. Acta Paediatr. 93: 1251-1253.
19. Atmar RL, Englund JA, Hammill H (1992) Complications of measles during pregnancy. Clin Infect Dis 14: 217–226.
20. Manirakiza A, Kipela JM, Sosler S, Daba RM, et al. Seroprevalence of measles and natural rubella antibodies among children in Bangui, Central African Republic. BMC Public Health 2011; 11:327.
21. Sultana R, Rahaman MM, et al. Prevalence of IgG antibody against measles, mumps and rubella in Bangladeshi children: a pilot study to evaluate the need for integrated vaccination strategy. Scand J Immunol 2006; 64:684-9.
22. Waaijenborg S, Hahne SJ, Mollema L, et al. Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccination strategies. J Infec Dis 2013; 208:10-6.
23. Begde F, Orhon FS, et al. Determining the persistence of maternally acquired antibodies to hepatitis A and varicella zoster during the first 2 years of life in Turkey. Eur J Pediatr 2015; 174:883-90.
24. Aaby P, Martins CL, Garly ML, et al. measles vaccination in the presence or absence of maternal measles antibody: impact on child survival. Clin Infect Dis 2014; 59:484-92.
25. Nic Lochlainn, L., de Gier, B., van der Maas, N., van Binnendijk, R., Strebel, P., Goodman, T., de Melker, H., Moss, W. and Hahné, S., 2019. Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, 19(11), pp.1246-1254.
26. Gans HA, Yasukawa LL, Sung P, et al. Measles humoral and cell-mediated immunity in children aged 5-10 years after primary measles immunization administered at 6 or 9 months of age. J Infect Dis 2013; 207:574-82.
27. Awofeso N, Rammohan A, Iqbal K. Age-appropriate vaccination against measles and DPT-3 in India- closing the gaps. BMC Public Health 2013; 13:358.
28. Saurabh K, Gupta R, Khare S, Sharma S. Atypical subacute sclerosing panencephalitis with short onset latency. Indian Pediatr. 2013; 50:244–5.
29. Dhawan, S.R., Sankhyan, N., Vyas, S. *et al*. Fulminant Early Onset Subacute Sclerosing Panencephalitis. *Indian J Pediatr* **84,** 154–155 (2017).