Neurology Asia 2022; 27(3) : 777 – 782

Adult onset subacute sclerosing panencephalitis presenting with acute ischemic stroke

Amlan Kusum Datta, Uddalak Chakraborty, Adreesh Mukherjee, Alak Pandit

Department of Neuromedicine, Bangur Institute of Neurosciences, IPGMER & SSKM Hospital, Kolkata, India

Abstract

Subacute sclerosing panencephalitis (SSPE) is a progressive, invariably fatal inflammatory disease of the brain, owing to persistent measles virus infection. It generally presents in childhood or adolescence, and usual presentation is with progressive cognitive decline and myoclonic jerks. An adult male, with an uneventful past medical history, presented with a rapidly progressive dementia and generalised myoclonus. During the course of his admission, he developed right sided spastic hemiparesis with evidence of subcortical infarct on brain imaging with focal narrowing of left middle cerebral artery. Subsequently diagnosed as SSPE, he was managed conservatively, without improvement. Intrathecal interferon could not be given owing to lack of consent from the patient's relatives. Histopathological confirmation could not be done for the same reason. A medium to small vessel intracranial vasculitis, secondary to measles virus infiltration was a proposed explanation of the vascular event. Persistence of measles virus in the brain may be a potential risk factor for intracranial vasculitis and strokes.

Keywords: Subacute sclerosing panencephalitis, measles, stroke, vasculitis, myoclonus

INTRODUCTION

Measles virus related neurological syndromes encompass four types: primary measles encephalitis, acute post-measles encephalitis, measles inclusion-body encephalitis, and subacute sclerosing panencephalitis (SSPE).[1] Although the global incidence of SSPE is reported to be 4-11 per 100,000 measles cases, figures are presumably higher in resource constrained nations such as India and Pakistan.[2] Subacute sclerosing panencephalitis (SSPE) is a progressive neurological disorder caused by persistent mutant measles virus.[3] Clinical hall marks are progressive cognitive decline coupled with periodic myoclonus. However, prior reports have suggested atypical presentations of adult onset SSPE. Amongst these, spastic hemiparesis may be one.[4] Even though vasculopathy and strokes are a well-documented complication of some viral infections such as varicella zoster virus (VZV)[5], it has rarely been described in context of measles virus and SSPE. Herein, we present one such case of adult onset SSPE presenting with possible vasculopathy and ischemic stroke.

CASE REPORT

A twenty-six-year-old male of South Asian-Indian origin, presented to the Department of Neurology, Bangur Institute of Neurosciences, Kolkata, with complaints of a progressive decline in cognitive abilities over the last three months, characterized by deficits related to attention, working memory, language and executive functions, as noticed by his father, who was accompanying him. He also developed myoclonic jerks involving all four limbs since a fortnight prior to presentation.

Upon admission, he was disoriented to time and place; his speech was dysarthric, with impaired comprehension. Motor examination revealed generalized "lead-pipe" rigidity with normal deep tendon reflexes (DTRs) and bilateral flexor plantar response. Most conspicuous physical finding was that of a generalized, slow-relaxing myoclonus occurring at a frequency of 8-12 per minute, sensitive to light and sensory stimuli. The jerks were persistent during sleep. He was evaluated for rapidly progressive dementia. Even though the patient was ambulatory at this stage with power of 4/5 in all limbs, his activities of daily living (ADLs) were impaired. Basic laboratory parameters, including complete blood counts, renal, hepatic, and thyroid function tests were within normal limits. Routine cerebrospinal fluid (CSF) analysis was unremarkable. Electroencephalogram study during sleep revealed bursts of periodic, high

Address correspondence to: Uddalak Chakraborty, 158, Chakdah Padma Pukur, Purba Putiary, Kolkata-700093, India. Email: uddaalakchakraborty@gmail.com

Date of Submission: 13 June 2021; Date of Acceptance: 4 June 2022

https://doi.org/10.54029/2022erz

amplitude, synchronous, sharp-slow wave discharges (Figure 1).

CSF showed high titers of anti-measles IgG antibodies (>1:8). Investigations were aimed at excluding other possible infectious, metabolic, and autoimmune etiologies (Table 1).

Brain magnetic resonance imaging (MRI) at this stage was normal. Subsequently, the patient was diagnosed to have SSPE as per Dyken criteria (Table 2). The differentials which were considered along with SSPE are detailed in Table 3.

Previously, Jafri *et al*. had demonstrated normal MRI in 46% and 29% SSPE patients of stage 2 and 3 disease, respectively.[6]

About two weeks into his hospital stay, the patient developed reduced spontaneous movement of right side of body with deviation of angle of mouth to left. Examination revealed spastic right sided pure motor hemiplegia (power 2/5) with right sided upper motor neuron type seventhcranial nerve palsy. MRI brain, done within 24 hours of onset of the focal deficit, revealed an acute left-sided subcortical deep white matter infarct. The subcortical location of the lesion, corresponding to middle cerebral artery (MCA) territory, coupled with true restricted diffusion on corresponding diffusion weighted (DW) and apparent diffusion coefficient (ADC) maps, were unequivocal proof of an acute vascular pathology, as opposed to other differentials, such as demyelination or neoplasm. Magnetic resonance angiography (MRA) demonstrated narrowing of M2 division of left MCA (Figure 2).

Extensive search for cardiovascular and metabolic risk factors did not reveal any suggestive abnormality. Complete coagulation profile was normal. Vasculitis profile and acute phase reactants were negative. Normal CSF and serum lactate and pyruvate levels as well as serum creatine kinase (CK) made possibility of mitochondrial disease less likely. Consent for neither genetic study nor muscle biopsy could be obtained from patient's kin. Reversible cerebral vasoconstriction syndrome (RCVS) was another possible differential.

Subsequently, the patient was diagnosed to have Myoclonus was partially controlled with per oral (PO) sodium valproate (500mg thrice daily PO), clonazepam (0.5mg twice daily PO), levetiracetam (750mg twice daily PO) and Isoprinosine (500mg twice daily PO). Option of intrathecal interferon therapy was offered but consent could not be obtained for the same. Patient was discharged after a month of admission. Three months later he had progressed to stage 3 (Table 3).

He was completely bed ridden at this stage, unable to communicate and care for himself. He was followed up at our outpatient department (OPD) six months later. His condition did not deteriorate further. The power of his left side

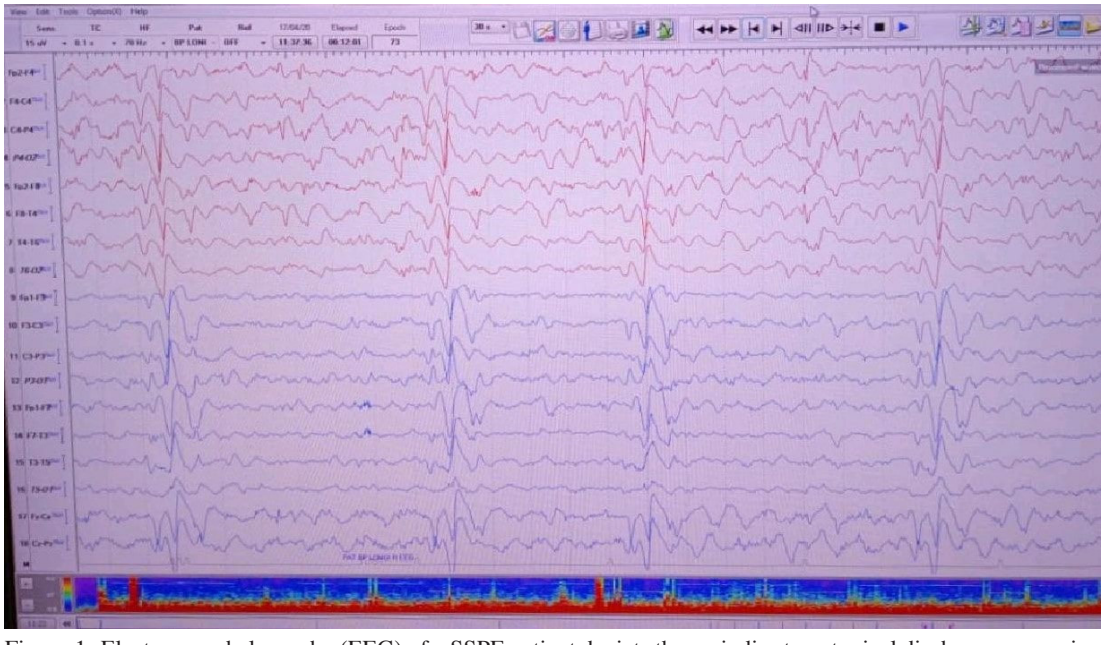

Figure 1. Electroencephalography (EEG) of a SSPE patient depicts the periodic stereotypical discharges occurring at an interval of 4 to 5 seconds, corresponding to myoclonic jerks (EEG machine setting–sweep: 30 mm/s; amplitude:15 μV/mm; filters: 1, 70; notch: 50 Hz)

Table 1: Laboratory investigations of the patient

Investigation	Result
Haemoglobin (Hb)	12.1 g/dl (13-17)
Total leucocyte count	7.7 X 10^9/L (4.5- 11 X 10^9)
Platelets	1.7 X 10^9/L (1.5-4 X 10^9/L)
C-reactive protein	Negative
Anti-nuclear antibody (ANA)	Negative
Serum angiotensin converting enzyme (SACE)	Negative
Anti N-methyl D-Aspartate receptor (NMDAR) antibody (CSF + Serum)	Negative
Anti GAD 65 antibody (serum)	Negative
Anti voltage gated potassium complex (VGKC) antibody (CSF + serum)	Negative
Human immunodeficiency virus (HIV) 1 and 2 antibodies	Negative
Serum sodium (Na), Potassium (K), Calcium (Ca), Magnesium (Mg)	Normal
Vitamin B12 levels	544 picogram/ml (160-950)
Arterial blood lactate	0.7 mmol/L (0.5-1.6)
CSF lactate	1.4 mmol/L (1.2-2.1)
CSF pyruvate	0.05 mmol/L (0.03-0.15)
CSF Herpes simplex virus (HSV) 1 and 2 polymerase chain reaction (PCR)	Negative
CSF varicella zoster PCR	Negative
Thyroid function tests	Normal
Anti-thyroid peroxidase antibody	Negative
CSF study	
Cells:	1/cc (<5)
Protein	45 mg/dl (15-60)
Glucose	41 mg/dl (20-45)
Oligoclonal bands	Absent
Venereal Disease Research Laboratory (VDRL)	Negative

improved to 3/5. Myoclonus persisted, although lesser in frequency and amplitude than before. His modified Rankin scale (mRS) score at this stage was 4, which was same as before. Follow-up brain imaging or histopathological investigations could not be done as patient's kin were unwilling to proceed for any further investigations.

Table 2: Dyken criteria for diagnosis of SSPE[7]

Definite diagnosis: criteria 5 with 3 more criteria Probable diagnosis: Any 3 of the five criteria.	
1. Clinical	Progressive, subacute mental deterioration with typical signs like myoclonus
2. EEG	Periodic, stereotyped, high voltage discharges
3. Cerebrospinal fluid	Raised gamma globulin or oligoclonal pattern
4. Measles antibodies	Raised titre in serum (≥1:256) and/or cerebrospinal fluid (≥1:4)
5. Brain biopsy	Suggestive of panencephalitis

Table 3: Differentials of SSPE

1. Infectious encephalitis: Herpes simplex, varicella zoster, human immunodeficiency virus (HIV), mumps, rubella, slow virus disease (Crutzfeldt-Jacob disease), progressive multifocal leukoencephalopathy (PML), neurosyphilis
2. Progressive myoclonic epilepsies: Unverricht-Lundborg disease, myoclonic epilepsy with ragged red fibre (MERRF), Lafora body disease
3. Progressive myoclonic encephalopathies: GM2 gangliosidoses, Niemann-Pick disease, juvenile Huntington's disease
4. Progressive myoclonic ataxias: Wilson's disease, coeliac disease, Whipple's disease
5. Leukodystrophies: Metachromatic leukodystrophy, adrenoleukodystropy, Krabbe's disease
6. Demyelination: Acute demyelinating encephalomyelitis, autoimmune encephalopathies
7. Neoplasms: Glioblastoma multiforme, central nervous system lymphoma
8. Toxins: Mercury, Bismuth, carbon monoxide, organic solvents

DISCUSSION

Considering a rapidly progressive course, dementia and myoclonus, various possibilities such as herpes simplex virus (HSV) encephalitis, autoimmune encephalopathies, neurosyphilis and progressive multifocal leukoencephalopathy (PML), amongst others, were considered (Table 3).[3] Diagnosis can be particularly challenging in early stages of the disease; however, our patient satisfied the Dyken criteria for SSPE.[7,8]

In a review of adult SSPE cases by Prashanth *et al*., the range of ages of presentation was 18-43 years with mean being 20.9 years[9]; as opposed to overall mean age of onset being

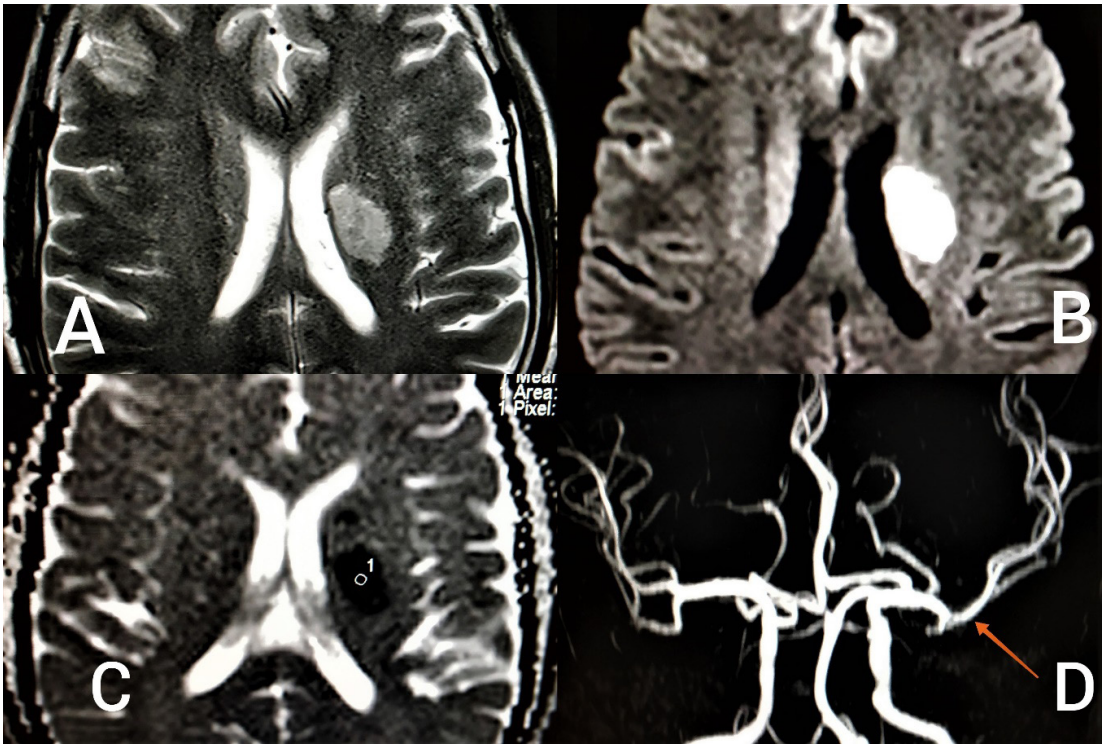

Figure 2: Magnetic resonance imaging (MRI) images, (A) Fluid attenuation inversion recovery (FLAIR) sequence showing corresponding left paraventricular deep white matter hyper-intensity (B) Diffusion weighted sequence (DWI) image and (C) Apparent Diffusion Co-efficient (ADC) map showing restriction in corresponding region of brain. (D) time of flight (TOF) MR angiography sequence showing narrowing of M2 division of left middle cerebral artery (MCA).

Table 4: Clinical stages of subacute sclerosing panencephalitis (SSPE) as per Modified Jabbour classification[8]

Stage	Clinical features
Stage 1	Mental and behavioural changes, forgetfulness, irritability and lethargy
Stage 2	Mycolonic jerks, dyskinesia, choreoathetosis, ataxia
Stage 3	Decerebrate rigidity and decorticate rigidity
Stage 4	Severe loss of all cortical function, flexion posturing of limbs and mutism

12 years (range 3-35 years).[10] In absence of histopathological correlation, we postulate that the aetiology of stroke in our case could be attributed to perivascular cuffing and infiltration of viral inclusion particles in penetrating branches of middle cerebral artery, as demonstrated by autopsy findings of a paediatric patient presenting with encephalopathy within two weeks of hemiparesis by Tamari *et al*.[11] However, this is the first report of its kind, wherein a distinct vascular phenomenon has been described in an adult SSPE patient with evidence of focal angiographic perturbation.

A direct causation between measles infection, active or latent, and ischemic stroke has not yet been documented as per literature.[12] The largest cohort of adult SSPE patients by Prashant LK et al did not have any presentation with pyramidal weakness.[9] The prevailing vaccination gap in low income countries contribute to a much higher incidence of SSPE than in their Western counterparts.[3] Hence, it might be prudent for clinicians in this part of the world to consider it as a differential in young patients presenting with progressive encephalopathy and pyramidal involvement.

Electroencephalography forms the backbone of diagnosis of SSPE, exhibiting high amplitude, bilateral, synchronous, periodic complexes (PC). Both cortical (frontal and peri-central cortex) and subcortical (thalamus) foci have been indicated as possible origin of those complexes.[13]

Although the prognosis for SSPE remains dismal, therapeutic options such as intrathecal alpha interferon and oral inosiplex have shown some promise and may be offered.[14]

A possible drawback of the present report is the absence of histopathological evidence of cerebral blood vessel involvement, as biopsy was not possible in the current set up. Also, lack of a follow-up angiogram leaves room for speculation regarding the nature of the primary vascular pathology, since, as mentioned prior, RCVS was a differential.

In conclusion, persistence of measles virus in the brain can lead to devastating consequences which have no proven medical remedy as of today. Apart from the spectrum of encephalitis, we postulate that vasculitis might also be a possible manifestation of latent CNS measles infection. Although causes of stroke are myriad, in countries with high vaccination gap, latent measles infection may be considered in its differential. However, larger well controlled studies are needed for establishment of the same.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Fisher DL, Defres S, Solomon T. Measles-induced encephalitis. *QJM* 2015;108:177-82. doi: 10.1093/qjmed/hcu113.
2. World Health Organization. Weekly epidemiological record. No. 2, 2006, 81, 13–20 http://www.who.int/vaccine_safety/committee/ reports/wer8102.pdf?ua=1. Accessed on 28 March, 2019.
3. Garg RK, Mahadevan A, Malhotra HS, Rizvi I, Kumar N, Uniyal R. Subacute sclerosing panencephalitis. *Rev Med Virol* 2019;29:e2058. doi: 10.1002/rmv.2058.
4. David P, Elia M, Mariotti P, Macchi G. Adult onset of subacute sclerosing panencephalitis: a case report. *Rivista di Neurologia* 1990;6:83-7.
5. Amlie-Lefond C, Gilden D. Varicella zoster virus: A common cause of stroke in children and adults. *J Stroke Cerebrovasc Dis* 2016;25:1561-9. doi: 10.1016/j.jstrokecerebrovasdis.2016.03.052.
6. Jafri SK, Husen Y, Ahmed K, Ibrahim SH. Spectrum of MRI brain findings in subacute sclerosing panencephalitis. *Asia Pac J Clin Trials NervSyst Dis* 2017;2:124-8
7. Dyken PR. Subacute sclerosing panencephalitis. Current status. *Neurol Clin* 1985;3:179-96.
8. Jabbour JT, Duenas DA, Sever JL, Krebs HM, Horta-Barbosa L. Epidemiology of subacute sclerosing panencephalitis (SSPE). A report of the SSPE registry. *JAMA* 1972;220:959-62.
9. Prashanth LK, Taly AB, Ravi V, Sinha S, Arunodaya GR. Adult onset subacute sclerosing panencephalitis: clinical profile of 39 patients from a tertiary care centre. *J Neurol Neurosurg Psychiatry 2006;77:630-3*. doi: 10.1136/jnnp.2005.085829.
10. Wendorf KA, Winter K, Zipprich J, *et al*. Subacute sclerosing panencephalitis: The devastating measles complication that might be more common than previously estimated. *Clin Infect Dis* 2017;65:226-32. doi: 10.1093/cid/cix302.

11. Tamari H, Matsukura M, Matsuda I, *et al*. An acute variant of subacute sclerosing panencephalitis: an autopsy case report. *Brain Dev* 1981;3:87-91.
12. Manousakis G, Jensen MB, Chacon MR, Sattin JA, Levine RL. The interface between stroke and infectious disease: infectious diseases leading to stroke and infections complicating stroke. *Curr Neurol Neurosci Rep* 2009;9:28-34. doi: 10.1007/s11910-009-0005-x.
13. Velmurugan J, Sinha S, Nagappa M, Mariyappa N, Bindu PS, Ravi GS, *et al*. Combined MEG-EEG source localisation in patients with sub-acute sclerosing pan-encephalitis. *Neurol Sci* 2016;37:1221-31. doi: 10.1007/s10072-016-2571-4.
14. Yalaz K, Anlar B, Oktem F, *et al*. Intraventricular interferon and oral inosiplex in the treatment of subacute sclerosing panencephalitis. *Neurology* 1992;42:488-91. doi: 10.1212/wnl.42.3.488.