CASE REPORT

A Clinical Exploration of SSPE in Adolescents : A Case Series

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Abstract:

Subacute Sclerosing Panencephalitis (SSPE) is a rare but devastating slowly progressive neurological disorder that typically occurs 6 to 10 years following an initial measles virus infection. SSPE remains a critical concern in the context of historical measles infections, particularly in unvaccinated populations. This case-based review focuses on the clinical features and diagnostic challenges for SSPE. Here, we demonstrate two cases that highlight the variability in presentation and progression of the disease.

The distinctive feature of SSPE is the gradual deterioration of neurological function, with progressive cognitive impairment, seizure and motor dysfunction leading to severe disability. But the clinical presentation of SSPE can often be subtle, and initial symptoms may be mistaken for other developmental disorders that leading to diagnostic difficulty. Thus, a high index of suspicion is essential. The combination of clinical features, EEG findings, and CSF analysis can provide a comprehensive approach to diagnosis. Enhanced EEG techniques and CSF analysis have been emphasized for early detection, with several studies showing that early intervention can lead to better outcomes. Atypical presentation of SSPE must be recognized in area with high incidence. EEG findings were found to be the most important indicator for diagnosis.

The review emphasizes the importance of early recognition and diagnosis to manage the progression of SSPE. While there is currently no curative treatment, symptomatic management and supportive care can improve quality of life for affected individuals. Increased awareness among clinicians regarding the late sequelae of measles virus infection is important for timely diagnosis and intervention. Ongoing research is needed to refine diagnostic methodologies and explore potential therapeutic modalities.

Keywords*: Subacute sclerosing panencephalitis, measles virus, neurological disorder, clinical features, diagnosis.*

DOI: https://doi.org/10.3329/jdmc.v32i2.83436
J Dhaka Med Coll. 2023; 32(2) : 139-144

Introduction:

Subacute sclerosing panencephalitis (SSPE) is a slowly progressive brain disorder, present as a late complication of measles infection, caused by mutant measles virus. Clinically, SSPE is characterized by florid panencephalitis. It is invariably fatal in most cases. Recent studies suggest that mutations in the F protein confer hyperfusogenic properties to the measles virus facilitating transneuronal viral spread. The inflammatory response in the brain leads to extensive tissue damage. SSPE usually has a prediction for children and younger adults. Early aged males from lower socioeconomic conditions suffer from SSPE. The male-to-female ratio of SSPE is approximately 3:1.[1,2,3] SSPE has broadly distinguished into typical and atypical SSPE. The typical SSPE usually occurs over a slow course of 6-10 years after primary measles infection as compared to the atypical form usually has a more fulminant course occurring within 1-6 months with a few occasional cases with deterioration occurring over a small span of 15 days. Although in the post-vaccination era there has been a substantial decline in the incidence of the

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Received: *24.01.2023* ***Accepted:*** *28.06.2023*

disease, it is still higher in the developing countries. An annual incidence of 21 per million populations in India in comparison with 2.4 per million populations in the Middle East.[4,5] A World Health Organization (WHO) expert group reported the global incidence of four to 11 SSPE patients per 100,000 measles cases. In developing countries, the incidence seems to be much higher with up to 27.9 SSPE patients per 100,000 cases of measles.[6,7] Measles infection is still common in Bangladesh. So, the chances of SSPE is still high in this country. There is no data about the incidence of SSPE in Bangladesh but it can be indirectly presumed from the high prevalence of measles despite wide vaccination coverage.[2] SSPE usually presents with the symptoms of motor involvement such as jerking movements, muscle spasms, ataxia, tremor, seizure, cognitive impairment etc.[8] However, several atypical presentations are also noted.[9-12] A wide spectrum of movement disorders is also observed throughout the clinical stages of SSPE.[8] The clinical manifestations of SSPE are not always typical and that may cause a delay in the diagnosis. Diagnosis of SSPE typically involves a combination of clinical history with various diagnostic tests that include EEG findings, CSF (cerebrospinal fluid) study, and neuroimaging. This article reviews the clinical features of SSPE, examines current investigation methodologies, and summarizes the findings from recent studies to further understand the disease's progression and diagnostic challenges. In this case-based review, we discuss two cases of SSPE one presenting with myoclonus with cognitive decline and another with psychiatric manifestations with seizure.

Case Finding:

Case 1

A 16-year-old male with a past medical history of Measles infection presented with a 2-years history of walking difficulty, repeated jerky movement of limbs and trunk, and generalized tonicclonic seizures occurring in both wakefulness and sleep. During illness, progressive cognitive decline and behavioral change were also observed. Family history was noncontributory. The birth was a full-term normal vaginal delivery without perinatal complications. He is developmentally normal and he was immunized according to the EPI schedule.

Neurological examination reveals a decline in cognitive function, MMSE 12, speech was slurred, and muscle power MRC (Medical Research Council) grade 4 in both upper and lower limbs with myoclonus. Deep tendon reflexes were brisk in all extremities, Babinski's signs were present bilaterally. Cranial nerve and sensory function were all normal. No incoordination or signs of meningeal irritation was noted.

EEG showed a generalized periodic high voltage complex. CSF study reveals CSF was clear and cytology revealed predominant lymphocytes and no red blood cells, anti-measles antibodies titer was markedly elevated (590.9mIU/ml, normal< 150mIU/ml). Magnetic resonance imaging (MRI) of the brain fluid-attenuated inversion recovery (FLAIR) showed multiple discrete

periventricular white matter hyperintensities.

Case 2

Kawser, a 15-year-old boy of nonconsanguineous parents with no significant birth and developmental history presented to the psychiatric department with low mood, personality, and behavioral change and gradual worsening of school performance. Later on, he developed generalized seizures and tremulous movement of both hands but no history of myoclonus or recurrent fall. No history of measles infection in childhood was reported by the parents.

Neurological examination revealed he was fully oriented and able to speak with labile mood, action, and intension tremor present, he had muscle power MRC (Medical Research Council) grade 4, ataxic gait with brisk reflex. Cranial nerve and sensory function were all normal.

On investigations, EEG showed generalized periodic spike-wave discharge, CSF study reveals CSF was clear and cytology revealed predominant lymphocytes, protein mildly raised, demonstrating positive anti-measles antibodies in high titer. Magnetic resonance imaging (MRI) of the brain was normal.

Discussion:

SSPE is a rare but serious neurodegenerative disorder that typically occurs in children and young adults as a late complication of measles virus infection. It is caused by persistent defective measles virus. SSPE is a commonly encountered disease in poor and resource-constrained countries.[13] The WHO has estimated its incidence to be approximately 4–11 cases per 100,000 measles cases.[15] Measles infection acquired very early in life is associated with a much higher risk.[16] The diagnosis of SSPE is based upon clinical manifestations, characteristic periodic EEG discharges, and demonstration of raised antibody titer against measles in the plasma and cerebrospinal fluid. SSPE is still common in developing and underdeveloped countries. One of the most important limitations in the treatment of SSPE is the difficulty in recognizing the early manifestation of the disease. The management of SSPE focuses on improvement of quality of life and prolongation of survival which can be achieved with the use of supportive care modalities and immunomodulators, respectively. Diagnosis is especially problematic in adult patients with SSPE.

Pathogenesis:

The occurrence of SSPE represents a defective cell-mediated immune response in the primary measles infection by mounting a premature humoral immunity and facilitating intraneuronal infection. Certain genetic polymorphisms have been attributed to this.[16] A persistent measles infection of brain clinically manifests several years after the acute measles infection. The brain infection leads to an exaggerated mononuclear inflammatory reaction to persisting measles virus. The mononuclear inflammatory response in the brain is mediated by CD4+ and CD8+ T cells along with monocytes and antibody secreting B lymphocytes. The antibody response against the measles virus is aggravated by high production of measles virus specific antibodies by plasma cells inhabiting the brain[17]. The parieto occipital cortex is most dominantly affected. Anterior parts of the cerebral cortex, periventricular white matter, thalamus, brainstem, and spinal cord are less severely involved.[18-19]

Clinical Feature:

Literature review shows that clinical presentation may vary from case to case. This includes progressive mental decline, behavioral abnormality, different types of movement disorders both hyperkinetic and hypokinetic, seizures including myoclonic, generalized, focal, and multiple types of seizure[20-21]. SSPE has four clinical stages[22] (Table 1). Here, between our two cases first one is present with some typical feature like myoclonus and cognitive decline. While the second case was presented with psychiatric feature in the psychiatry department, later he developed generalized convulsion and after EEG periodic discharge was found and thereafter CSF showed high titre of anti-measles antibodies. A comparison of the clinical spectrum of these two patients is shown in Table II.

Table I

Clinical staging of subacute sclerosing panencephalitis (SSPE)

Stages	Clinical features	Disability Status
Stage 1	Subtle decline in mental and scholastic performance	No or mild disability, no or mild impairment to walking
Stage 2	Periodic myoclonus and severe mental decline	Moderate disability with significant impairment to walking
Stage 3	Akinetic mutism with generalized spasticity	Confined to bed and totally dependent
Stage 4	Vegetative state	Impaired consciousness and requires 24 h nursing care

Table II
Clinical spectrum of SSPE patients

	Case 1	Case 2
Age of patient	16 years	15 years
P/H of Measles	Present	Absent
Measles vaccination	Vaccinated	Not vaccinated
Clinical Features	Walking difficulty	Depression and Personality
	Myoclonus	change
	Seizure	Emotional lability
	Progressive cognitive decline	Decrease school performance
		Seizure
		Tremor
MRI of brain	multiple discrete periventricular white matter hyperintensities (in FLAIR)	Normal
EEG Findings	generalized periodic spike-wave complex	generalized periodic spike-wave discharge
CSF Anti-measles Antibody	Positive in high titre (590.9 mIU/ml)	Positive in high titre (445.3 mIU/ml)

Diagnosis:
The diagnosis of SSPE relies on the modified Dyken's criteria that consist of major and minor criteria. Two major and one minor criterion must be satisfied to confirm the diagnosis of SSPE. The major criteria include clinical history and CSF measles antibody titers while minor criteria include EEG, MRI, and brain biopsy. Brain biopsy given its invasive nature, is incompatible with routine use and is therefore restricted to cases where clinical suspicion is high and the antibody titer is negative in a subacute sclerosing.[23]

Electroencephalography:
Almost all the patients of SSPE showed periodic high-voltage complexes, which usually occur in patients with a disease duration of more than four months. EEG in SSPE includes generalized periodic complexes or discharges[24]. Periodic EEG complexes consist of giant slow wave with several sharp wave. A typical discharge is polyphasic with duration varying from 0.5 to 2 seconds, high voltage (300 1500 mV), and repetitive (occurring every 4 to 15 s). Periodic discharges persist during sleep.[25-27] The typical pattern of EEG is more common in SSPE; however, we should also keep in mind that atypical and normal patterns of EEG can also occur in SSPE.[24] In the developing world with limited resources, EEG can be used as a good diagnostic tool for the suspected cases of SSPE. Figure 1 shows the EEG of an SSPE patient.

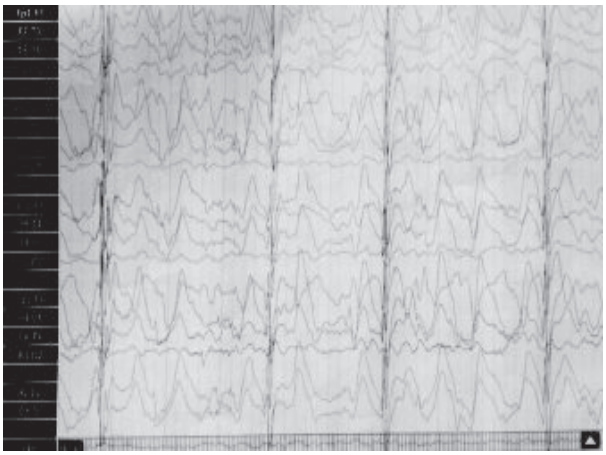

Figure 1: *Electroencephalogram of a patient with SSPE stage- ii showing periodic discharge appearing every 3 seconds and lasting for 1 second.*

CSF Examination:

The detection of CSF IgG against the measles virus using the Enzyme-linked immunosorbent assay (ELISA) technique has a very high sensitivity and specificity value which explains why it is a major criterion in the diagnosis of SSPEA high titer of measles antibodies, in the CSF and serum, is the gold standard for the diagnosis of SSPE. Other CSF findings are oligoclonal bands and lymphocytosis, protein may be normal or mildly elevated [28,29]. Here, anti-measles antibody titer was markedly elevated in both cases, the value was 590.9 mIU/ml in case 1 and 445.3 mIU/ml in case 2 where the normal value was normal < 150mIU/ml.

Neuroimaging:

Neuroimaging modalities may include a CT or MRI brain:

CT Scan:

It is normal in the early stages of SSPE. Later, focal white matter hypodensities in parietooccipital regions can be seen.[30]

Magnetic resonance imaging:

MRI is a better imaging modality for showing brain abnormalities of SSPE. MRI may be normal in the initial stage of SSPE. At later stages, abnormalities are usually located in subcortical, periventricular, and cortical gray matter. Corpus callosum, basal ganglia, cerebellum, and brainstem are less frequently affected. A typical neuroimaging picture shows bilateral asymmetric periventricular and subcortical white matter hyperintensity. Classical T2 weighted images or fluid attenuated inversion recovery (FLAIR) images show hyperintense signals.[31,32]

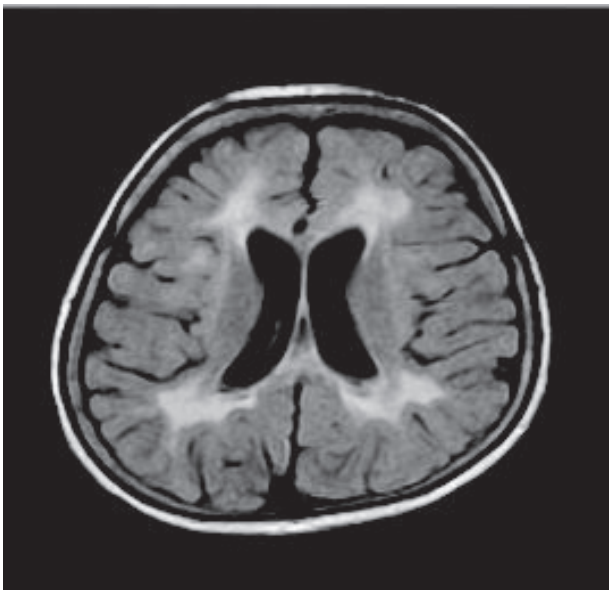

Figure 2: *MRI of an SSPE patient showing bilateral periventricular and subcortical hyperintensities in T2, FLAIR image.*

Conclusion

SSPE is a complex and devastating neurological condition that requires a high index of suspicion for diagnosis, particularly in individuals with a history of measles. EEG is particularly valuable in diagnosis, especially for developing countries like us. Early identification and clinical intervention are crucial, although effective treatments remain limited and primarily focus on managing symptoms and providing supportive care. While SSPE remains a challenging condition with no definite cure, ongoing research is necessary to better understand its pathogenesis and explore potential therapeutic options.

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