Section: General Medicine

Case Report

A RARE CASE OF ADULT-ONSET SUBACUTE SCLEROSING PANENCEPHALITIS : A CASE REPORT AND REVIEW OF LITERATURE

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Abstract

Subacute sclerosing panencephalitis (SSPE) is a rare and devastating neurological disorder primarily affecting children and young adults, stemming from measles virus infection. It manifests through a range of symptoms including behavioral changes, myoclonic jerks, progressive dementia, visual disturbances and psychiatric symptoms, along with pyramidal and extrapyramidal signs. Unfortunately, SSPE's course is relentlessly progressive, typically leading to death within 2-4 years. Diagnosis involves recognizing characteristic clinical features, periodic EEG discharges, and elevated measles antibody titers in both serum and cerebrospinal fluid. Despite advancements, treatment remains elusive and the management mainly revolves around supportive care and symptomatic relief. Various experimental therapies have been attempted, but none have shown consistent efficacy in halting the disease progression. SSPE underscores the importance of measles vaccination to prevent both acute infection and its potential long-term complications. Ongoing research aims to better understand the disease mechanisms and develop targeted therapies.

INTRODUCTION

Rare but severe implications of measles involve the central nervous system (CNS). CNS issues occurring months to years post-infection include measles inclusion body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE). SSPE stems from persistent measles virus presence. It is a slowly advancing condition marked by seizures and cognitive/motor decline, often leading to death 5–15 years post-measles infection, primarily affecting those infected under 2 years of age (1). Thus, SSPE poses a significant long-term risk following measles, particularly in young children, with devastating consequences for cognitive and motor function over time.

CASE REPORT

A 21-year old male, hailing from Srikona (Silchar - Assam), admitted to GMCH (Gauhati Medical College and Hospital) presented with complaints of altered behaviour in the form of inappropriate talking and irritability for the last 6 months. His parents had noticed that he was having intermittent jerky movements of all four limbs for last 5 months. The abnormal movements gradually increased in frequency and severity. Patient also developed repetition of words, laughing without a reason and poor scholastic performance. Progressive cognitive decline and gradual slowing of gait requiring support for activities of daily living were noted. He developed cachexia with drooling of saliva, low tone, and incomprehensible dysarthric speech. There was bradykinesia with generalised rigidity and patient became bed ridden over time. No history of loss of consciousness, seizures or trauma.

Past History

No family history of similar illness. His parents gave history of fever with maculopapular rash at the age of 9 years, which initially started behind the ears and over the face, then progressed to involve the entire body and subsided after 10 days spontaneously. He pertains from a low socio-economic stratum of society and has incomplete vaccination status; his parents could not specify whether measles vaccination was given or not.

Examination

On clinical examination, the patient was bed ridden, afebrile, normotensive, with normal heart rate, no

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hyper/hypopigmentation or lymphadenopathy, pupils were normal in size and reacting to light and signs of meningism were absent.

Compromised orientation to time, place, registration, recall, attention, calculation, language, repetition and complex commands but preserved orientation to person. The rest of the examination showed generalised intermittent hypertonic movements with hyperreflexia, symmetrical and bilateral cogwheel rigidity at the wrists, upper limb myoclonus, spasticity in all four limbs, and hypersomnolence. Bilateral plantar response was flexor.

Slit lamp examination of both eyes revealed no KF ring. All other systemic examinations were within normal limit.

Treatment and Follow Up

Started on Tab. Isoprinosine 1500 mg t.i.d and Anticonvulsants to control myoclonic jerks with supportive treatment and regular physiotherapy. Patient was discharged after 1 month of hospitalization. On follow-up after a month, there had been no improvement and he discontinued treatment after 3 months. The patient continued to deteriorate slowly over the next 6 months.

Table 1: Medical investigations. (tables and images)

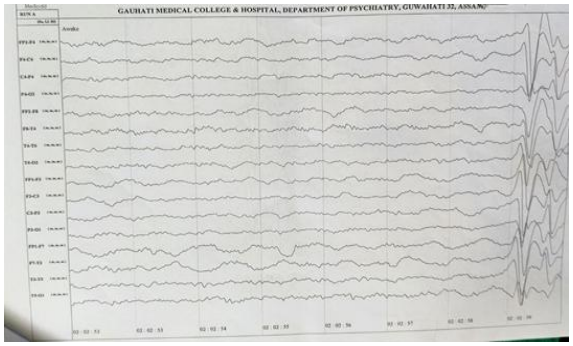
Blood test	Results	Reference range
Complete Blood Count (CBC)	Normal range	Normal / abnormal.
Liver Function Test (LFT) Renal Function Test (RFT) RBS, Thyroid Function Tests (TSH),free T3, free T4,	Normal range	Normal / abnormal.
Serum vitamin b12 and folate levels.	Normal Range B 12 – 886 pg/ml Folic acid -17.4 ng/ml	Normal / abnormal. B 12 :(239-931 pg/ml) Folic acid - >5.38pg/ml
C-reactive protein (CRP)	9.3	0 to 10 mg/L
Anti streptolysin O Titre	90 IU/ML	0 – 200 IU/ML
VDRL HIV(1&2) HBsAg Anti HCV	NON -REACTIVE	NON REACTIVE / REACTIVE .
Anti-Nuclear Antibody (ANA by IFA)	Negative	negative
Serum Measles IGG	3228 IU/L	Positive > 275IU/L
Serum Measles IGM	0.07 IU/L	Negative: < 0.8 IU/L

Table 2:

Cerebrospinal Fluid (CSF) study	Results	Reference Range
Appearance, Opening pressure and glucose.	Normal	Normal /abnormal
Protein	58 mg/dl	5-40 mg/dl
Cell count: White blood cells, lymphocytes, Polymorphous/pus cells, red blood cells, yeast cells.	2 cells/mm (Lymphocytes)	Normal :0- 5 cells /mm
Gram stain, acid fast bacilli, culture, Cytology	Negative	Normal: negative
Measles IGG in CSF	3840.8 IU/L	Positive: >275 IU/L
Measles IGM in CSF	0.08	Negative : <0.8 IU/L
INDIA INK TEST FOR Cryptococcus, Anti -GAD antibody	Negative	Negative / positive
REAL TIME PCR Test for Herpes simplex virus 1 & Herpes simplex virus 2	Not detected	Detected /not detected

Table 3:

Mantoux test Quantiferon test for tuberculosis	Negative	Positive or Negative
Electrocardiogram Chest x ray	Normal	Normal/Abnormal
CT scan of the brain And USG whole abdomen	Normal	Normal/Abnormal
EEG(Electroencephalography)	Periodic complexes consisting of bilaterally symmetrical, synchronous, high voltage burst of polyphasic, stereotyped delta waves.	
Nerve conduction study of all four limbs (NCS)	Normal NCS study	



EEG (Electroencephalography): (Periodic complexes consisting of bilaterally symmetrical, synchronous, high voltage burst of polyphasic, stereotyped delta waves.)

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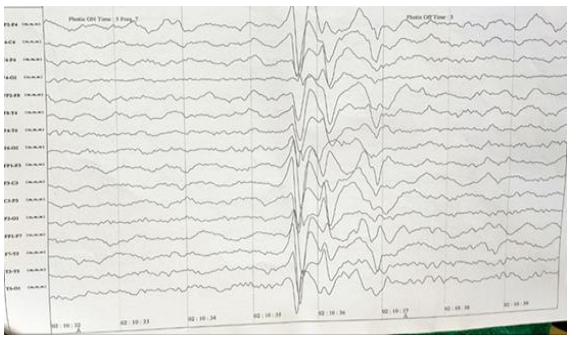
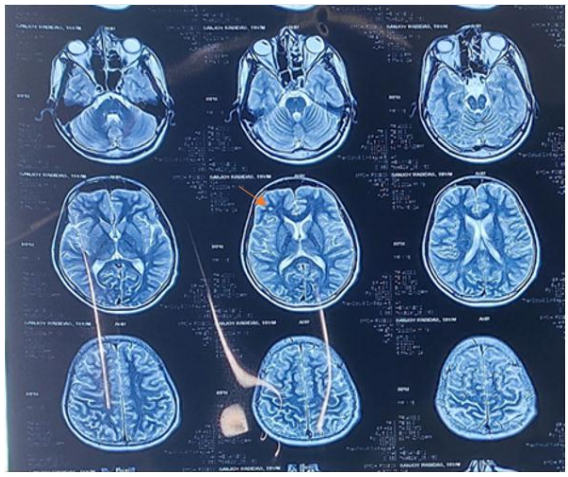
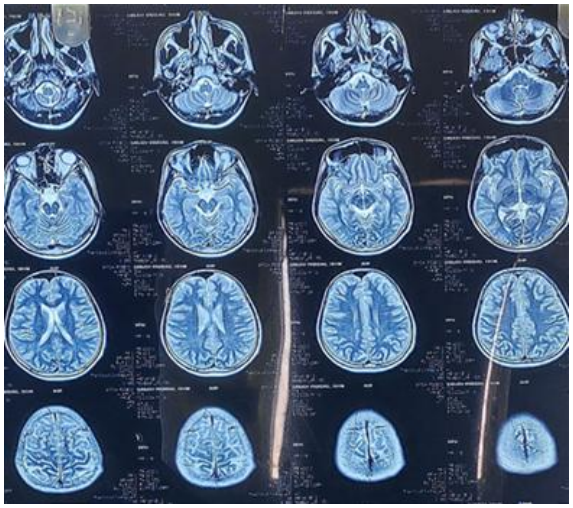
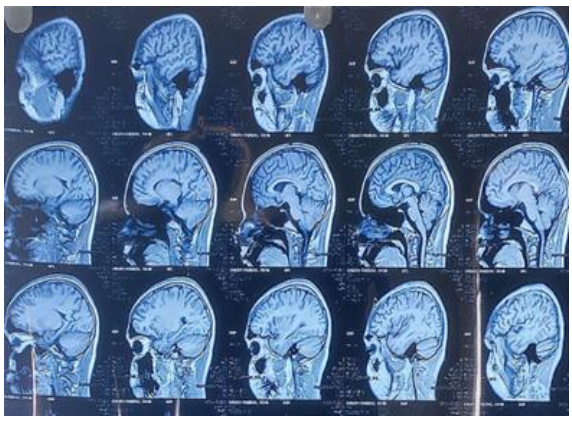




MRI revealed several small periventricular foci in frontal lobe region suggestive of demyelination. (arrow showing)



MRI- T2-weighted revealed confluent high signal intensity areas in the bilateral periventricular white matter. Multifocal areas of subcortical white matter signal alteration were seen bilaterally especially in the frontal lobe.



MRI – Mild cerebral atrophic changes.

DISCUSSION

Subacute sclerosing panencephalitis (SSPE) is a rare late complication of measles, caused by persistent nonproductive measles virus infection of neurons and glia, and occurs in immunocompetent patients (1). The pathogenesis of SSPE is related to defective measles virus maturation in neural cells. Aberrant M (matrix) protein as well as other envelope proteins interfere with assembly and budding of infectious virus. The virus remains in intracellular form and spreads by cell-to-cell contact.[1-3]

Epidemiology

SSPE has an annual incidence from under 0.1 cases to 5 or 6 cases per million in unimmunized populations. In areas of high early-life measles attack rates, SSPE accounts for a portion of childhood neurodegenerative conditions. Children infected in the first 2 years of life are at greater risk while children infected with measles under the age of 1 year carry a risk of 16 times greater than those infected at age 5 years or later.[2-4] The incidence is higher among rural children, having two or more siblings, and those with mental retardation. It is also more common in children with a lower birth order and in children living in overcrowded areas. Studies consistently show SSPE to be more frequent in male child (male/ female ratio 3 : 1). The median interval between acute measles infection and SSPE is 8 years, with a range of 2 to 12 years.[1]

Pathogenesis

Measles is caused by an RNA virus, which belongs to the marbillivirus subgroup of paramyxoviruses. Despite the long interval between the acute infection and symptoms of SSPE, there is evidence that measles virus infection of brain occurs soon after the acute infection with subsequent spread throughout the brain.[5] Measles virus is thought to reach the brain through infection of cerebral endothelial cells, perhaps during the acute exanthem of measles when other endothelial cells are also infected.[6,7] Access into the brain by circulating inflammatory cells is also possible.[6] Measles virus isolated from specimens of the brains of such patients may interfere with the replication of the wild type of measles virus and may have a clonal origin.[7] There is evidence that

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persistent measles virus infection can be found throughout the body in patients with SSPE.[8]

Recently studies have suggested that apoptosis of various cell types may contribute to the neuropathogenesis of measles virus infection in the human central nervous system, either as a direct effect of viral infection or of cytokine mediated responses, resulting in oligodendroglial and neuronal cell death in SSPE.[9,10]

With initial infection, the measles virus causes heavy immunosuppression that can continue for a considerable number of months. This results in many secondary infections.[11]

SSPE is a more prevalent complication in younger patients exposed to the measles virus, likely secondary to their immature immune systems.[11] The immune response to infection starts with T-helper 1 cells that release interferon-alpha and IL-2. These cytokines help to eliminate the viral infection from cells. The humoral response then plays a role in making antibodies for long term protection from the virus. These antibodies will trigger T-helper 2 cells that release large amounts of IL-4 and IL-2 and interferon-alpha. It is a possibility that SSPE is the result of a low cellular immune response. There is evidence to suggest that patients who go on to develop SSPE have a reduced cellular immune response and an elevated humoral immune response, which would prevent the patient from completely eradicating the virus.[12] One of the proposed mechanisms of neuronal spread is via neurokinin-1, while substance P and fusion inhibitory peptide block viral transmission. The virus typically remains dormant for some time before triggering an inflammatory response resulting in neuronal destruction, which presents as SSPE.[12]

However, the exact pathogenesis of this complication is still not known, given that neurons do not express target cell receptors, SLAM, or nectin-4.[11,13] It has been proposed that SSPE occurs as a result of antigenic drift. However, a study found that both SSPE and wild strains of the measles virus behave in similar manners and can be neutralized in the same capacity, thus disproving the antigenic drift theory.[14]

Clinical features:

Subacute sclerosing panencephalitis is characterized by progressive cognitive decline. Symptoms typically present after 8 to 11 years of post-measles infection. Initially, personality and behavioural changes are present, in addition to poor scholastic performance and intellectual deterioration.[12] There is a steady decline in motor function with myoclonus in most cases, autonomic dysfunction, and focal paralysis. Some patients have seizures, either focal or generalized, and about one-third of patients with SSPE develop epilepsy. Patients eventually fall into a vegetative state or akinetic mutism, which is shortly followed by death.[10,12,13]

The course of SSPE has been divided into four stages, each of which describes a certain phase of the disease.[13]

Stage I Includes many personality or behavioral changes such as irritability, lethargy, dementia, social withdrawal and speech regression.

Stage II Manifests as progressive reduction in motor function, including myoclonus, dyskinesia, and dystonia.

Stage III Consists of patients who have progressed to extrapyramidal symptoms and spasticity.

Stage IV Occurs when the patients develop akinetic mutism, autonomic failure, or enter a vegetative state.[13]

Visual symptoms sometimes precede disease onset by about two years, with the most common lesion being focal necrotizing macular retinitis. Ocular symptoms can range from retinal haemorrhage or vitreous haemorrhage to papilledema to complete vision loss. Most structures of the eye may be affected.[12,13,15]

Atypical manifestations of Subacute Sclerosing Panencephalitis (SSPE) encompass psychiatric manifestations, refractory seizure disorders, and exclusive extrapyramidal symptoms. When such atypical signs manifest, SSPE often progresses rapidly, with neurological impairments surfacing within three months or death occurring within six months in roughly two-thirds of instances. Risk factors for this aggressive, atypical course include measles infection before age two, heightened viral virulence, and concurrent viral coinfections.[12,13]

The original SSPE diagnostic criteria, introduced earlier, mandated specific symptoms and CSF/serum findings with EEG and brain biopsy findings, necessitating three of five criteria for confirmation. However, due to SSPE's diverse presentation, a revised set of criteria emerged in 2010. This updated diagnostic framework comprises major and minor criteria, with a diagnosis necessitating two major and one minor criteria. When evidence is lacking but diagnosis is probable, histopathological and molecular testing serve as options.[13]

Major Criteria

- Features having either a typical or atypical presentation. The typical presentation is defined as either acute, rapid, subacute, or chronic progressive and chronic relapsing-remitting.
- The atypical presentation includes prolonged stage I, seizures or unusual age of presentation. Another major criterion is elevated anti-measles antibodies greater than or equal to 1:4 in the CSF or 1:256 in the serum.

Minor Criteria

- The minor criteria includes supporting evidence of clinical presentation, one of which is EEG findings suggestive of high-amplitude slow waves occurring bilaterally and synchronously at regular intervals. These are called slow-wave complexes or Radermecker complexes.
- Another minor criterion is an elevated level of globulin in the CSF, that makes up more than 20% of the total protein found in CSF.
- Brain biopsy findings suggestive of SSPE.

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- A molecular test used to identify the genome mutations in the wild strain of the measles virus is a minor criterion.[13,16] The sensitivity and specificity of the newer criteria have yet to be assessed in general public and pregnant females.

Imaging can be used as supportive evidence of a diagnosis, but it does not always have abnormal findings.

Magnetic resonance imaging (MRI) is pivotal in revealing decreased gray matter volume, hyperintensities, and atrophy alongside marked ventriculomegaly in SSPE cases.[13] It aids in monitoring disease advancement, with initial scans possibly appearing normal before transitioning to periventricular white matter lesions, eventually spreading to deeper brain structures and the brainstem. Some SSPE patients exhibit primary brainstem lesions, contrary to the typical progression and historically associated with autoimmune or metabolic disorders, underscoring the need for SSPE consideration in such cases.[1,2,17]

Treatment

There is no cure for SSPE. An estimated 30–35% of patients have improved or stabilized after one or several 6-week treatments with intraventricular interferon alfa through an Ommaya reservoir (starting at 100,000 U/m2 body surface area per day, with daily increments up to 106 U/m2/day over 5 hospital days, then 106 U/m2 twice a week for 6 months), combined with oral isoprinosine (inosiplex), 100 mg/kg/day to a maximum of 3 g/day taken orally in three divided doses for 6 months (Gascon, 2003; Gutierrez et al., 2010).[2]

Response to IV ribavirin in combination with intrathecal interferon alfa (Tomoda et al., 2001) and symptomatic improvement in myoclonus and encephalopathy with levetiracetam have been reported.[2]

The laboratory endpoint of treatment is eradication of detectable measles virus antigen from the CSF. Systemic (subcutaneous) interferon alfa in daily doses of up to 5 million units used with intrathecal interferon alfa to treat the peripheral reservoirs of measles virus, lymphoid, and glandular tissue. Prolonged or repeated treatments carry the risk of meningitis, interferon alfa-induced encephalopathy, and interferon alfa upper and lower motor neuron toxicity. Spontaneous remissions are estimated at 5%.[2]

Prognosis

SSPE typically follows a progressive trajectory, with death occurring within 1–3 years. However, variations include a chronic very slow progressive form, a rapid fulminant form leading to death within weeks, and a "stuttering" pattern with remissions and relapses. Notably, around 5% of patients may experience significant spontaneous long-term improvement.[21]

CONCLUSION

SSPE, stemming from measles virus aberration, poses challenges in early diagnosis due to potentially reversible inflammatory changes. Diagnostic complexities heighten in adult patients. The measles virus can lie dormant in the CNS for years, averaging 4–10 years post-childhood infection, with longer latency in adults, presenting around 20 years 11 months on average (18). Treatments, albeit expensive and non-curative, are available only in select centers worldwide, placing significant physical, psychological, and financial strains on patient families, necessitating extensive external support for coping.

In our case, the virus lay dormant for 12 years post-measles infection. Measles can trigger extensive perivascular infiltrates in the brain. Its advanced stages entail nerve cell degeneration, neuronal loss, astrogliosis, dendritic degeneration, demyelination, neurofibrillary tangles, and inflammatory cell infiltration throughout various brain regions including the frontal, parietal, temporal, and occipital cortex, basal ganglia, thalamus, pons, and medulla(19,20) . Currently, effective measles vaccination appears to be the sole solution to combat this dreaded neurological disorder.

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