SUBACUTE SCLEROSING PANENCEPHALITIS: CLINICAL REVIEW OF PATHOGENESIS, DIAGNOSIS AND MANAGEMENT

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Abstract

Introduction: Subacute sclerosing panencephalitis (SSPE) is a rare, chronic, progressive and fatal neurodegenerative disorder caused by persistent infection with mutant Measles virus. It develops years after primary measles infection and predominantly affects children and adolescents, leading to severe neurological deterioration.
Aim: The aim of this paper is to review the etiology, pathogenesis, clinical representation, diagnostic criteria, treatment options and prevention strategies related to SSPE.
Methodology: This paper is based on a literature review using medical textbooks and scientific articles addressing the epidemiology, diagnosis and management of SSPE.
Results: SSPE commonly presents with behavioral and cognitive decline, myoclonic jerks, motor dysfunction, seizures and progressive loss of neurological function. Diagnosis is established through characteristic clinical findings, electroencephalography changes, neuroimaging and elevated measles antibody in cerebrospinal fluid. Current treatment options including antiviral and immunomodulatory therapies, may slow disease progression in some patients, but prognosis remains poor in most cases.
Conclusion: SSPE remains a devastating late complication of measles infection with limited therapeutic success. Early recognition is important for supportive management, while prevention through effective measles vaccination remains the most important strategy for reducing the incidence, morbidity and mortality associated with this disease.

Keywords: SSPE, measles, encephalitis, neurodegeneration, vaccination

Introduction

Measles (Rubeola) is a highly contagious, acute, exanthematous respiratory disease with a characteristic clinical picture and a pathognomic enanthem: Koplik's spots, an eruption on the buccal mucous membranes. It remains one of the most contagious viral infections worldwide and continues to be a major public health concern despite the availabilty of effective vaccination.
Like many other disease if not managed correctly it could lead to several complications affecting both the respiratory system and central nervous system. Among one of the most serious neurological complications is Subacute Sclerosing Panencephalitis (SSPE).
Subacute sclerosing panencephalitis (SSPE), a protracted, chronic, extremely rare form of measles encephalitis—sometimes follows measles and is particularly common among children who have measles before the age of 2 years. (Dennis L. Kasper, Anthony S. Fauci, 2010)
It was first described by Dawson in 1934 under the title "inclusion body encephalitis" and extensively studied by Van Bogaert, who renamed it subacute sclerosing panencephalitis. It is now recognized to be the result of chronic measles infection.
Never a common disease, the condition occurred until recently at a rate of about one case per million children per year. With the introduction and widespread use of measles vaccine, it has practically disappeared. It mostly affects children and teens for the most part, rarely appearing

beyond the age of 10 years. Typically there is a history of primary measles infection at a very early age, often before 2 years, followed by a 6- to 8-year asymptomatic period.
As the disease advances death occurs within 1 to 3 years. In about 10 percent of cases the course is more prolonged, with one or more remissions. In a similar number the course is fulminant, leading to death within months of onset. (Adams and Viktor's Principles of Neurology)
The incidence of Subacute Sclerosing Panencephalitis ranges from four to eleven cases per 100,000 measels infections globally. In lower and middle income countries, SSPE rates can reach up to 27.9 cases per 100,000 measels cases. While SSPE has become rare in regions with high vaccination coverage, outbreaks still lead to cases.
For instance, Georgia and the UK reported SSPE following recent measels outbreaks, especially in children who were exposed to measels during infancy.
SSPE continues to affect countries like India, Pakistan and Papua New Guinea, where the incidence remains notable high. (Garg & Pandey)
The illness evolves in several stages. Initially there is a decline in proficiency at school, temper outbursts and other changes in personality, difficulty with language, and loss of interest in usual activities. These soon give way to a severe and progressive intellectual deterioration in association with focal or generalized seizures, widespread myoclonus, ataxia, and sometimes visual disturbances due to progressive chorioretinitis. (Adams and Viktor's Principles of Neurology)
The diagnosis of SSPE is based on a combination of clinical presentation, characteristic findings on electroencephalography (EEG), and detection of measles-specific antibodies in the cerebrospinal fluid (CSF). While these tools are effective in confirming the diagnosis, early identification remains a challenge due to the insidious onset of symptoms. Treatment options are limited, and no definitive cure exists. Antiviral therapies and immunomodulatory interventions have shown promise in some cases, but outcomes remain highly variable. As such, the focus often shifts toward supportive care and efforts to improve quality of life for the affected individuals. (Garg & Pandey)
Given its rarity yet devastating outcome of SSPE, improved understanding of its pathogenesis, recognition and prevention remains essential. Throughout this paper to educate and further spread the current knowledge and to highlight the importance of early diagnosis and prevention.

Etiology And Pathogenesis

Measles virus (MV) is a negative-sense, single-stranded RNA virus in the *Morbillivirus* genus (family *Paramyxoviridae*). It has six structural proteins: N, P, M, F, H, and L. The N, P, and L proteins are crucial for replication and transcription. It’s RNA forms ribonucleoprotein (RNP) complexes with the N protein and the RNA-dependent RNA polymerase (made of P and L). The P gene also produces accessory proteins C and V.
MV can cause both acute infections and rare persistent infections. Evidence shows the virus can remain in the body for years and later reactivate, sometimes leading to **subacute sclerosing panencephalitis (SSPE)** long after the initial infection.
SSPE strains are not related to current circulating viruses but to strains present during the original infection, confirming persistence. These strains (SSPEVs) carry many mutations,

especially in the **M gene**, often causing defective M protein production due to hypermutation. This slows viral spread and promotes long-term infection.
Mutations also occur in the **F and H proteins**. The F protein can increase neurovirulence through enhanced fusion activity, while the H protein contributes to neurovirulence but is not essential for neuron-to-neuron transmission.
During acute measles virus (MV) infection, the virus alters host cell machinery to favor its own replication. It suppresses host protein synthesis ("shut-off") while ensuring preferential translation of viral mRNA.
In persistent MV infection, which may remain clinically silent for years, viral replication appears to stay in balance with host cell activity. The exact cellular changes that allow this long-term persistence and eventual progression to disease are not yet fully understood.
MV infection also significantly modulates host gene expression. It upregulates interferon-α but does not effectively activate certain antiviral pathways, such as double-stranded RNA-dependent protein kinases. It also alters NF-κB signaling and induces cellular responses related to endoplasmic reticulum (ER) stress and apoptosis. These changes are believed to contribute to the development of subacute sclerosing panencephalitis.
In neuronal cells, persistent MV infection affects lipid metabolism, leading to decreased cholesterol synthesis and impaired β-oxidation. Since proper lipid balance is essential for myelin production and maintenance, these disruptions can impair myelination in the central nervous system, contributing to disease progression.
Persistent measles virus (MV) infection causes both immunosuppression and abnormal immune activation. After acute infection, immune suppression can last for weeks due to cytokine imbalance and reduced lymphocyte activity. In contrast, persistent brain infection (as in subacute sclerosing panencephalitis) triggers an exaggerated immune response with very high levels of antiviral antibodies in serum and cerebrospinal fluid.
Persistent MV can directly damage cells, including oligodendrocytes, leading to demyelination. Immune cells (T and B cells) may also attack infected brain cells, contributing to tissue damage and possibly triggering autoimmune responses.
Autoimmunity may play a role, with antibodies targeting myelin components such as CD9, and cross-reactivity between viral proteins and myelin proteins (e.g., myelin basic protein).
Another proposed mechanism involves superantigens, which can broadly activate T cells, allowing them to enter the brain, increase blood-brain barrier permeability, and cause widespread inflammation and CNS damage. (Tomoyuki Honda)

Epidemiolgy, Risk Factors And Prevention Measures

The global prevalence of SSPE is approximately 4–11 cases per 100,000 cases of measles worldwide. Measles occurring during infancy, particularly before 12 months of age, increases the likelihood of SSPE to 18 cases per 100,000 children. A local population survey in Germany showed that children under 5 who had measles had a 1 in 1700 to 1 in 3300 chance of developing SSPE.
The widespread implementation of measles vaccination programs has considerably decreased SSPE incidence in several countries, but it is still significant in emerging economies, especially in Asia and Africa. However, the recent surge in SSPE cases is due to reluctance towards vaccination, poor patient education, and fewer initiatives for early immunization. Additionally, the COVID-19 pandemic has also impacted SSPE vaccination efforts, causing disruptions in

routine immunization programs and potentially leading to delays in monitoring and diagnostics of SSPE cases.

MV is an airborne pathogen transmitted by inhalation of droplets and through direct contact with infected individuals; the virus does not survive for a long time on the fomites as it is inactivated by heat and UV radiations. Several risk factors increase young children's susceptibility to contracting measles and developing SSPE, like: undernutrition, poor socioeconomic conditions, limited parental education, lack of measles vaccination, having more siblings, being born later in the birth order, and increased likelihood of exposure to measles before the age of 5.

Prevention of SSPE primarily involves preventing measles through vaccination wich is relatively cheap and easily available. Still, a huge part of the population remains unvaccinated for several reasons. Infants born to unvaccinated mothers are at higher risk of contracting measles right after birth and therefore have the highest risk of developing SSPE. Antimeasles antibodies transmitted through the placenta can temporarily protect infants from measles; however, the sustainability varies. To prevent outbreaks and transmission to infants too young to be vaccinated, more than 95% of the population should be immune to measles. The WHO advises the administration of the initial dose of the measles-containing vaccine (MCV) at 9 months where measles is prevalent and at 12–15 months in the nonendemic regions. (Zainab Mubbashir, February 2025)

Clinical Presentation

Stage	Clinical features
Stage 1	Subtle behavioral changes, personality alterations, irritability, and mild intellectual decline Episodes of inappropriate laughter Poor school performance Subtle myoclonic jerks
Stage 2	Marked myoclonic jerks, often periodic and synchronous Progressive cognitive decline, speech deterioration Gait disturbances Pyramidal signs
Stage 3	Severe cognitive decline with loss of speech and voluntary movements Akinetic mutism Autonomic dysfunction (e.g., hyperthermia, tachycardia, diaphoresis)
Stage 4	Coma or persistent vegetative state Loss of cortical function Autonomic instability, leading to death due to infections or respiratory failure

SSPE: subacute sclerosing panencephalitis

Fig.1

The classical clinical course of SSPE progresses through several stages. Initially, subtle cognitive decline and poor academic performance are observed, followed by forgetfulness, behavioral changes, and gait abnormalities. As the disease advances, verbal output decreases and patients experience difficulty walking. Eventually, they become akinetic and mute. In the terminal stages, patients enter in a vegetative state. One of the hallmark clinical features of SSPE is periodic myoclonus. These sudden, involuntary muscle contractions predominantly involve axial muscles. A slow relaxation phase is a characteristic feature of periodic myoclonus

in SSPE. Periodic myoclonus results in difficulties with walking and frequent falls. While myoclonic jerks do not impair consciousness, they can be worsened by excitement. In some cases, myoclonus appears as a subtle, periodic slow blinking or upward rolling of eyes. Seizures are another common symptom of SSPE, which may present as generalized tonic–clonic, focal, or atonic episodes and are often challenging to manage. Many patients display repetitive motor behaviors and vocalizations, such as clapping, finger-clicking, hand rubbing, and palilalia.

As SSPE advances, patients may develop pyramidal and extrapyramidal signs, including ataxia, dystonia, and dyskinesia. The intensity of myoclonus may diminish in the advanced stage. In the terminal stages, hypothalamic failure may occur, resulting in intermittent autonomic abnormalities. In the final stages of SSPE, patients may experience irregular breathing, decerebrate and decorticate rigidity, and become vegetative.

In addition to periodic myoclonus, SSPE can also exhibit several kinds of hyperkinetic and hypokinetic movement disorders. Hyperkinetic movement disorders, such as dystonia, chorea, and tremors, are more common and often manifest in the early stages of SSPE. On the contrary, hypokinetic movement disorders, including parkinsonism, tend to occur in later stages. Development of movement disorders in SSPE is thought to be related to the inflammation and degeneration of specific brain regions, including the basal ganglia and thalamus.

Vision loss is a common presenting complaint in SSPE. Vision loss in SSPE can occur due to various reasons, including retinal lesions, optic nerve involvement, and cortical vision loss. A systematic review of 96 cases with vision loss revealed that the majority of patients experienced visual manifestations before the onset of encephalopathy. The optic nerve is commonly affected, with optic atrophy and papillitis being characteristic findings.

Many patients initially present with psychiatric symptoms, including schizophrenia-like psychosis featuring hallucinations, delusions, and disorganized thinking. They may also develop catatonia, marked by motor immobility, rigidity, altered consciousness, and affective disturbances such as mania and depression. (Garg & Pandey)

Diagnosis

Doctors should consider SSPE in a child or young adult who presents with a dementia-like illness, especially if they develop seizures or their vision is affected. Brain scans may be normal in the early phase, but eventually magnetic resonance imaging (MRI) scans may detect changes affecting certain parts of the brain (the cerebral cortex, deep nuclei and white matter).

If the diagnosis is suspected, the level of specific measles antibodies (measles IgG) can be measured in the cerebrospinal fluid (CSF) and blood. A lumbar puncture is needed to obtain the spinal fluid. Parts of the measles virus (RNA) can also be detected in the CSF.

In the early stages of the illness an electroencephalogram (EEG) may be performed. This looks at brain wave activity. The findings on an EEG can be suggestive of SSPE with characteristic patterns of wave forms being noted. These are not seizures in themselves but show a disturbance of the normal electrical activity in the brain caused by the disease process. (Kneen, 2026)

CSF findings can include pleocytosis and increased immunoglobulins as described in the criteria with normal glucose and protein levels. ELISA of CSF will typically show the presence of the measles virus.

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

Magnetic resonance imaging (MRI) can show decreased gray matter volume, hyperintensities, and atrophy with marked ventriculomegaly. MRI helps clinicians follow disease progression. Initial imaging can be normal, then progress to lesions in the periventricular white matter, followed by spread into deep brain structures and the brainstem. Case reports have shown that some patients with SSPE develop primary brainstem lesions rather than the typical progression described above. Historically, these lesions in the brainstem have been suggestive of autoimmune or metabolic disorders. However, this evidence demonstrates that SSPE must also be considered with primary brainstem lesions on imaging.

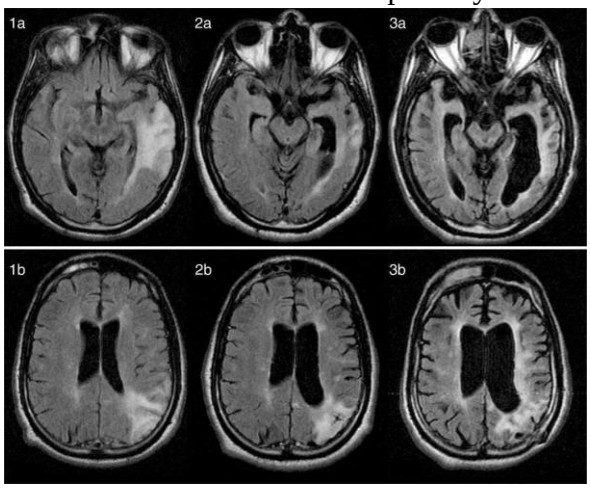

Fig.2. MRI findings

Magnetic resonance spectroscopy can also be used to evaluate patients for SSPE. If caught early in the course, there will be a decrease in N-acetyl-aspartate and an increase in choline, which is evidence of inflammation and demyelination. Later on in the disease course, there should be elevated ratios of choline to creatinine or inositol to creatinine with normal N-acetyl-aspartate to choline ratio or decreased N-acetyl-aspartate to creatinine ratio. These findings are suggestive of reduced brain volume. (Rocke & Belyayeva, May 2023)

Electroencephalography: The characteristic EEG pattern in SSPE features periodic discharges, also known as Radermecker complexes, which consist of distinctive high-amplitude, slow-wave complexes. These complexes typically are stereotyped and recur at regular intervals, often every 3–10 sec, and may be accompanied by muscle contractions or myoclonic jerks. As the disease progresses, the EEG pattern may evolve, with the periodic discharges becoming more frequent and the background activity becoming increasingly disorganized. (Garg & Pandey)

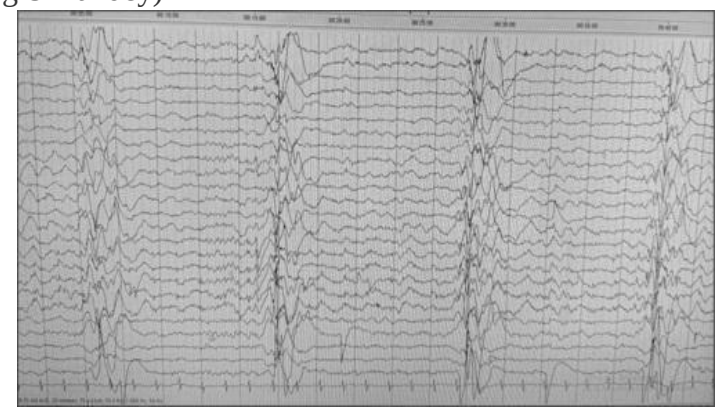

Fig.3. *Findings in a EEG*

Diferential diagnosis: Any patients with acute, progressive myoclonus, dementia, and/or seizures should be evaluated for the following:

- Viral encephalitis
- Autoimmune encephalitis
- Atypical multiple sclerosis
- Creutzfeldt-Jakob disease
- NMDA receptor encephalitis
- Neurometabolic encephalopathies
- Neoplasms
- Paraneoplastic syndromes
- Leukodystrophies
  (Rocke & Belyayeva, May 2023)

Treatment

There is currently no cure for Subacute sclerosing panencephalitis, and management is primarily supportive. Only about one-third of patients derive measurable benefit from available therapies. When improvement occurs, it is usually modest and may include slowing of disease progression, temporary stabilization, prolonged survival, or—rarely—clinical improvement.
Medical therapy: Several drugs are used, often in combination, although no standardized treatment guidelines exist:

- **Inosine pranobex (Isoprinosine):** An oral antiviral and immunomodulator that inhibits measles virus replication. It is typically given at 100 mg/kg/day (maximum 3000 mg/day). Some patients show slowed disease progression. Common side effects include elevated uric acid levels and occasional nausea.
- **Interferon alpha:** An immunomodulatory therapy administered intrathecally (into the cerebrospinal fluid), usually weekly. Long-term treatment is required for maximal effect.
- **Ribavirin:** A broad-spectrum antiviral that has shown limited success. It may provide mild additional benefit when used alongside interferon-alpha.
- **Antiepileptic drugs:**These are essential for controlling seizures and may also help reduce myoclonic jerks and associated encephalopathy.

Experimental and emerging therapies

Research into new treatments is ongoing:

[9] **Small interfering RNA (siRNA):** Shows promise in laboratory studies by inhibiting viral replication, but has not yet been tested in humans with SSPE.

[10] **Antiapoptotic agents:** Aim to prevent neuronal cell death.

[11] **Fusion inhibitors:** Proposed therapies that could block the spread of the measles virus within the central nervous system.

Ketogenic diet

The **Ketogenic diet** has been explored as an adjunct therapy. It may help reduce myoclonus, particularly in patients who do not respond to medications. Its potential benefits include:

[6] Reduction of oxidative stress

[7] Improved mitochondrial function
[8] Suppression of apoptosis

Some case reports describe significant improvement, including recovery of cognitive and motor function and complete suppression of myoclonus after prolonged use. However, outcomes are inconsistent, and benefits may be temporary in some patients.

Prevention (most effective strategy)

The best approach to SSPE is prevention through vaccination against the measles virus, the underlying cause of the disease.

[5] The **Measles vaccine** is highly safe and effective.
[6] It is given in two doses:
- First dose at 12–15 months
- Second dose at 3–5 years

[7] Because it is a live-attenuated vaccine, it is generally contraindicated in severely immunosuppressed individuals. However, the World Health Organization recommends vaccination in HIV-positive individuals who are not severely immunocompromised.
[8] Approximately 95% population immunity is required to eliminate measles transmission.

In recent years, measles has re-emerged in some developed countries, largely due to declining vaccination rates and vaccine hesitancy—highlighting the critical importance of maintaining high immunization coverage to prevent devastating complications like SSPE. (Rocke & Belyayeva, May 2023)

Conclusion

In conclusion, Subacute Sclerosing Panencephalitis (SSPE) is a rare but devastating progressive neurological disorder caused by persistent measles virus infection. Despite advances in medical research, there is currently no definitive cure, and available treatments mainly aim to slow disease progression and manage symptoms, with limited success. Therapies such as inosine pranobex, interferon-alpha, and antiepileptic drugs may provide partial benefit in some patients, while emerging approaches remain under investigation. Supportive strategies, including the ketogenic diet, may offer additional symptomatic relief in select cases. Ultimately, prevention through effective measles vaccination remains the most reliable and impactful strategy in reducing the incidence of SSPE. Maintaining high vaccination coverage is essential to prevent measles infection and its severe long-term complications.

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