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# DIAGNOSTIC APPROACHES AND MANAGEMENT OF SUBACUTE SCLEROSING PANENCEPHALITIS IN CHILDREN

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***Abstract: Subacute Sclerosing Panencephalitis (SSPE) is a progressive neurodegenerative disease that attacks the central nervous system, especially in the population of children and early adolescents, due to persistent measles virus infection.*** *The incidence of SSPE is quite rare, and data shows that in developing countries it is still quite high compared to developed countries. Diagnosis is based on clinical, supporting examinations such as EEG, as well as increased antibodies against measles virus in serum and cerebrospinal fluid. Symptoms can include changes in behavior, myoclonus, memory problems, and persistent pyramidal or extrapyramidal movements. Management to date has not provided satisfactory results and is individualized. Most SSPE patients experience a progressive and gradual course, leading to death within 1-3 years. The challenge of SSPE in children is the approach to diagnosis and management. Until now, the approach to treating SSPE in children is still based on the pathophysiological mechanisms from several existing research studies. That why therapy guidelines for children with SSPE are still varied. This paper aims to discuss the topic of SSPE in children with a major focus on diagnostic and therapeutic approaches based on the latest scientific evidence.*

***Keywords****: Subacute Sclerosing Panencephalitis (SSPE), children, diagnosis, therapy*

## INTRODUCTION

Subacute Sclerosing Panencephalitis (SSPE) is a progressive neurodegenerative disease that attacks the central nervous system, especially in the population of children and early adolescents due to persistent measles virus infection. The incidence of SSPE is quite rare, and data shows that in developing countries it is still quite high compared to developed countries. The diagnosis is based on patient's clinical condition, supporting examinations such as EEG, as well as increased antibodies against measles virus in serum and cerebrospinal fluid. Symptoms are includes the behavior changes, myoclonus, memory problems, and persistent pyramidal or extrapyramidal movements. The recent management guideline is individualized and has not provided satisfactory results. Most SSPE patients are experience a progressive and gradual course, it's leading to death within 1-3 years. The challenge of SSPE in children needs an approach to be diagnosed and treated. Until now, the approach to treating SSPE in children is still based on the pathophysiological mechanisms from several existing research studies. That why the guidelines of management SSPE in children are still varied. This paper aims to discuss the topic of SSPE in children with a major focus on diagnostic and therapeutic approaches based on the latest scientific evidence.

## DEFINITION

Subacute sclerosing panencephalitis, also called as Dawson's disease, is a fairly rare form of chronic progressive brain inflammation caused by a persistent hypermutated measles virus infection.[1] SSPE disease is a fatal long-term complication of measles infection, caused by intracerebral spread of the measles virus which causes nerve damage. Most patients survive 1 to 3 years after diagnosed, with a mean range about 18 months.[2]

## EPIDEMIOLOGY

Subacute Sclerosing Panencephalitis is a serious disease of the central nervous system due to a persistent infection of measles virus which is defective and the disease runs slowly. The incidence number of SSPE reached 18/100.000 in children under 5 years and 1,1/100.000 in children over 5 years. Several risk factors includes low socioeconomic and high population density. In developed countries, the incidence is less than 10 cases per year with prevalence 1 per 1 million population. Its prevalence can reach 21 per 1 million population in developing countries. The incidence decreased significantly after the measles vaccine was introduced. Most patients with SSPE have a history of primary measles infection at an early age (< 2 years), which continues with latent period of infection.[3,4] Most patients survive 1 to 3 years after diagnosed, with mean survival time is about 18 months.[2]

The neurological manifestations that appear will be progressive, and causes the death. Children who were infected with measles when they were under 1 year of age had 16 times greater risk of SSPE than those infected at 5 years of age or older. The incidence in boys is 3 times more frequent than girls. Other predisposing factors are those related to countryside lives and the number of family members living in one house.[5]

## PATHOGENESIS

Several host cell modifications, viral reactivation mechanism and immunopathology in the pathogenesis of SSPE have been described in several studies, all of this results has developed our understanding and knowledge about this disease. It has been known that there is an

interval time between primary measles infection with the manifestations of SSPE. It has been proven by the latent infection of the virus until it has spread to all parts of the brain. Measles virus infection is supposed to be getting pass through the cerebral endothelial cells and circulating inflammatory cells, resulting in latent infection of the central nervous system. Measles virus particles are pleomorphic, with a round structure and the diameter is about 100-250 nm. It's consisting of 6 constituent proteins. Unlike measles virus infection in non-neuronal cells which is extracellular, viral infection in neuronal cells is more intracellular and it occurs trans-synaptically. Hence, the levels of antibodies that responding the circulating viruses are very high, both in serum and cerebrospinal fluid.[6]

It has been known that persistent measles infection is usually asymptomatic, but eventually become SSPE. Latent measles infection should be reactivated during the disease onset and causing the SSPE symptoms. Several molecular and cellular mechanism play a role in virus reactivation. The potential molecules involved in reactivation of measles in SSPE are heat shock protein 72 and peroxiredoxin 1. Age-related modification such as hyperoxidation may explain why it takes several years after acute measles virus infection for the first symptoms of SSPE to appear.[7]

Measles virus that was isolated from the brain tissue of SSPE sufferers precisely inhibits the replication of the wild type of measles virus. This is related to point mutations that occur in the viral genome, causing a defect and persistent infection.[8] Mutations in the gene coding for matrix protein (protein M) are thought to be responsible for disruption of new viral particle assembly and budding, and also causes the spread of virus through the trans-synaptic route.[9] Transmembrane protein type 2 (H protein) will mediate viral adhesion by binding to a cell surface receptor, CD46, which is a complement regulatory protein on neuron nuclei cells and as an important cofactor for viruses to fuse. The presence of antibodies against the wild-type measles virus can actually change the expression of this defective measles virus. Therefore, although maternal antibodies to wild type measles virus persist until 9 months of age, measles virus infection at 1 year of age has a potential to alter its self expression. Both intracellular infection and cytokine-mediated inflammatory response can triggers apoptosis programs leading to neuronal cell death, including oligodendrocyte cells in SSPE patients.[10] The latency period for measles virus infection usually lasts 7-10 years after measles infection, but this usually occurs between 1 month to 27 years time frame. Shorter latency was reported in cases of children with earlier onset of measles (< 2 years).[11]

## CLINICAL MANIFESTATIONS

Patients that suffering from SSPE die within a few years of the initial clinical manisfestations, although there are rarely reported cases of spontaneous remission.[12] Epilepsy has been reported in one third of patients with SSPE. The initial clinical manifestations of SSPE usually include progressive decline in intellectual ability at school and behavioral changes followed by focal or generalized seizures and myoclonic movements, ataxia, visual disturbances and subsequently a vegetative state.[12,13]

As the disease progresses, there will be impaired of motor function and myoclonic jerks that stereotypic and periodic. Jerks often involve the head, trunk, upper and lower limbs. The muscle contractions that occur are followed by a relaxation period within 1-2 second. The patient does not

experience impaired consciousness caused by the myoclonic jerk that happened. The jerk will disappear during sleep and become more severe when the patient is active or awake. Myoclonus usually presents as difficulty in walking, periodic head movements, and even sudden falls. At a later stage, pyramidal and extrapyramidal signs may develop, accompanied by ataxia, dystonia and dyskinesia. Generalized tonic-clonic seizures and partial seizures may also occur. [4] Ocular and visual manifestations are reported in 10-50% of patients, including cortical blindness, chorioretinitis (focal necrotizing macular retinitis), and optic atrophy.[14] Visual symptoms are usually present with the appearance of neurological manifestations. In the later stages of the disease, the patient becomes quadriparetic, spastic, with myoclonic jerk that begins to disappear. Finally, there is autonomic failure with loss of thermoregulation, progressive loss of consciousness to coma, and the patient is in a vegetative state. Most patients with SSPE survive for 1-3 years after diagnosed, with a 18-months median survival.[15]

## PATHOLOGY

Brain biopsy that performed in the early stages of SSPE showed mild inflammation of the meninges and brain parenchyma, including cortical and subcortical white matter and gray matter. In addition, there was also neuronal degeneration, gliosis, astrocyte proliferation, perivascular cuffing, lymphocyte and plasma cell infiltration, and demyelination due to oligodendrocyte infection. In the more advanced stages of SSPE, the cerebral cortex atrophy is shown. Parieto-occipital region is the most commonly affected area. Inclusion bodies are seen in the nucleus and cytoplasm of neurons and glial cells. These inclusion bodies showed a homogeneous eosinophilic infiltration, seen in patients with rapidly progressive and fatal disease. Inclusion bodies that found in the brainstem are referred to as Cowdry type-B inclusion bodies. Neurofibrillary tangles showed the presence of viral activity, which is found in many neurons and oligodendrocytes. Significant histopathological changes, characterized by parenchymal necrosis and gliosis.[5]

## DIAGNOSIS

Clinical diagnostic setting is easier to enforce when there are manifestations of myoclonus, because early behavior changes are often not detected by either parents or teachers. Moreover, the diagnosis of SSPE are also based on typical EEG images and the results of cerebrospinal fluid analysis. If 3 of 5 Dyken criteria are met, the SSPE diagnosis can be determined. The diagnostic criteria refer to clinical findings, EEG source imaging, cerebrospinal fluid examination, antibody levels against measles and brain biopsy (Table 1).[4]

Table 1. SSPE diagnostic criteria[4]

| No. | Criteria | Diagnose |
|---|---|---|
| 1 | Clinical | Progressive, subacute mental deterioration with typical sign like myoclonus |
| 2 | EEG | Periodic, stereotyped, high voltage discharge |
| 3 | Cerebrospinal fluid | Raised gammaglobulin or oligoclonal pattern |
| 4 | Measles antibodies | Raised titre in serum (≥ 1:256) and/or cerebrospinal fluid (≥ 1:4) |
| 5 | Brain biopsy | Suggestive of panencephalitis |

Cerebrospinal fluid analysis usually shows normal results, or there may be a slight increase in protein. Significant increases in gammaglobulin levels is the most common result in SSPE patients, more than 20% (≥1: 4) of total cerebrospinal fluid protein (cerebrospinal fluid IgG concentration reaches 10–54 µg/dl, with normal value between 5-10 µg/dl). During agarose gel electrophoresis examination, an oligoclonal immunoglobulin band will be obtained against the measles virus, which indicates there is a B cell clones that has differentiated into plasma cells in the central nervous system due to the viral infection. The serum antibody levels againts measles virus also increased significantly (≥ 1: 256). Ratio of cerebrospinal fluid titre to serum titre in SSPE patients ranges from 1: 4 to 1: 128 (under 200), where this ratio is lower than the normal ratio due to other viral infections (1: 200–1: 500). Another serological method that used is ELISA (Enzyme Linked ImmunoSorbent Assay), this is sensitive in detecting measles virus specific IgG and IgM. The measles viral genome detected by PCR is more accurate to diagnose SSPE.[4]

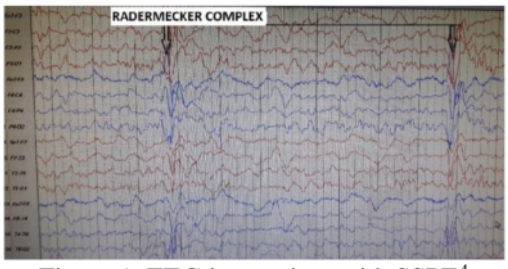


Figure 1. EEG in a patient with SSPE[4]

At the first of disease progress, EEG may be normal or shows only general, non-specific retardation. The EEG pattern is usually seen only when myoclonic symptoms appear and can be used as a diagnostic basis. A typical EEG display graphs is characterized by the presence of a periodic complex (Radermecker complex) consisting of polyphasic, stereotypical, bilateral symmetrical, synchronous delta waves with high voltage burst (200-500 mv). The waveform is identical at each lead. This periodic complex repeats at 4-10 second intervals regularly and has a 1:1 association with myoclonic (Figure 1). In the late or more advanced stages of the disease, the waves interval becomes shorter, even the EEG can become more irregular and show high amplitude and slowed dysrhythmias. Some variants of EEG display graphs that can be appear are the presence of periodic giant delta waves, mixed with rapid spikes and a slow EEG background. In addition, there may also be long spike wave eruptions interrupted by giant delta waves, it is indicating a poor prognosis.[16]

Imaging technology has a limited role in the initial diagnosis of SSPE. Head CT scan results often shows a normal results in early stage. But in the later stages, small ventricles and hemispheric sulcus obliteration and interhemic fissures due to cerebral edema may appear. Three to five years post symptom, there may be signs of cerebral atrophy and ventricular dilatation. MRI examination is more sensitive in detecting abnormalities in white matter. The initial change that occurs is the presence of high signal intensity area on T2-weighted image, especially in subcortical white matter of occipital region. In other cases, there was also gray matter involvements with asymmetric characteristics and especially in posterior part of the cerebral hemisphere (Figure 2). Parenchymal lesion volume correlates significantly with disease duration, until finally shows cerebral atrophy. A brain biopsy is rarely required to diagnose SSPE. Immunofluorescence examination can shows the presence of measles virus antigen.[17]

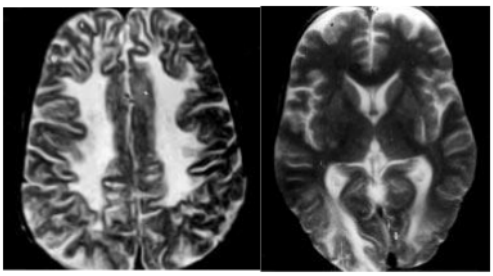

Figure 2. MRI of a patient with SSPE. The left display shows white matter demyelination diffuse and the right shows the hyperintensity of the occipital region.[17]

## TREATMENT

There is still no satisfactory treatment has been found for the effective management of SSPE. Only supportive treatment to extending the patients lifespan, although a small number of cases may experience spontaneous remission after long-term treatment. Isoprinosine is an immunomodulator that plays a role in increasing the number of CD4+ lymphocytes, increasing the function of NK and interferon cells, increasing the production of interleukin-1 and interleukin-2. Treatment with isoprinosine remains controversial because of contradicting results. The dose required is 100 mg/kg/day given once daily, especially if the patient is detected early and has not shown severe myoclonus. Interferon alpha is thought useful since the cerebrospinal fluid interferon in patients with SSPE is in lower level. Administration of exogenous interferon may suppress the viral addition and replication, and also strengthen the immune system. Intraventricular treatment regimen consists of six weeks of interferon alfa administration, starting at 100.000 units/$m^2$ of body surface area, then can be increased to 1 million units/$m^2$ for five days a week. Repetitions can be done up to six times, with 2-6 months interval. In some studies, combined oral isoprinosine treatment and intraventricular interferon alpha showed more effective for SSPE. The side effects of interferon alpha are fever, lethargy, anorexia, elevated liver enzymes and chemical meningitis.[4]

Ribavirin (40-60 mg/kgBW/day) and lamivudine (10 mg/kgBW/day) are antivirals that have been tested in experimental animals with SSPE and found to be effective. Use in combination with high dose of intraventricular interferon alpha has not been very satisfactory. Symptomatic treatment and good general care are the most important aspects in supportive treatment for SSPE. The use of anti-seizure drugs such as valproic acid has been very helpful in controlling myoclonus. Spontaneous remissions can occur at any stage of the disease and last for varying periods of time. The predisposing factors for spontaneous remission were the age at onset of SSPE is less than 12 years old and loss of the periodic complex on the EEG source imaging.[18]

## CONCLUSION

Subacute sclerosing panencephalitis is a neurodegenerative disease caused by persistent measles virus infection that has mutated in the central nervous system. The mechanism of its occurrence is not known, it is thought that the measles virus lives in an inactive form inside the cells after acute infection, it takes about 6 to 8 years to develop SSPE after measles virus infection. The onset of the disease occurs very suddenly. The first sign that appears is a mental status and behavioral changes or a decrease in learning achievement. The next symptom that appears is the Myoclonic Jerks movement. The next progressive process will involve subcortical gray matter and brainstem, this causing mental and motor deterioration. The death can occur in any stages, depending on the progression and severity of the disease. Diagnosis is

based on clinical manifestations, EEG source imaging, neuroimaging, laboratory findings. There is no satisfactory treatment. The symptomatic and supportive therapy can be given to extending the patients lifespan. Isoprinosin, interferon and antiviral administration is still controversial. SSPE has a generally poor prognosis.

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