
Personal Practice

Subacute Sclerosing Panencephalitis

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Subacute sclerosing panencephalitis (SSPE) is a common and serious disease of the central nervous system (CNS), and is caused by a mutant measles virus. Measles virus is an RNA virus which belongs to the morbillivirus subgroup of paramyxoviruses. SSPE is an example of CNS disease caused by aberrant viral gene expression and persistent viral infection of neural cells.

Epidemiology

In western part of world it is considered a rare disease, with less than 10 cases per year reported in the United States(1). The incidence has declined substantially since introduction of an effective measles vaccine. The annual incidence of SSPE is quite high but variable among developing countries. Saha *et al.*(2) reported an annual incidence rate of 21 per million population in India, in comparison to 2.4 per million population in Middle East(3). Most patient give history of primary measles infection at an early age (< 2 years), which is followed after a latent period of 6 to 8 years by the onset of a progressive neurological dis-

order. Children infected with measles under age of 1 year carry a risk of 16 times greater than those infected at age 5 years or later(4,5). A higher incidence (male/female ratio 3:1) has been noted in boys. The incidence is higher among rural children than city children, children with two or more siblings, children of lower socio-economic status, and mentally retarded children. Neither the age of exposure to measles, nor severity of infection seem to affect the age of onset of SSPE or course of illness. Widespread immunization has produced greater than 90% reduction in the incidence of SSPE in developed nations (6). In vaccinated children a prolongation of age of onset and latency of infection had been observed. There is no evidence to suggest that attenuated vaccine virus is responsible for sporadic cases of SSPE(1).

Pathogenesis

SSPE virus is distinguished from the wild type of measles virus in that there appears to be a defect in assembly of the virus within the nervous system, and which is related to an abnormality of matrix of 'M' protein of the virus. These conclusions are based on the studies that show that the matrix protein is the only structural protein which is undetected in brain cells from patients with SSPE, and on observation of a selective decrease in antibodies to the matrix protein in these patients. Studies on SSPE cell lines further suggest that the M protein may be synthesized but fails to accumulate and there may be defective translation of matrix messenger RNA. Thus, an immune response can be made against the viral hemagglutination resulting in very high levels of neutralizing antibody, and yet the antibody is ineffec-

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tive in eradicating the virus. So, M-protein is necessary for correct assembly of progeny virus at the surface of infected cells, mutations in this protein lead to an antigenically distinct form, that can no longer bind to viral nucleocapsid that initiate virus maturation. The absence of functionally intact, budding virus particle, results in intracellular accumulation of incomplete measles virus in brain cells(7-12).

In addition, modulation of measles antigen on the surface of infected cells by antimeasles antibody has been described, and this modulation might make the cell vulnerable to attack by the immune system and could alter expression of virus within the cell. It is also possible that antigenic challenge of a second infection could alter the dormant state of SSPE virus and result in disease expression. Sero-epidemiological data suggest that an exposure to another virus, such as Epstein-Barr virus or influenza type I virus may transform the measles virus into a defective virus(13,14).

Pathology

Brain biopsy performed in the early stages of SSPE shows mild inflammation of the meninges and brain parenchyma involving cortical and subcortical grey matter as well as white matter, with cuffs of plasma cells and lymphocytes around blood vessels. In the subsequent stage, gross examination of brain may reveal mild to moderate atrophy of cerebral cortex. Microscopic examination shows widespread degeneration of neurons and disorganization in the cortex. Parieto-occipital region of cerebral hemisphere is most severely affected; subsequently, it spreads to the anterior portions of cerebral hemisphere, the subcortical structures, brainstem and spinal cord. Focal or diffuse perivascular infiltrates of lymphocytes, plasma cells and phagocytes are present in

the meninges and in the brain parenchyma. Inclusion bodies are seen within both nucleus and cytoplasm of neurons and glial cells. Cowdry type-A inclusion bodies consisting of homogenous eosinophilic material, are diffusely seen in neurons and oligodendroglia in patients with rapidly progressive fatal disease. Another, Cowdry type-B inclusion bodies are small and multiple, and are almost always present in brainstem. These later type of inclusions are less often seen. Late in the course of the disease it may be difficult to find typical areas of inflammation, and the main histopathological changes are marked with parenchymal necrosis and gliosis(1,14,15).

Measles viral antigens can be demonstrated by labeled antibody technique within the inclusions as well in cells without inclusions. Data from several studies suggest that the endothelial cells in the brain are frequently infected during acute fatal measles. This site of infection may provide a portal of entry for virus in persons who subsequently develop SSPE or measles inclusion body encephalitis(16,17).

Clinical Features and Classification

The clinical features and time course of SSPE are highly variable. The initial symptoms are subtle and include intellectual deterioration and behavioral changes without neurological signs or findings. As disease progresses non-specific manifestations give way to marked disturbance in motor function and the development of periodic myoclonic jerks. Myoclonic jerks initially involve the head and subsequently trunk and limbs. Muscular contraction is followed by 1 to 2 seconds of relaxation associated with a decrease in muscle action potential or complete electrical silence. The myoclonic jerks do not interfere with consciousness. They are exaggerated by excitement, and may disappear during sleep.

Initially they are infrequent and might be regarded as stumbling or clumsiness. At this stage seizures may occur. Macular chorioretinitis is seen in up to 50% of cases. Retinopathy and optic atrophy may develop in addition to cerebellar ataxia and dystonia. Few patients may present with cortical blindness. The late stage of the disease is marked by stupor and coma, autonomic failure with loss of thermoregulation leading to temperature fluctuations and disturbed sweating. In late stages, myoclonic jerks diminish in intensity and eventually disappear. In majority of cases death occurs between 1 and 3 years after onset of symptoms. Ten per cent of the patients have a fulminant course, dying within months, and 10 per cent survive for 4-10 years with extended periods of stabilization. Spontaneous improvement may also occur during any of the stage of the disease and may last for a variable period of time before eventual relapse occurs(5,18,19).

Staging of SSPE is done according to modified Jabbour classification(20), as follows: Stage-I: mental and behavioral changes, forgetfulness, irritability and lethargy; Stage-II: myoclonic jerks, dyskinesia, choreoathetosis, ataxia; Stage-III: decerebrate rigidity and decorticate rigidity; and Stage-IV: severe loss of all cortical function, flexion posturing of limbs and mutism.

Diagnosis

Despite characteristic signs and symptoms early diagnosis of SSPE is not always easy, early detection of myoclonus is important to make reasonable diagnosis. Subtle behavioral changes are easily missed by the relatives and these patients are often treated by a psychiatrist at this stage. In some cases myoclonus is not present in the early stages, only atonia may be present and can be overlooked. Occasionally, the patient can demonstrate lateralizing neuro-

logical signs, partial seizures, or papilloedema, these findings can lead to an erroneous diagnosis of an intracranial space-occupying lesion.

Cerebrospinal Fluid (CSF)

The CSF pattern may be diagnostic. The fluid is usually cellular with a normal or mildly elevated protein level and a markedly elevated gamma-globulin level (comprising at least 20% of total CSF protein)(21,22).

Electroencephalography (EEG)

Early in the course of disease, the EEG may be normal or show only moderate, non-specific slowing. The typical EEG pattern is usually seen in myoclonic phase and is diagnostic. EEG picture is characterized by periodic complexes consisting of bilaterally symmetrical, synchronous, high-voltage (200-500mv) bursts of polyphasic stereotyped delta waves. They remain identical in any given lead. These periodic complexes repeat at fairly regular 4 to 10 second intervals and have a 1:1 relationship with myoclonic jerks (*Fig. 1*). Earlier each complex lasts between 0.5 and 2 seconds, may recur as infrequently as every 5 minutes. These complexes may be present only during sleep, and may be elicited by afferent stimuli. Later in the course of illness, the EEG becomes increasingly disorganized and shows high-amplitude, random dysrhythmic slowing, in terminal stages the amplitude may fall(23-25).

In addition to type-I EEG abnormalities just described, few other types of EEG abnormalities have also been recognized which have some effect on prognosis of the disease. Type-II abnormalities are characterized by periodic giant delta waves intermixed with rapid spikes as fast activity. EEG background is usually slow. Type-III EEG pattern in patients of SSPE is charac-

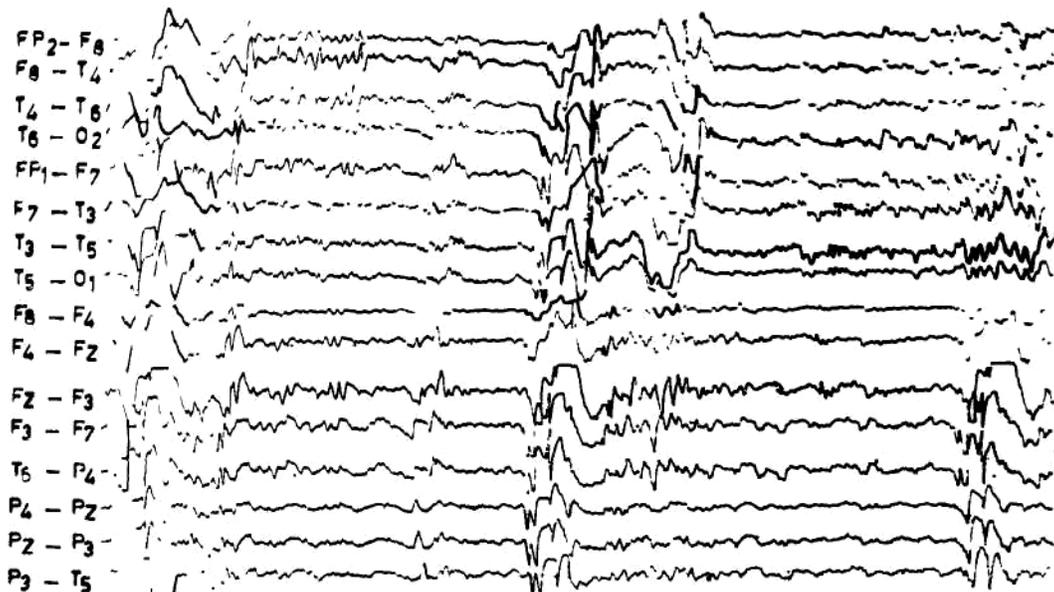


Fig 1 EEG periodic complexes in 9 year old boy with 4 months history of myoclonus and mental deterioration. The EEG is showing giant polyphasic delta waves at regular interval of 2-3 seconds. The background activity shows theta and alpha waves.

terized by long spike-wave discharges interrupted by giant delta waves(24,26). Yaqub(24) recently demonstrated that video-split electroencephalographic monitoring is a more sensitive technique for early diagnosis and detection of atonia or myoclonus time-related to EEG periodic complexes. He further observed that type-III EEG discharges were related to worst outcome while patients with type-II had the best outcome. In this study outcome was determined by the progression of the disease.

Neuroimaging

Computed tomography (CT) and magnetic resonance (MR) imaging have limited role in the early diagnosis of SSPE. CT scan of brain is normal in early stages of disease, in later stages it shows small ventricles and obliteration of hemispheric sulci and inter-hemispheric fissure due to diffuse cerebral edema. Generalized or focal cerebral atrophy and ex-vacuo ventricular dilation can

be seen after a prolonged course, but CT scans are normal sometimes as late as 5 years after onset of the disease(27,28). Low attenuation areas in the basal ganglion have also been observed(19). MR is better in visualizing white matter lesions. White matter involvement is usually multifocal and more prominent in parieto-occipital region and is better seen in T2-weighted images. This finding is non-specific and of relatively poor diagnostic value in SSPE(29). Single photon emission computed tomography (SPECT) may reveal hypoperfusion of cerebral blood flow in the occipital areas and other affected parts of the brain as early as stage-I of SSPE.

Brain Biopsy

Brain biopsy or autopsy reveals perivascular inflammation, neuronal loss, astrocytosis and gliosis and intranuclear inclusions in neurons or glial cells. Brain biopsy is rarely required for establishing a proper diagnosis(16).

Virological Studies

Antibodies against measles virus can be demonstrated in both serum and CSF by a variety of techniques. Usually, the ratio of antibody content in CSF compared to serum is disproportionately high. When the CSF is examined by electrophoresis or isoelectric focusing oligoclonal band of immunoglobulins are often observed. IgG and IgM antibodies to measles virus are not normally found in unconcentrated CSF. In patients of SSPE these antibodies make up most of the immunoglobulins of CSF, and can be detected in dilutions of 1: 4 or more.

Various serological methods used are complement fixation, hemagglutination inhibition (HAI), enzyme linked immunosorbent assay (ELISA)(30-32) and virus neutralization(14). Quantitation of measles virus-specific antibodies reveals that the majority of IgG antibodies in CSF are measles specific, with the specific antibody index for measles virus usually greater than ten(22). In rare instances measles antibodies may be undetectable, but become positive on subsequent study(33). Antibody titers may fluctuate during natural course of illness, and during therapy. In a study by Saha *et al.*(2), antibody titer (HAI method) ranged from 2 to 32 in CSF and in sera from 8 to 2048. The normal ratio of titer in serum to titer in CSF is reduced (below 200) for measles antibodies, whereas serum-CSF ratios are normal for other viral antibodies and for albumin, indicating that increased amounts of measles antibodies in CSF of children with SSPE result from synthesis within the nervous system and the blood brain barrier is normal.

Measles virus can also be cultivated from brain tissue using special cultivation technique. Viral antigen can be identified immunocytochemically and viral genome can be detected by *in situ* hybridization or

polymerase-chain reaction (PCR) amplification method(1).

Diagnostic Criteria

SSPE can be diagnosed if the patient fulfills three of the following five criteria: (a) typical clinical presentation; (b) typical electroencephalographic changes with stereotyped periodic complexes; (c) typical histo-pathological finding in brain biopsy or autopsy; (d) elevated CSF globulin levels, greater than 20% of total CSF protein; and (e) elevated CSF measles antibody titers of 1/4 or more by hemagglutination inhibition method, or 1/20 or more by ELISA(25).

Treatment

No adequate therapy is currently available for the patients of SSPE. Observations of some non-randomized studies suggest that certain immuno-modulator anti-viral agents can prolong life if long-term treatment is given. Issue of treatment is further complicated by extremely variable natural course as few patients may have spontaneous prolonged remission(34).

Isoprinosine (Inosiplex)

Isoprinosine is an anti-viral drug which acts by activating body's immunological system against measles virus. This drug increase the number of CD4+lymphocytes, augment natural killer (NK) cell functions, potentiate interferons and increase the production of interleukin-1 and interleukin-2. Treatment with isoprinosine (Inosiplex) remains controversial but has been reported to prolong survival and produce clinical improvement in some patients. This drug is recommended in daily dose of 100 mg/kg/day and without major side effects(1,14). Nunes *et al.* (35) observed good results combining trihexyphenidyl and isoprinosine in controlling myoclonus refractory to sodium valproate.

a-interferons

The pathophysiology of natural remissions and relapses in SSPE is unknown. The stable state may depend on a balance between viral replication and body's immune response, as state of immune system possibly has a role in remissions. The CSF interferon levels are low in these patients. Exogenous interferons suppress replication of virus and also influence immune system. Intravenous administration of *a*-interferon has not proved useful because of poor penetration of blood brain barrier. The modest improvement with intraventricular and intrathecal routes (6 million unit/dose/week) of administration have been observed in small number of patients(36). There are early relapses after discontinuing interferon therapy. A prolonged therapy is needed for sustained response(37). Several authors have reported combined use of *a*-interferon plus isoprinosine. In a recent study, Anlar *et al.*(38) observed a higher survival rate in the 22 patients after long-term (56-108 months) treatment with intraventricular alpha-interferon and inosiplex as compared to those who did not receive *a*-interferon regimen. However, this combination did not affect oligoclonal bands and intrathecal CSF immunoglobulin (IgG) synthesis(39).

Intravenous Immunoglobulins

In isolated case report intravenous immunoglobulins have been found effective in SSPE when administered along with prolonged therapy with inosiplex. However, this form of treatment need further evaluation before it can be recommended for regular management of SSPE(40).

Cimetidine

Cimetidine, an H₂-receptor antagonist, was used in SSPE due to its immunomodulatory effect. Anlar *et al.*(41) did not

observe any worsening in cimetidine-treated group during the study period, whereas placebo group deteriorated significantly.

Symptomatic Treatment

The good general nursing care is the most important aspect in the management of SSPE. Anticonvulsants, sodium valproate and clonazepam, are helpful in controlling the myoclonus. If spasticity is marked, beclufen and other antispastic drugs may be tried.

Conclusion

One of the most important limitation in treatment of SSPE is the inability to detect early manifestations of the disease, when the inflammatory changes are possibly still reversible. There is a need for more awareness of the disease amongst primary care physicians and pediatricians. Home care system for these handicapped children is very important and meaningful to increase "quality of life" in them and their families. Their families have to have a lot of physical, psychological and economical stress to endure. A great deal of external support is needed for these suffering families to cope up these stresses.

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