

Review Article

SUBACUTE SCLEROSING PANENCEPHALITIS REVISITED

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ABSTRACT

Subacute sclerosing panencephalitis (SSPE) is a chronic progressive neurological disorder occurring after infection with defective measles virus, the virus is able to persist in CNS for years, causing demyelination and degeneration. Only 5% of individuals with SSPE undergo spontaneous remission, with the remaining 95% dying within 5 years of diagnosis. The prevalence of the disease varies depending on the measles vaccine immunization status. The clinical manifestations occur, on an average 6 years after measles virus infection and may initially present with a varied clinical picture ranging from psychiatric to ophthalmological to neurological symptoms and signs. The diagnosis is based upon characteristic clinical manifestations of myoclonus, the presence of characteristic periodic EEG discharges, and demonstration of raised antibody titre against measles in the plasma and cerebrospinal fluid with or without neuroimaging findings. Management includes symptomatic treatment for seizures and complications related to progressive disability and autonomic failure. Treatment with isoprinosine and immunoglobulin alpha have been tried with variable success rates and appears to be the best treatment option available at hand. However, primary prevention by measles vaccination is the most effective method of reducing disease burden in developing countries.

Key Words: *Subacute Sclerosing Panencephalitis (Sspe), Slow Myoclonus, Periodic Complexes, Antimeasles Antibodies*

INTRODUCTION

Subacute Sclerosing Panencephalitis(SSPE), is a slow virus infection, a rare chronic encephalitis caused by persistent defective measles virus infection of the central nervous system. SSPE had originally been described as three different neuropathological entities. In 1933, Dawson described condition subacute inclusion body encephalitis in a child with progressive mental deterioration and involuntary movements, who at necropsy had dominant involvement of grey matter with abundance of neuronal eosinophilic inclusion bodies (Dawson, 1933). Later, Pette and Doring (1939) reported a case with equally severe lesions in both grey and white matter which they addressed as “nodular panencephalitis” (Pette *et al.*, 1939). Six years later, Van Bogaert used the term “subacute sclerosing leukoencephalitis” for the presence of dominant demyelination and glial proliferation in the white matter (Van Bogaert, 1945) It was Greenfield who in 1960 gave the term “Subacute sclerosing panencephalitis”, for a condition due to persistent infection by a virus involving both grey matter and white matter (Greenfield, 1950). Dawson proposed a viral etiology for SSPE, but it was Bouteille *et al.*, in 1965, who on electron microscopy demonstrated the presence of viral structures resembling nucleocapsids of paramyxovirus virus in the brain (Boutteille *et al.*, 1965). This finding was followed by search for antibodies against paramyxovirus in the blood and CSF of patients with SSPE which yielded raised titers of anti- measles antibodies in the blood and CSF of all patients studied (Connolly *et al.*, 1967). In 1969 measles virus was actually recovered from the brain of a patient with SSPE (Horta-Barbosa *et al.*, 1969).

Epidemiology

SSPE though reported from all parts of the world, is considered a rare disease in developed countries, with fewer than 10 cases per year reported in the United States (Garg, 2002 and Jabbour *et al.*, 1972). The incidence of SSPE is still high in developing countries such as India and Eastern Europe. Saha *et al.*,

Review Article

(1999) reported an annual incidence of 21 per million population in India, in comparison with 2.4 per million population in the Middle East (Radhakrishnan *et al.*, 1988 and Yakub, 1996).

Children with SSPE are more likely to have been infected with natural measles than vaccine virus. Youngsters with history of measles who subsequently developed SSPE had contracted it at an early age, usually younger than 2 years, followed by a latent period of 6 to 8 years before onset of neurological symptoms (Okuno *et al.*, 1989). 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. Males suffer three times more than females with higher incidence among rural males, children with two or more siblings, children with lower birth order, children living in overcrowded conditions and children with mental retardation (Halsey *et al.*, 1980; Miller *et al.*, 1992; Zilber *et al.*, 1998; Modlin *et al.*, 1979 and Roger Detels *et al.*, 1973). It has been suggested that these features (age of exposure, sex, and geography) are indicative of intensive measles exposure as a risk factor (Aaby *et al.*, 1984 and Kirk *et al.*, 1991). A close temporal relationship of measles with another viral infection such as Epstein-Barr virus or parainfluenza type-1 virus, also identified as risk factors for SSPE, may modify the course of acute measles infection.

Maternal measles or incomplete maternal transfer of antibodies to the newborn is associated with a higher risk for developing early SSPE with a fulminant course (Anlar *et al.*, 2001; Campbell *et al.*, 2007 and Prashanth *et al.*, 2006). Individuals with acquired immunodeficiency syndrome or children whose mothers have acquired immunodeficiency syndrome might be at higher risk of a fulminant course and earlier onset of SSPE (Koppel *et al.*, 1996 and Sivadasan *et al.*, 2012).

The incidence of SSPE has decreased over years since the introduction of live attenuated measles vaccine, by at least 90 percent in countries that have practiced widespread immunization with measles vaccine (Miller *et al.*, 2004).

Pathogenesis

Measles virus possibly enters the nervous system at the time of original systemic infection and enters the central nervous system either by direct infection of endothelial cells or in infected leukocytes. The major entry receptor for measles virus appears to be Signalling Lymphocytic Activation Molecule (SLAM, CD150) and CD46, although additional unidentified receptors have been reported too (Ludlow *et al.*, 2009 and Andres *et al.*, 2003). Once inside the cell the virus modulates the cell machinery to escape immune system (Inoue *et al.*, 2002 and Cattaneo *et al.*, 1986).

Various factors lead to chronic brain infection with measles virus, most important one is defective viral replication. Extensive sequence analysis of viral RNA obtained from tissue has shown that SSPE viruses are related to wild-type strains circulating at the time of the primary infection, but frequently have undergone mutations in the viral genes encoding the M, F, and H proteins (Baczko *et al.*, 1986; Cattaneo *et al.*, 1989; Jin *et al.*, 2002 and Schmid *et al.*, 1992). In general, expression of M protein is low (Liebert *et al.*, 1986; Sheppard *et al.*, 1986 and Stephenson *et al.*, 1981). Multiple defects have been found in the mRNA encoding M protein (Cattaneo *et al.*, 1989). Most common mutation encountered is replacement of U with C known as biased hypermutation, and it is suggested that it may be due to mutation of double-stranded RNA in persistently infected cells by adenosine deaminase (Cattaneo *et al.*, 1992 and Wong *et al.*, 1991). M transcripts often lack initiator codon and, when it is expressed, M proteins have defects in binding to viral nucleocapsids and in downregulating transcription (Hirano *et al.*, 1993; Suryanarayana *et al.*, 1994). H proteins are often defective in intracellular transport and protein-protein interactions important for cell-cell fusion (Cattaneo *et al.*, 1993). Truncations, mutations, and deletions in the cytoplasmic domain of F are almost always found. Truncations do not affect fusion, but may interfere with virus budding.

Human neuronal cells are mainly Signalling Lymphocytic Activation Molecule (SLAM) and nectin 4 negative and fusion-enhancing mutations in the extracellular domain of the F protein induces syncytium formation in cells lacking SLAM and nectin 4, when expressed together with the attachment protein hemagglutinin, regardless of M protein defect, contribute to the virus spread via cell-cell fusion in CNS (Watanabe *et al.*, 2013).

Review Article

In acute phase, B-cell lymphoma-2 induce apoptosis and DNA fragmentation have been suggested as early causes of neuron and oligodendrocytes death, and lipid peroxidation and disturbed Glutamate transport have been implicated in subsequent neuronal degeneration (Hayashi *et al.*, 2002).

Antibody response to virus is vigorous, with significant production of MV-specific antibody by plasma cells residing in the CNS (Burgoon *et al.*, 2005), and is evident both in serum and CSF (Esiri *et al.*, 1982; Tourtellote *et al.*, 1981) at the time of neurological symptoms. Antibody produced in the CNS is of restricted heterogeneity, leading to the appearance of oligoclonal immunoglobulin bands on electrophoretic analysis of CSF. Antibodies against the N and P proteins present in the ribonucleoprotein complex are particularly abundant, while the antibody against the M protein is particularly deficient (Hall *et al.*, 1979).

Shahar *et al.*, (2009) found that measles virus co-localized to lipid rafts in both acute and persistent infection models and that in persistent infection there is downregulation of majority of genes associated with cholesterol synthesis, suggesting decreased cholesterol synthesis as a possible link with the defective viral budding in persistent infection.

Neurofibrillary tangles (NFTs) have been shown in 20% of subacute sclerosing panencephalitis (SSPE) cases and Apo E3 role has been proposed in controlling its formation (Yuksel *et al.*, 2012). A recent study by Anlar *et al* has shown elevated percentage of CD8+ cells in SSPE patients compared to age-matched control children. Rapidly progressive course was associated with increased CD4+ cells. It was suggested that the proportions of lymphocyte subsets have a role in the evolution or manifestations of SSPE, if not in the pathogenesis (Anlar *et al.*, 2005).

In view of clinical similarity between Dravet syndrome and SSPE it has been thought recently that SCN1A gene mutation could be associated with SSPE also (Garg, 2012).

Pathology

The inflammatory changes initially tend to be more pronounced in the posterior areas of the brain, with marked involvement of the medial thalamus and deep structures followed by spread to anterior areas (Singer *et al.*, 1997), with relative sparing of the cerebellum (Hayashi *et al.*, 2002).

The pathological findings depend upon when the tissue is sampled during the course of disease. In the initial stage of disease, oedema appears to be the predominant finding (Tuncay *et al.*, 1996). Cortical and subcortical perivascular infiltration of inflammatory cells, spongiosis, and demyelination are reported in the acute phase, followed by neuronal loss as the disease evolves (Tomoda *et al.*, 1997; Tuncay *et al.*, 1996; Singer *et al.*, 1997). Studies of inflammatory cell infiltrate in brain tissue from patients with SSPE have shown that the perivascular cells are predominantly CD4+ T cells, with B cells seen more frequently in the parenchymal inflammatory infiltrate (Nagano *et al.*, 1991).

During the acute inflammatory phase, nucleocapsids have been found in oligodendrocytes and neurons along with nuclear bodies with granulofilamentous inclusions in astrocytes (Tomoda *et al.*, 1997; Lewandowska *et al.*, 2001). Cowdry type-A inclusion bodies which consists of homogeneous eosinophilic material, are diffusely seen in neurons and oligodendroglia in patients with rapidly progressive fatal disease. Another Cowdry type-B inclusion bodies, small and multiple, are almost always present in the brainstem. Subsequent studies have shown that these nuclear inclusions contain viral antigens (Scully *et al.*, 1986). Late in the course of disease histopathological changes are marked with parenchymal necrosis and gliosis, making it difficult to find typical areas of inflammation and even inclusion bodies (Ohya *et al.*, 1974).

Neurofibrillary tangles may also be seen within neurons and oligodendrocytes. In situ hybridisation methods have shown that cells containing tangles often contain the viral genome, suggesting that viral infection causes the formation of tangles (McQuaid *et al.*, 1994).

Clinical Features

Patients of SSPE may be found consulting Psychiatrist, Ophthalmologist and Neurologist depending upon the complaints. The wide spectrum of clinical presentation includes falling attacks, changing gait, abnormal movements, speech impairment, inability to walk or stand, seizures, dementia, visual

Review Article

disturbances, pyramidal and extrapyramidal signs. In initial stages child can present at psychiatric department for behavioural changes, cognitive decline, depression (Datta *et al.*, 2006) and rarely catatonia (Aggarwal *et al.*, 2011). Ocular and visual manifestation are reported in 10-50% patients, which at times can precede the neurological manifestations by several years (Green *et al.*, 1997; Caruso *et al.*, 1997). Visual disturbance may present as cortical blindness, anton's syndrome, chorioretinitis (Yimenicioglu *et al.*, 2012), optical atrophy and can also present as neuromyelitis optica (Raut *et al.*, 2012). Various ophthalmologic features reported are retinitis, macular pigment disturbances, optic neuritis, visual agnosia (Cochereau-Massin *et al.*, 1992; Colpak *et al.*, 2012).

Once the myoclonus is evident diagnosis becomes clear. The myoclonus in these patients appears as a jerk followed by momentary sustained position and then gradually melts away to the static position. These myoclonic movements often occur in upper extremities have Electromyographic (EMG) burst duration greater than 200 msec and have a consistent relationship to periodic complexes on routine EEG. The complex nature of EEG discharge makes it difficult to measure latency between the EEG discharge and the jerk EMG discharge. The complexes are typically widespread and synchronous.

In advanced stages, patients become quadriparetic, spasticity increases, and myoclonus may decrease or disappear. There is marked temperature fluctuation due to autonomic failure which leads to loss of thermoregulation. There is progressive deterioration of sensorium to a comatose state and ultimately the patient becomes vegetative. Decerebrate and decorticate rigidity appear, breathing becomes noisy and irregular. At this stage, patients frequently die due to hyperpyrexia, cardiovascular collapse, or hypothalamic disturbances (Risk *et al.*, 2007).

Typical patient of SSPE having acquired mental subnormality with characteristic myoclonic jerks possess no diagnostic difficulty. What is important is to diagnose very early cases and late cases of SSPE. **Table1** shows diagnostic criteria for SSPE. **Table2** and **Table3** show various proposed staging systems for SSPE. A Neurological disability index (NDI) can be calculated as suggested by Dyken *et al* and its modified form is given by Anlar *et al* (**Table4**). Conditions mimicking SSPE due to rapidly evolving dementia, myoclonus and seizures should be differentiated (**Table 5**).

Adult-Onset SSPE

The mean age of onset of SSPE has been reported to be increasing (Dyken, 1985), the adult onset SSPE (above 18 years of age) is uncommon. The incidence of adult onset SSPE reported to vary between 1–1.75% and 2.6% (Haddad *et al.*, 1977; Yalaz *et al.*, 1987). Patients with positive available history of measles exposure usually contract it either earlier (younger than 3 years old) or later (after 9 years) than the usual childhood measles infection (Singer *et al.*, 1997). Where the primary infection is known, unusually long measles-to-SSPE intervals have been documented, ranging from 14 to 22 years. None of the reported cases followed measles vaccination. The largest series reported by Prashanth *et al.*, (2006) of 39 patients constituted 12.7% of the cohort evaluated over a decade. Mean age in these 39 patients was 20.9 years. Thirty two patients in this series presented with either cognitive or behavioral changes or myoclonus and only two had ophthalmic symptoms whereas Singer *et al* observed only two of 13 have personality changes while eight has purely ophthalmic manifestations. The course of the disease was progressive and fatal in the majority (Garg, 2002; Nagaraja *et al.*, 1985), but there may be a higher rate of spontaneous remission as compared with childhood-onset SSPE.

INVESTIGATIONS

Electroencephalography (EEG)

Early in the course of the disease, the electroencephalogram (EEG) may be normal or show only moderate, non-specific generalised slowing. The typical EEG pattern is usually seen in myoclonic phase and is virtually diagnostic (Garg, 2002). Periodic complexes (**fig. 1**) are found in 65 to 83% of individuals with SSPE (Halsey *et al.*, 1980) and are described as stereotyped, bilaterally synchronous, and symmetrical 100–1000mV, 1–3Hz waves, sometimes intermingled with spikes or sharp wave (Kurata *et al.*, 2004; Ekmekci *et al.*, 2005) Their duration ranges from 1 to 3 seconds and the interval between

Review Article

complexes varies from 2 to 20 seconds, although in the early phases they can recur every 5 minutes (Ekmekci *et al.*, 2005), usually having a 1:1 relationship with myoclonic jerks. The periodic complexes of SSPE first appear during sleep, when they may not be accompanied by myoclonic spasms. Late in the course of disease, the EEG may become increasingly disorganised and show high amplitudes and random dysrhythmic slowing. In terminal stages the amplitude of waveforms may fall (Garg, 2002). It is thought that the periodic complex is secondary to widespread neuronal excitability, pathological hypersynchronization and rhythmic triggering by a pacemaker, potentially in the brainstem or perithalamic area. It is hypothesized, based on EEG studies, that during the initial phase of the disease the cortex exhibits Bereitschaft potentials (readiness potentials) with rising EEG shifts in the parietal region and positive shifts of lower amplitudes in the central regions, as if it were preparing for volitional movement. (Praveen-kumar *et al.*, 2007).



Figure1: EEG of SSPE patient showing typical, superimposed periodic complexes lasting for 1-2 seconds

In addition to type I periodic electroencephalographic complexes just described, few other forms of periodic complexes have also been recognised which have been shown to have some association with the prognosis of the disease also. According to work done by Yakub, Type II abnormalities which are characterised by periodic giant delta waves intermixed with rapid spikes as fast activity are usually associated with best outcome. In this pattern of periodic complexes, EEG background is usually slow. The type III periodic complexes pattern is characterised by long spike-wave discharges interrupted by giant delta waves, and it is associated with worst outcome (Yakub, 1996).

Besides periodic complexes, several atypical EEG findings which may be found includes frontal rhythmic delta activity in intervals between periodic complexes, electrodecremental periods following EEG complexes, diffuse sharp waves and sharp-and-slow-wave complexes over frontal regions, and focal abnormalities, such as sharp wave and sharp and slow wave foci (Dogulu *et al.*, 1995).

Review Article

Cerebro-spinal Fluid (CSF) Examination

CSF examination may be normal. Acellular CSF with normal or mildly elevated protein is a frequent finding. A highly raised gammaglobulin level which is usually greater than 20% of total csf protein is the most remarkable feature. CSF IgG increases from 5-10 µg/dl to 10-54 µg/dl (Mehta *et al.*, 1977; Tourtellote *et al.*, 1981; Reiber *et al.*, 1991), most of which is directed against measles virus. So raised titres of antimeasles antibodies in the CSF are diagnostic of SSPE. Antimeasles antibody titres are raised in serum as well. Raised titres of 1:256 or greater in serum, and 1:4 or greater in cerebrospinal fluid is considered diagnostic of SSPE. The characteristic ratio of cerebrospinal fluid titre to serum titre ranges from 1:4 to 1:128 (below 200), which is low compared with the normal ratio (1:200–1:500). Serum cerebrospinal fluid ratios are normal for other viral antibodies and for albumin, indicating that the increased amounts of measles antibodies result from synthesis within the central nervous system and that the blood brain barrier is also normal (Mehta *et al.*, 1994; Salmi *et al.*, 1972; Abdelnoor *et al.*, 1982). ELISA is highly sensitive for detecting measles virus specific IgG as well as IgM. Complement fixation, virus neutralisation and haemagglutination inhibition can also be used for this (Lakshmi *et al.*, 1993).

Detection of measles virus RNA by reverse transcription PCR can also be accurate method for diagnosis of SSPE. Some studies have found elevation of soluble CD8 in CSF and decreased serum b2-microglobulin associated with clinical worsening; lower levels of CD8 in CSF and higher levels of b2-microglobulin in serum correlate with clinical improvement. Their widespread application as a marker for disease activity is still uncertain (Mehta *et al.*, 1992).

Neuro-Imaging Studies

MRI abnormalities described in SSPE include asymmetric, focal regions of signal changes (hyperintense on T₂ weighted/FLAIR image and hypointense on T₁ weighted image) involving cerebral cortex, subcortical periventricular white matter, basal ganglia, thalamus and corpus callosum (**fig 2**). The Brainstem and the Cerebellum are involved late (Tuncay *et al.*, 1996; Anlar *et al.*, 1996; Brismar *et al.*, 1996; Tsuchiya *et al.*, 1988). Early, lesions usually appear in occipital region and then progress to involve frontal cortex and subsequently subcortical white matter, brainstem and spinal cord (Tsuchiya *et al.*, 1988). After initial, asymmetrical cortical and subcortical involvement, older lesions may disappear and multifocal deep white matter involvement with cortical atrophy develops (Tsuchiya *et al.*, 1988).

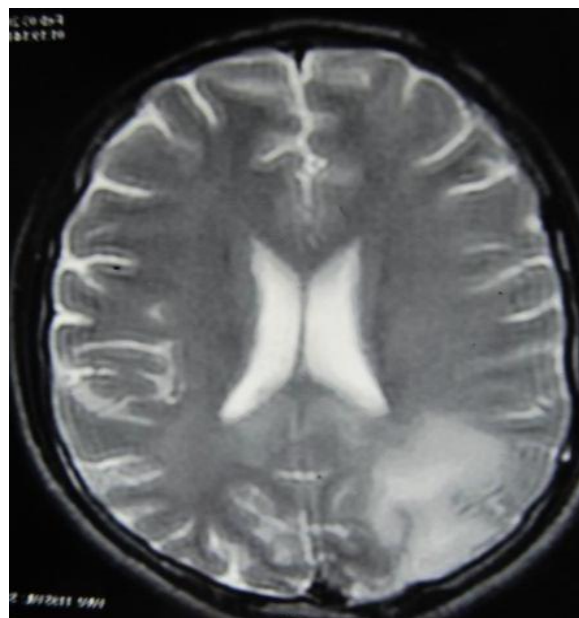


Figure 2: T2 weighted MRI showing hyperintense signal changes in right parieto-occipital white grey matter of a 23 years old male of SSPE (Stage-2)

Review Article

In the most advanced neuro-vegetative state, an almost total loss of white matter can occur. At this stage, the corpus callosum becomes thin. Basal ganglia changes, usually involving the putamina, were seen in one third of patients and cortical gray matter changes were seen in one fourth of patients examined with MR imaging. In one of the study by Brismar *et al.*, (1996) in 2 of 20 patients, MR changes were shown to regress in parallel with clinical improvement following therapy, although in many clinical improvement is accompanied by progression of MR changes.

Diffusion weighted MRI may be promising in assessing severity of white matter disorganization. Apparent diffusion coefficient (ADC) values depend on motion of water molecule and provide information regarding tissue integrity (Sener RN 2001). A study conducted showed that the ADC values of all the areas of the subacute sclerosing panencephalitis patients were found to be significantly higher compared to the control group. The ADC values of all the areas of the Stage III patients were found to be significantly high compared to the Stage II values (Abuhandan *et al.*, 2012) indicating higher degree of disorganization of white matter.

MR spectroscopy (MRS) appears to be a promising diagnostic modality for early diagnosis as it can show findings suggestive of inflammation in stage II and findings of demyelination, gliosis, cellular necrosis, and anaerobic metabolism in stage III (Alpay Alkan *et al.*, 2003).

18-Fluorodeoxyglucose Positron emission tomography (18F-FDG PET) show metabolic impairments early when MRI findings show no obvious abnormalities (Seo *et al.*, 2010), but not widely available and widely utilized diagnostic tool.

Treatment

There is no curative therapy available for SSPE at present. Certain drugs seem to slow the progression of disease and can prolong life if long term treatment is given. The issue of the success of treatment is frequently complicated by an extremely variable natural course as few patients may have very prolonged spontaneous remissions (Risk *et al.*, 1979; Grunewald *et al.*, 1998; Santoshkumar *et al.*, 1998). Primary prevention of measles by immunization is the most promising way of reducing disease burden.

Symptomatic Treatment

Good general nursing along with anticonvulsants like sodium valproate, clonazepam and Lamotrigine, is a major aspect of treatment. Myoclonus usually responds atleast partially. If spasticity is marked and affecting nursing care, baclofen and other antispasticity drugs may be used (Garg, 2002).

Chemotherapeutic Agents

The chemotherapeutic agents though offer modest benefit is better than the reported 5% spontaneous remission in literature and to no treatment at all. So far the best results have been from isoprinosine and interferon alpha and their combination (Nasirian *et al.*, 2007; Dyken *et al.*, 1982; Anlar *et al.*, 1997; Yalaz *et al.*, 1992; Gokcil *et al.*, 1999; Gascon, 2003; Gascon *et al.*, 1993; DuRant *et al* 1982; Huttenlocher *et al.*, 1979; Filipowicz *et al.*, 1987; Cianchetti *et al.*, 1998).

Inosine pranobex (Isoprinosine or Methisoprinol) is a combination of inosine, acetamidobenzoic acid, and dimethylaminoisopropanol. It has immunomodulatory and antiviral properties, which result from an apparent in vivo enhancement of host immune. Isoprinosine's mechanism of antiviral action is associated with inhibition of viral RNA and increases mRNA synthesis in lymphocytes possessing antiviral properties of interferon alpha and gamma. It stimulates the differentiation of T and B lymphocytes and increases NK cell (natural killer cell) function; also it promotes chemotaxis and phagocytosis by white blood cells (Tomoda *et al.*, 2003).

Daily dosage is 100mg/kg/day given orally. Recurrence of symptoms has been reported frequently; treatment needs to be continued even after apparent remission, possibly for life (Garg, 2002). Myoclonus refractory to sodium valproate is reported to have better outcome by combining trihexyphenidyl with Isoprinosine (Nunes *et al.*, 1995). Due to the metabolism of the inosine component in metisoprinol into uric acid, a moderate increase of serum and urine uric acid could occur, thus isoprinosine must be given under medical supervision in patients with a history of hyperuricemia and gout. Other side effect includes dizziness, stomach pain, digestion problem, itching and allergic reactions. When given with ribavarin

Review Article

drop in the white blood cells count should be watched. It should be avoided in children under 3 years of age (body weight 15-20 kg), and contraindicated in Gout, Urolithiasis, Arrhythmia, Chronic renal failure, Hypersensitivity to the drug.

The cerebrospinal fluid levels of interferon are found to be low in patients with SSPE.

Interferon alfa, is a natural interferon alpha (IFN- α) containing various subtypes, is obtained from the leukocyte fraction of human blood following induction with Sendai virus. Overall, IFN- α has a general inflammatory action which skews the immune response towards a Th1 inflammatory profile (Campbell *et al.*, 2007; Miyazaki *et al.*, 2005; Hosoya *et al.*, 2001).

It can be given either intrathecally or intravenously. The treatment regimen consists of six week courses of natural interferon alfa, started as 100 000 units/m² of body surface area and subsequently increased to 1 million units/m² body surface area per day given for five days a week. Courses are repeated up to six times, at 2–6 months intervals (Garg *et al.*, 2002).

Anlar *et al.*, (2004) suggested long term administration offers better clinical efficacy than short-term administration. The end part is eradication of detectable anti-measles antibodies from the CSF. Gokcilz *et al.*, (1999) reported 59% of patients showed significant stabilization or improvement with Interferon alfa with or without Isoprinosine.

Side effects of interferon alfa include fever, lethargy, anorexia, chemical meningitis and prolonged treatment carry risk of interferon alfa induced encephalopathy and upper and lower motor neuron toxicity (Cianchetti *et al.*, 1994). At times, treatment needs to be temporarily discontinued because of an increase in liver enzyme levels. Cerebrospinal fluid measles antibody and renal and hepatic functions need to be followed up during treatment.

Ribavirin, has been used alone in high doses to treat SSPE with somewhat unconvincing results (Hosoya, 2001). It is a prodrug, when metabolized resembles purine RNA nucleotides and interferes with RNA metabolism required for viral replication by getting incorporated into RNA (Takahashi *et al.*, 1998). The primary observed serious adverse side effect of ribavirin is hemolytic anemia, which may worsen preexisting cardiac disease.

Flupirtine may stop the progressive course of subacute sclerosing panencephalitis and is under study (Burak Tatli *et al.*, 2010). The other molecules of interest are the cytidine deaminase APOBEC3G (apolipoprotein B mRNA-editing enzymecatalytic polypeptide 3G; A3G) which exerts antiviral activity against retroviruses, hepatitis B virus, adeno-associated virus and transposable elements and studies are going on for its antiviral properties against measles virus (Markus Fehrholz *et al.*, 2011). A recent study has showed cells infected with persistent measles virus can be cured by the transduction of lentivirus mediating the long lasting expression of anti-MV short hairpin RNA (Michael *et al.*, 2009).

Other molecules which have been tried without proven success rates are Amantadine, Cimetidine. Isolated reports of intravenous immunoglobulin (Anlar *et al.*, 1998 and Garg, 2002), plasmapheresis, and corticosteroids are available with variable results. These forms of treatment need more evaluation before they can be considered for regular management of SSPE (Gurer *et al.*, 1996 and Garg, 2002).

Prognosis

Classically, the disease is invariably progressive with death in 95% of affected individuals (Tomoda *et al.*, 2003; Risk *et al.*, 1979) with mean survival of 1 year 9 months to 3 years in children (Tomoda *et al.*, 1997; Hassan *et al.*, 2005 and Risk, 1979). Apart from the classical course a fulminant course leading to death in weeks has also been seen. The rate of spontaneous remission is between 5 to 6.2% (Tomoda *et al.*, 2003; Prashanth, 2006; Risk, 1979) with adults reporting higher remission rates, but among those who survive in adults, the survival period is shorter (Singer, 1997). There is controversy regarding whether the treatment reduces mortality or increases survival (Singer, 1997 and Gascon, 2003).

CONCLUSION

SSPE continues to be a fatal disease. Risk factor appears to be the poor access to healthcare and unawareness regarding immunization. The presentation varies with intellectual deterioration occurring in

Review Article

initial stages, noticed by vigilant parents or care takers followed by myoclonus, seizures, visual disturbances, sooner or later leading to autonomic failure and death. It is important to recognize early manifestations of disease and have high degree of suspicion in adult onset SSPE to avoid delay in diagnosing.

Brain tissue biopsy confirms the disease but is usually not necessary and impractical, once typical clinical profile supported by EEG and CSF finding evolve. The best tool appears to be effective immunization, especially in developing countries. The good quality of vaccines also needs to be assured by maintaining proper cold chain. Intrathecal INF and daily oral isoprinosine is the most sought after approach once the disease process is set in, however these are not curative and the disease process progresses. The treatment at times is frustrating and the prognosis remains grim due to unavailability of curative treatment. The age of onset of SSPE may be increasing. Adult onset SSPE patient need to be evaluated more to know if disease behaves differently in them.

Table 1: Dyken's Diagnostic criteria of SSPE (Dyken PR, 1985)

1. Clinical Progressive, subacute mental deterioration with typical signs like myoclonus
 2. EEG Periodic, stereotyped, high voltage discharges
 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
- Definitive: criteria 5 with three more criteria;
Probable: three of the five criteria

Table 2: SSPE Staging (Garg, 2008)

Stage 1- The onset is insidious with symptoms of progressive cortical dysfunction, behavioural changes, deterioration of intellectual capacity, and sometimes awkwardness, stumbling or visual symptoms of retinitis, optical neuritis or cortical blindness, over months.

Stage2- Later, manifest motor disability and paroxysmal disorder develop: mioclonus jerks (pathognomonic electroencephalographic alterations-Rodermacker complexes).

Stage 3- Pyramidal and extrapyramidal manifestations, disappearance of myoclonus and alteration in sensorium.

Stage 4- Vegetative state and death.

Table 3: SSPE grading (Gascon) (Jan Brismar et al., 1996)

G: IA. Behavioral, cognitive, and personality changes, walking

G: IB. Aperiodic, myoclonic spasms

G: IIA. Further mental deterioration, periodic generalized myoclonic spasms, possibly no walking because of drop spells

G: IIB. Language difficulties, spasticity, ataxia, walking with assistance

G: IIIA. Speaking less, visual difficulties; sitting up independently, possible standing, but no independent ambulation; frequent myoclonic spasms, possible seizures

G: IIIB. No speech, poor comprehension, possible blindness, confinement to bed, dysphagia, possible need of tubal feeding, possible choreoathetosis.

G: IV. Neurovegetative stage, no spasms, very low background EEG activity

Review Article

Table 4: SSPE Scoring System (Modified from Dyken et al., (1982))

Behavioral and Mental	Myoclonia (before Carbamazepine)
Irritability: absent 0 Mild hyperactivity, restlessness 1 Moderate restlessness 2 Marked irritability or delirium, lethargy 3 Stupor, coma 4	Location : No myoclonia 0 Focal, mild 1 Focal 2 body parts, moderate amplitude 2 More than 2 body parts 3 Immobility 4
Personality	Repetition
Normal 0 Mild changes(excessive talking, apathy etc) 1 Oppositional behavior, aggressive 2 Defiant or lethargic 3 Stupor, coma 4	No myoclonia 0 Irregular, less than once a day 1 Irregular, less than once per hour 2 Regular, more than once per hour 3 Immobility 4
Introversion or Autism	Convulsions (other than myoclonia)
None 0 Shy or withdrawn 1 Limited interactions, stereotypies 2 Marked autistic behavior/lethargy 3 Stupor, coma 4	None 0 Less than once a week 1 Once a month/ once a week 2 Once a week/ once a day 3 More than once a day 4
Mental-perceptive	Daily functions
Normal 0 Dull 1 Borderline 2 Marked mental deficiency or lethargy 3 Stupor, coma 4	Dresses and feeds himself/herself 0 Can feed but not dress himself/herself 1 Needs helps while eating 2 Express hunger/thirst, cannot feed himself 3 Totally dependent 4
Speech	Following commands
Normal 0 Mild speech disturbance 1 Moderate speech disturbance 2 Severe speech disturbance 3 Stupor, coma 4	Normal 0 Mild impairment 1 Moderate impairment 2 Hear commands, does not comply 3 Stupor, coma 4
Motor and Sensory	Vegetative and Systemic
Reflex-tone Normal 0 Mild hyperreflexia or hypertonia 1 Mild hyperreflexia and hypertonia 2 Moderate hyperreflexia and hypertonia 3 Severe hyperreflexia and hypertonia 4 Strength Normal 0 Mild weakness or atrophy 1 Mild weakness and atrophy 2 Moderate weakness and atrophy 3 Marked weakness and atrophy 4	Vision Normal 0 Mild impairment 1 Moderate impairment 2 Marked impairment 3 Total loss of vision 4 Hearing Normal 0 Mild impairment 1 Moderate impairment 2 Marked impairment 3 No hearing 4
Posture/ movement	Sensory (touch, pressure and pain)
Normal 0 Mild chorea/ athetosis 1 Mild dystonia, moderate chorea/ athetosis 2 Moderate dystonia, choreo-athetosis, mild rigidity	Normal 0 Does not feel touch, feels pressure 1 Does not feel touch and pressure, feels pain 2 Feels only deep pain 3

Review Article

3 Severe extrapyramidal signs 4	Does not feel deep pain 4
Co-ordination	Autonomic functions
Normal 0 Mild impairment 1 Moderate impairment 2 Marked impairment 3 Severe incoordination 4	Normal 0 Mild impairment 1 Moderate impairment 2 Marked impairment 3 Severe impairment 4
Upper limb movements	Nutrition
Uses objects appropriately 0 Uses some objects appropriately 1 Reaches, holds, may put in mouth 2 Reaches, cannot hold 3 Does not reach for objects 4	Normal 0 Mild impairment 1 Moderate impairment 2 Marked impairment 3 Severe impairment 4

Total score (Maximum 80)

Higher score indicates greater impairment

Table 5: Differential diagnosis of SSPE (Herguner *et al.*, 2007; Duclos *et al.*, 1998; Oguz *et al.*, 2007)

Acute disseminated encephalomyelitis	Unverricht–Lundborg disease
Acute viral encephalitis	Lafora disease
Tumours	Juvenile ceroid lipofuscinosis
Multiple sclerosis	Myoclonic epilepsy with red ragged fibres
Metabolic white matter disease	Neuraminidase deficiency
Chronic Rasmussen encephalitis	

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