

## REVIEW

## Subacute sclerosing panencephalitis

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Subacute sclerosing panencephalitis (SSPE) is a progressive neurological disorder of childhood and early adolescence. It is caused by persistent defective measles virus. Brain biopsies or postmortem histopathological examination show evidence of astrogliosis, neuronal loss, degeneration of dendrites, demyelination, neurofibrillary tangles, and infiltration of inflammatory cells. Patients usually have behavioral changes, myoclonus, dementia, visual disturbances, and pyramidal and extrapyramidal signs. The disease has a gradual progressive course leading to death within 1-3 years. The diagnosis is based upon characteristic clinical manifestations, the presence of characteristic periodic EEG discharges, and demonstration of raised antibody titre against measles in the plasma and cerebrospinal fluid. Treatment for SSPE is still undetermined. A combination of oral inosiplex (Inosiplex) and intraventricular interferon alfa appears to be the best effective treatment. Patients responding to treatment need to receive it life long. Effective immunisation against measles is the only solution presently available to the problem of this dreaded disease.

the presence of viral structures resembling measles virus in the brain.<sup>5</sup> In 1969 measles virus was actually recovered from the brain of a patient with SSPE.<sup>6</sup> Since then a lot of progress has been made towards understanding of this potentially lethal disorder. Various treatment modalities have been tried with little success. In this article all recent information will be reviewed.

## EPIDEMIOLOGY

SSPE has been reported from all parts of the world, but in the West it is considered a rare disease with fewer than 10 cases per year reported in the United States.<sup>7</sup> The reported frequency of SSPE in the United States was approximately one per million childhood population from 1960 to 1970.<sup>8</sup> The incidence declined substantially after introduction of an effective measles vaccine. The annual incidence of SSPE is still quite high but variable among developing countries. Saha *et al* reported an annual incidence of 21 per million population in India,<sup>9</sup> in comparison with 2.4 per million population in the Middle East.<sup>10 11</sup>

Most patients with SSPE have a history of primary measles infection at an early age (<2 years), which is followed, after a latent period of 6-8 years, by the onset of progressive neurological disorder. 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. Since the incubation period is typically less than a decade, SSPE is commonly a disease of childhood. A higher incidence (male/female ratio 3:1) has been noted in boys, although primary measles infection shows no such sex disparity. The incidence is higher among rural children, children with two or more siblings, and children with mental retardation. It is also more common in children with a lower birth order and in children living in overcrowded environments.<sup>12-15</sup> Aaby *et al* have suggested that these features (age of exposure, sex, and geography) are indicative of intensive measles exposure as a risk factor.<sup>16</sup> Other factors, also identified as risk factors for SSPE, may modify the course of acute measles infection—for example, a close temporal relationship of measles with another viral infection such as Epstein-Barr virus or parainfluenza type-1 virus.

Widespread immunisation has produced greater than 90% reduction in the incidence of SSPE in developed nations.<sup>17</sup> When the disease occurs in vaccinated children, it is thought to

Subacute sclerosing panencephalitis (SSPE) is a serious disorder of the central nervous system. It is a slow virus infection caused by defective measles virus (table 1). The term subacute sclerosing panencephalitis has been used since Greenfield suggested it in 1960 to designate a condition due to a persistent infection by a virus involving both grey matter and white matter.<sup>1</sup> In fact, SSPE had originally been described as three different neuropathological entities. In 1933 Dawson, for the first time, described a child with progressive mental deterioration and involuntary movements who, at necropsy, was found to have a dominant involvement of grey matter in which neuronal inclusion bodies were abundant.<sup>2</sup> He suggested the term "subacute inclusion body encephalitis". Later Pette and Doring (1939) reported a single case of what they called "nodular panencephalitis" a disease with equally severe lesions in both grey and white matter.<sup>3</sup> Six years later, Van Bogaert drew attention to the presence of dominant demyelination and glial proliferation in the white matter and suggested the term "subacute sclerosing leukoencephalitis".<sup>4</sup> A viral aetiology was suggested by Dawson, but it was Bouteille *et al*, in 1965, who on electron microscopy demonstrated

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**Abbreviations:** EEG, electroencephalogram; ELISA, enzyme linked immunosorbent assay; MRI, magnetic resonance imaging; SSPE, subacute sclerosing panencephalitis

Table 1 Various neurological complications of measles

• Post-measles encephalitis	Develops soon after infection, reflect an autoimmune reaction
• Measles inclusion body encephalitis	Develops weeks or months after infection, in patients with defective cell mediated immunities like HIV infection
• Subacute sclerosing panencephalitis	Persistent defective measles virus infection
• Postinfectious	Acute immune reaction
• Transverse myelitis	Rare, acute immune reaction

result from a subclinical measles infection that occurred before the age of 1 year, when immunisation is usually begun. There is no evidence to suggest that attenuated vaccine virus is responsible for sporadic cases of SSPE.<sup>1</sup>

### **PATHOGENESIS**

Measles is caused by an RNA virus, which belongs to the morbillivirus subgroup of paramyxoviruses. Despite the long interval between the acute infection and symptoms of SSPE, there is evidence that measles virus infection of brain occurs soon after the acute infection with subsequent spread throughout the brain.<sup>18</sup> Measles virus is thought to reach the brain through infection of cerebral endothelial cells, perhaps during the acute exanthema of measles when other endothelial cells are also infected.<sup>19</sup> Access into the brain by circulating inflammatory cells is also possible.<sup>20</sup> The measles virus particles are pleomorphic, spherical structures having a diameter of 100 to 250 nm and consisting of six proteins. The inner capsid is composed of a coiled helix of RNA and three proteins. The outer envelope consists of a matrix protein bearing two types of short surface glycoprotein projections of peplomers. One peplomer is a conical haemagglutinin (H) and the other dumbbell shaped fusion (F) protein. The envelope carries projections of the H and F proteins. The M (matrix) protein sits within the envelope membrane and can interact with cytoplasmic domains of H and F proteins. In contrast to measles virus infection of non-neuronal cells, which is cytopathic and spreads both by extracellular virus and by cell fusion resulting in multinucleated syncytia formation, little extracellular infectious virus can be recovered from brains of SSPE patients unless neuronal tissues are cocultured with fibroblasts.<sup>21</sup> High levels of neutralising antibody are present in the serum and cerebrospinal fluid of SSPE patients; it further suggests that extracellular virus might not be responsible for measles virus spread in the central nervous system.<sup>22</sup> Recently, a trans-synaptic transmission of virus has been suggested.<sup>23</sup>

Measles virus isolated from specimens of the brains of such patients may interfere with the replication of the wild type of measles virus and may have a clonal origin.<sup>18, 24</sup> Numerous alterations in M protein have been described in SSPE because of extensive point mutations in viral genome, possibly resulting in persistent viral infection.<sup>25-30</sup> The type II transmembrane protein H mediates virus cell attachment by binding to the cell surface protein CD46 (it is a measles virus receptor protein, which is, in fact, a complement regulating protein with isoforms present on neurons),<sup>31</sup> and is an essential cofactor for fusion.<sup>32</sup> Changes in the H and F proteins can also be associated with persistent infection, with M protein remaining relatively unaffected.<sup>33, 34</sup> Since all three proteins are associated with viral budding from infected cells and the putative fusion with uninfected cells, the persistent nature of the infection is thought to be due to defects in these two processes.<sup>35</sup> The exact factors and influences that allow the measles infection to persist are unclear, but may include several immunological factors. For example, in tissue culture, the addition of antibodies against measles virus may alter the pattern of viral gene expression.<sup>36</sup> This observation may explain why measles infection at a very early age, when

maternal antibodies are still present in the blood of the patient, carries an increased risk of SSPE.<sup>35</sup> There is evidence that persistent measles virus infection can be found throughout the body in patients with SSPE.<sup>37</sup>

Recently studies have suggested that apoptosis of various cell types may contribute to the neuropathogenesis of measles virus infection in the human central nervous system, either as a direct effect of viral infection or of cytokine mediated responses, resulting in oligodendroglial and neuronal cell death in SSPE.<sup>38, 39</sup>

### **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. There is often evidence of neuronal degeneration, gliosis, proliferation of astrocytes, perivascular cuffing, lymphocytic and plasma cell infiltration, and demyelination. Viral infection of oligodendrocytes may be responsible for extensive demyelination, which is often present in patients with SSPE.<sup>40</sup> In later stages, gross examination of brain may reveal mild to moderate atrophy of the cerebral cortex. Microscopic examination shows widespread degeneration of neurons and disorganisation of cortical structures. The parieto-occipital region of the brain is most severely affected, subsequently; pathological involvement spreads to the anterior portions of cerebral hemispheres, 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 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 correspond to viral particles and contain viral antigens.<sup>22</sup> Neurofibrillary tangles may also be seen within neurons and oligodendrocytes.<sup>41</sup> In situ hybridisation methods have shown that cells containing tangles often contain the viral genome, suggesting that viral infection causes the formation of tangles.<sup>42</sup> Late in the course of disease it may be difficult find typical areas of inflammation and even inclusion bodies. The histopathological changes are marked with parenchymal necrosis and gliosis.<sup>43</sup> 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.<sup>44</sup> Little infectious virus can be recovered from the brain tissue but viral antigen can be identified immunocytochemically and viral genome can be detected by in situ hybridisation method or by polymerase chain reaction amplification method.<sup>22, 45, 46</sup>

### **CLINICAL FEATURES**

The initial symptoms are usually subtle and include mild intellectual deterioration and behavioural changes without any apparent neurological signs or findings. Parents and

**Box 1: Ophthalmological abnormalities with SSPE**

- Papillo-oedema.
- Papillitis.
- Optic atrophy.
- Macular or perimacular chorioretinitis.
- Cortical blindness.
- Anton's syndrome (cortical blindness with denial of blindness).

teachers may notice progressive deterioration in scholastic performance. As disease advances non-specific manifestations evolve into disturbances in motor function and development of periodic stereotyped myoclonic jerks. Myoclonic jerks initially involve the head and subsequently trunk and limbs. Muscular contraction is followed by 1–2 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. Myoclonus can present as a difficulty in gait, periodic dropping of the head, and falling. The myoclonus may not be obvious early in the disease but can be elicited by the patient standing with feet together and arms held forward and then watching for periodic dropping of the head, neck, trunk, or arm; these are often concomitant with contraction of facial musculature and slow eye blinks. Patients may, frequently, develop pyramidal and extrapyramidal signs. Few patients may develop ataxia, dystonia, and dyskinesia. Generalised tonic-clonic seizures and partial seizures may also occur.<sup>7,9,47</sup> Ocular and visual manifestations (box 1) are reported in 10%–50% of patients, which include cortical blindness, chorioretinitis, and optic atrophy. Visual symptoms usually concurrent with neurological manifestations but they may precede neurological manifestation by several years.<sup>48,49</sup> Park *et al*, in a patient presenting with chorioretinitis, have demonstrated numerous filamentous, microtubular, and intranuclear viral inclusions in the nuclear layers of retina consistent with the measles virus.<sup>50</sup>

In advanced stages of the disease, patients become quadriparetic, spasticity increases, and myoclonus may decrease or disappear. There is autonomic failure with loss of thermoregulation leading to marked temperature fluctuations. 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.<sup>51</sup>

**DIAGNOSIS**

Once myoclonus is evident the clinical diagnosis is seldom a problem. However, subtle behavioural changes at an early stage of disease are frequently missed by relatives. Many such patients are often treated by a psychiatrist at this stage. In some cases myoclonus is not present; atonia may be present but can be overlooked.<sup>11</sup> At times SSPE may need to be distinguished from various neurodegenerative conditions in which myoclonus and some other progressive neurological disorder are dominant clinical manifestations (box 2). Occasionally, patients with SSPE can present with lateralising neurological signs, partial seizures, or papillo-oedema; these findings can lead to an erroneous diagnosis of an intracranial space occupying lesion.<sup>52</sup> The diagnosis is based upon typical cerebrospinal fluid changes and a characteristic electroencephalography pattern. The diagnosis of SSPE can be reliably established if patient fulfils three of the five criteria given by Dyken<sup>47</sup> (table 2).

**Table 2** Diagnostic criteria of SSPE<sup>47</sup>

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 ( $\geq 1:256$ ) and/or cerebrospinal fluid ( $\geq 1:4$ )
5. Brain biopsy	Suggestive of panencephalitis

Definitive: criteria 5 with three more criteria; probable: three of the five criteria.

**(A) Cerebrospinal fluid**

Cerebrospinal fluid examination is usually normal. Frequently, it is acellular with normal or a mildly raised protein concentration. The most remarkable feature of the cerebrospinal fluid examination is a markedly raised gammaglobulin level, which is usually greater than 20% of total cerebrospinal fluid protein. Because of the large increase of intrathecal synthesis of IgG, cerebrospinal fluid IgG concentration ranges from 10–54  $\mu\text{g/dl}$  compared with 5–10  $\mu\text{g/dl}$  in normal children.<sup>53,54</sup> In most cases raised levels of locally synthesised gammaglobulins indicate either an infection or other type of inflammatory process within the central nervous system. When the cerebrospinal fluid is examined by agarose gel electrophoresis or isoelectric focussing, an oligoclonal band of immunoglobulins are often observed. The oligoclonal band signifies the production of gammaglobulin of a restricted class and also implies that there are clones of B cells that have differentiated into plasma cells within the central nervous system.<sup>55</sup>

In patients with SSPE most of IgG in the cerebrospinal fluid has been shown to be directed against measles virus, and the oligoclonal bands can be adsorbed by measles virus.<sup>56</sup> So raised titres of antimeasles antibodies in the cerebrospinal fluid are diagnostic of SSPE. Antimeasles antibody titres are also raised in serum as well. Raised antimeasles antibody 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

**Box 2: Other neurodegenerative myoclonic conditions****A. Progressive myoclonic epilepsies (early myoclonus and generalised tonic-clonic seizures)**

- Unverricht-Lundborg syndrome.
- Myoclonic epilepsy ragged red fibre (MERRF).
- Lafora body disease.
- Neuronal ceroid lipofuscinoses.
- Sialidoses.
- Hereditary dentatorubral-pallidolusian atrophy.

**B. Progressive myoclonic encephalopathies (where myoclonus is generally overshadowed by other clinical manifestations)**

- GM2 gangliosidosis.
- Non-ketotic hyperglycaemia.
- Niemann-Pick disease.
- Juvenile Huntington's disease.
- Alzheimer's disease.
- Creutzfeldt-Jakob disease.

**C. Progressive myoclonic ataxias (seizures are either absent or late)**

- Spinocerebellar degeneration.
- Wilson's disease.
- Coeliac disease.
- Whipple's disease.

cerebrospinal fluid titre to serum titre ranges from 1:4 to 1:128 (below 200), this ratio 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.<sup>57–58</sup> Various serological methods used are complement fixation, haemagglutination inhibition, virus neutralisation, and enzyme linked immunosorbent assay (ELISA). ELISA is highly sensitive in detecting measles virus specific IgG as well as IgM.<sup>59</sup>

It is possible to make an accurate diagnosis of SSPE by detecting the measles virus genome in the cerebrospinal fluid. Measles virus RNA can be detected by reverse transcription polymerase chain reaction.

### (B) Electroencephalography

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. The EEG picture is characterised by periodic complexes consisting of bilaterally symmetrical, synchronous, high voltage (200–500 mv) bursts of polyphasic, stereotyped delta waves. Waveforms remain identical in any given lead. These periodic complexes repeat at fairly regular 4–10 second intervals and have 1:1 relationship with myoclonic jerks (fig 1). Frequently there is shortening of interval between periodic complexes with progression of the disease.<sup>60</sup> The periodic complexes of SSPE first appear during sleep, when they are not accompanied by myoclonic spasms. Often these periodic complexes can be brought out when the patient is awake, if diazepam is administered intravenously during the routine electroencephalographic recording. 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.

In addition to type I periodic electroencephalographic complexes just described, few other forms of periodic complexes have also been recognised.<sup>11</sup> These various types of periodic complexes have been shown to have some association with the prognosis of the disease. Type II abnormalities are characterised by periodic giant delta waves intermixed with rapid spikes as fast activity. 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. Yakub demonstrated that video-split EEG monitoring is a more sensitive technique for early diagnosis and detection of atonia or myoclonus,<sup>11</sup> which are time related to EEG periodic complexes. He further observed that type III periodic complexes were associated with the worst outcome, while patients with type II periodic complexes had the best outcome. In this study outcome was determined by the rate of progression of disease.

### (C) Neuroimaging

Neuroimaging has a limited role in the early diagnosis of SSPE. Computed tomography of brain is normal in early stages of disease, in later stages it shows small ventricles and obliteration of hemispheric sulci and interhemispheric fissure due to diffuse cerebral oedema. Generalised or focal cerebral atrophy and ex vacuo ventricular dilatation can be seen after a very prolonged course, but sometimes, computed tomograms are normal as late as five years after the onset of the disease. Low attenuation areas in the cortex and basal ganglion have also been observed.<sup>61</sup>

Magnetic resonance imaging (MRI) is more sensitive in detecting white matter abnormalities. Early changes are ill defined high signal intensity areas on T2-weighted images (fig 2), more commonly seen in the occipital subcortical white

matter than in the frontal region. In most of the cases the grey matter is spared even in advanced clinical and MRI stages. However, Tuncay *et al* observed early involvement of grey matter.<sup>62</sup> In this study, early lesions were dominantly involving grey matter and subcortical white matter. These lesions were asymmetrical and had a predilection for the posterior parts of cerebral hemispheres (fig 3). Later, high signal changes in deep white matter and severe cerebral atrophy were observed. Parenchymal lesions were significantly correlated with the duration of disease. Though mass effect and contrast enhancement of lesions are not usual feature of SSPE, some authors have reported mild mass effect and contrast enhancement in few patients, especially in the early stages of the disease.<sup>63</sup>

Brismar *et al* have developed a staging system based on neuroimaging findings for SSPE that reflects the degree of white matter changes and atrophy.<sup>64</sup> Though, the radiological staging of this SSPE is not always exactly correlated with its clinical manifestations, even then, sequential MRI may be useful for following the course of the disease.<sup>64</sup>

### (D) Brain biopsy

Brain biopsy is seldom required to establish the diagnosis of SSPE. When performed, it will often show the typical histopathological findings described earlier. Examination of frozen sections by immunofluorescence technique may demonstrate the presence of measles virus antigens. Reverse transcription polymerase chain reaction can detect various regions of the measles virus RNA in frozen and even paraffin embedded brain tissue specimens of patients with SSPE. Nucleic acid hybridisation techniques have also been used to demonstrate the measles virus genome.

### SSPE IN ADULTS

SSPE, being a disorder of childhood and adolescence, may not be readily recognised when a patient presents later in the life. Approximately 50 cases of SSPE have been reported in those over 18 years of age. Patients with adult onset SSPE present at a mean age of 25.4 years (range 20–35 years). A higher proportion of adult patients have either negative or an undocumented history of prior measles infection in childhood. Visual manifestations, especially cortical blindness, are the commonest mode of clinical presentation. The disease apparently has a more aggressive course in adults and disease is rapidly fatal in majority of the patients.<sup>65</sup> In a preliminary study, Gokcil *et al* observed that treatment with oral isoprinosine plus interferon alfa is effective for adult onset SSPE.<sup>66</sup>

### SSPE AND PREGNANCY

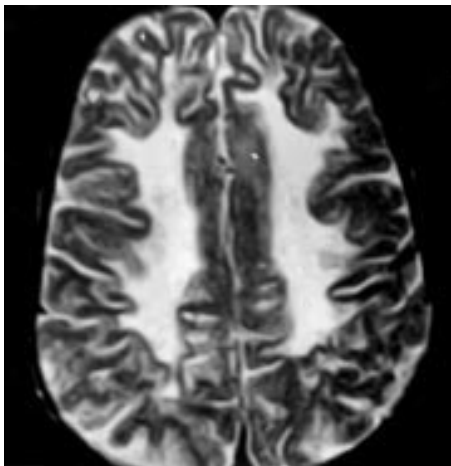
SSPE can rapidly progress during pregnancy. It has been suggested that the relative older age of presentation, and unusually rapid neurological deterioration, are partially due to immunological and hormonal alterations of pregnancy. In several reported cases, the disease was associated with the death of the child in utero, or in the immediate peripartum period.<sup>67</sup> Thiel *et al* reported a 20 year old woman who delivered a healthy infant by caesarean section in the 28th gestational week.<sup>68</sup> Serum analysis of the infant revealed slowly diminishing IgG measles virus antibody titres. After six months, the maternal measles antibodies were no longer detectable in the child's serum. Cortical blindness has been reported as the most common presenting manifestation of SSPE even in pregnancy. Characteristic myoclonus may not be apparent; the clinical picture resembles that of eclampsia (see case report).

### ACUTE FULMINANT SSPE

Most of the patients with SSPE survive for 1–3 years after diagnosis, with a mean survival of about 18 months. In acute fulminant SSPE the disease rapidly evolves leading to death within three months of the diagnosis. In the series of Risk and



**Figure 1** EEG showing a periodic pattern with slow wave complexes recurring at intervals of 4–6 seconds.



**Figure 2** T2-weighted MRI scan showing diffuse white matter demyelination in an 8-year-old boy with SSPE.

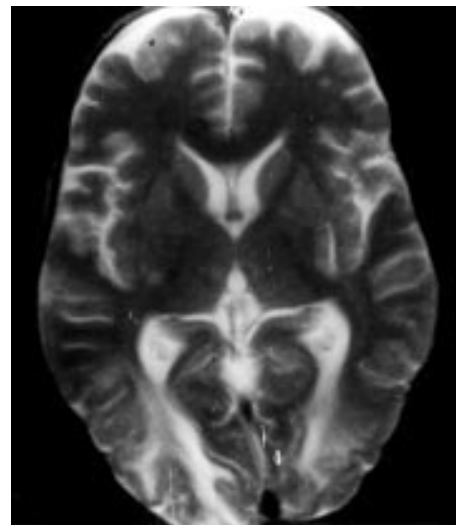
Haddad, approximately 10% of patients had such a fulminant course.<sup>51</sup> In rapidly evolving SSPE various stages of disease cannot be recognised. The exact mechanism producing an acute fulminant course is not known. Several factors such as exposure to measles at an early age, viral virulence, impaired host defence mechanisms, and concurrent infections with other viruses, have been suggested as responsible for producing a rapid course of the disease.<sup>69–71</sup>

### TREATMENT

No adequate therapy is currently available for the treatment of SSPE. Observations of some non-randomised trials suggest that certain antiviral drugs and immunomodulator agents can prolong life if long term treatment is given (box 3). The issue of the success of treatment is frequently complicated by an extremely variable natural course as a few patients may have very prolonged spontaneous remissions.<sup>51 72 73</sup>

#### (A) Isoprinosine (Inosiplex)

Isoprinosine is an antiviral drug, which acts by activating the body's immunological system against measles virus. This drug increases the number of CD4+ lymphocytes, augment natural killer cells function, potentiates the function of interferons,



**Figure 3** T2-weighted MRI scan showing hyperintensity in the both occipital regions (see case report).

### Box 3: Drugs used in the treatment of SSPE

- Amantadine.
- Cimetidine.
- Corticosteroids.
- Interferon alfa.
- Interferon beta.
- Isoprinosine (Inosiplex).
- Intravenous immunoglobulin.
- Ribavirin.

Combination of intraventricular interferon alfa plus oral isoprinosine is the best effective treatment available.

and increases the production of interleukin-1 and interleukin-2. Treatment with isoprinosine remains controversial because of conflicting results.<sup>74</sup> Few uncontrolled studies have reported that isoprinosine prolongs the survival and produces clinical improvement in some patients.<sup>75 76</sup> Nunes *et al*

observed good results combining trihexyphenidyl and isoprinosine in controlling myoclonus refractory to sodium valproate.<sup>77</sup> This drug is administered in daily doses of 100 mg/kg/day and without major side effects. Recurrence of symptoms has been reported frequently; treatment needs to be continued even after apparent remission, possibly for life. Uric acid levels should be monitored, because isoprinosine can cause hyperuricaemia and renal stones.<sup>35</sup>

### (B) Interferon alfa

The pathophysiology of natural remissions and relapses in SSPE is unknown. The stable state may depend on a balance between viral replication and the body's immune response, as the state of the immune system has a role in producing remission. The cerebrospinal fluid interferon levels are found to be low in patients with SSPE. Exogenous administration of interferons possibly suppresses viral replication and augments the immune system of the body. Interferon alfa was initially given by the intravenous and intrathecal routes with questionable effect. Panitch *et al* were the first to use the drug by the intraventricular route with the help of an Ommaya reservoir planted subcutaneously and a catheter placed in the frontal horn of the right lateral ventricle under general anaesthesia.<sup>78</sup> In this series, the authors found improvement in all the three patients; two of them, however, relapsed after completion of treatment.

The treatment regimen consists of six week courses of natural interferon alfa, started as 100 000 units/m<sup>2</sup> of body surface area and subsequently increased to 1 million units/m<sup>2</sup> body surface area per day given for five days a week. Courses are repeated up to six times, at 2–6 months intervals.

At present, combined treatment of oral isoprinosine and intraventricular interferon alfa appears to be a more effective treatment for SSPE.<sup>79–81</sup> Gokcil *et al*, in their recent article, reviewed 53 patients who had been treated by intraventricular interferon alfa with or without oral isoprinosine; 30 (59%) of these patients showed significant stabilisation or improvement.<sup>66</sup> They also reported better efficacy with a combination of oral isoprinosine and intraventricular interferon alfa even in adult patients with SSPE. Cerebrospinal fluid measles antibody, and renal and hepatic functions, need to be followed up during treatment. The laboratory end point of treatment is the eradication of detectable measles antibody from the cerebrospinal fluid. Systemic (subcutaneous) interferon alfa, in daily doses of up to 5 million units, has been used with intrathecal interferon alfa simultaneously to treat peripheral reservoirs of measles virus and lymphoid and glandular tissue.

Side effects of interferon alfa include fever, lethargy, anorexia, and chemical meningitis. At times, treatment needs to be temporarily discontinued because of an increase in liver enzyme levels. Although, most of the patients treated with intraventricular interferon and oral isoprinosine have not shown side effects of a serious nature, prolonged repeated treatments do carry risks of developing meningitis, interferon alfa induced encephalopathy, and upper and lower motor neuron toxicity.<sup>82</sup>

### (C) Ribavirin

The antiviral drug ribavirin has been tested in animal models of SSPE and was found effective. Recently, this drug has been used in patients with SSPE. Tomoda *et al* used a combined treatment of high dose intraventricular interferon alfa along with intravenous ribavirin in two non-responding cases of SSPE.<sup>83</sup> In both the patients no further progression was noted. In one patient the hypertonicity, bladder incontinence, and dysphagia improved three months after starting the combination treatment. Similar efficacy of high doses of ribavirin and intraventricular interferon alfa has been noted by Hosoya *et al* in two patients.<sup>84</sup>

### (D) Other drugs used for the treatment of SSPE

Amantadine is an anti-RNA agent that retards the maturation of viruses by not allowing them to replicate. This drug is very well absorbed from the gastrointestinal tract, and crosses the blood brain barrier, but the response to treatment in few cases of SSPE is disappointing.<sup>85</sup> Cimetidine, an H<sub>2</sub>-receptor antagonist, was used in the treatment of SSPE. Anlar *et al* did not observe any worsening in seven cimetidine treated patients during a study period of two months, whereas seven patients in the placebo group deteriorated significantly.<sup>86</sup> In isolated reports interferon beta plus Inosiplex,<sup>87</sup> intravenous immunoglobulin,<sup>88</sup> plasmapheresis, and corticosteroids have been tried with variable results. These forms of treatment need more evaluation before they can be considered for regular management of SSPE.

### (E) Symptomatic treatment

Good general nursing care is the most important aspect in the management of SSPE. Anticonvulsants, like sodium valproate and clonazepam, are helpful in controlling the myoclonus. If spasticity is marked and affecting nursing care, baclofen and other antispasticity drugs may be used.

### PROGNOSIS

SSPE is a progressive disorder and death usually occurs in 1–3 years. Apart from this classical course, a chronic very slowly progressive form, a very fulminant form leading to death in weeks, and a “stuttering” form of disease with remission and relapses, have been observed. Approximately 5% of the patients can have substantial spontaneous long term improvement. Santoshkumar and Radhakrishnan reported a woman with SSPE with almost 17 months of progressive neurological deterioration to the extent that she was completely bedridden and incapable of self care.<sup>73</sup> She experienced a substantial spontaneous improvement; during the next seven years the patient became ambulatory and was independent for her daily activities. Grunewald *et al* recently reported a 35 year old patient who remained in remission for almost 25 years.<sup>72</sup> Spontaneous remission may occur during any stage of the disease and last for a variable period of time before eventual relapse occurs. Santoshkumar and Radhakrishnan have noted the factors that may predict spontaneous remission and prolonged survival in SSPE.<sup>73</sup> The age of onset of SSPE less than 12 years, disappearance of periodic complexes, the tendency for normalisation of the background of follow up EEGs, and a progressive increase in measles antibody titres in cerebrospinal fluid are the factors that appear to be associated with favourable outcome in SSPE. However, these observations need further evaluation. The exact mechanisms responsible for spontaneous improvement are not known.

### CONCLUSION

SSPE is a slow virus infection caused by aberrant measles virus. This disease is still common in developing and underdeveloped countries. One of the most important limitations in treatment of SSPE is difficulty in recognising early manifestations of disease, when the inflammatory changes are, possibly, still reversible. Diagnosis is especially problematic in adult patients with SSPE; differential diagnoses are also different. Treatments available are very costly and are available only at a few centres in the world. Moreover, these treatments are not curative and only help in buying time for these patients. The families of patients with SSPE have a lot of physical, psychological, and economical stresses to endure. A great deal of external support is required for these suffering families to cope with these stresses. At present effective measles vaccination seems to be the only solution to problem of this dreaded neurological disorder (box 4).

**Box 4: Summary points**

- SSPE is a slow virus disease caused by persistent mutant measles virus infection.
- It affects children, it is uncommon after 18 years of age, and the disease has a more aggressive course in adults.
- The disease is very rare in developed countries, but is still common in developing and poor countries.
- Measles vaccine is not associated with an increased risk of SSPE.
- A defective expression of either the matrix, the fusion, or the haemagglutinin proteins of measles virus is responsible for viral persistence in brain cells and its escape by immune surveillance mechanisms.
- Pathological changes involve both white and grey matter. Neurons and oligodendrocytes contain eosinophilic inclusion bodies. Marked gliosis occurs in brain along with perivascular lymphocytes and plasma cell cuffing.
- The disease starts with subtle mental deterioration followed by seizures, dementia, ataxia, stereotyped myoclonus, and visual disturbances, usually leading to a decorticated state, and death after 1–3 years.
- The EEG is characteristic and reveals periodic, stereotyped high voltage discharges occurring every few seconds.
- Cerebrospinal fluid shows raised gammaglobulin with IgG oligoclonal bands.
- Raised measles antibody titre in cerebrospinal fluid and serum is diagnostic.
- No curative treatment is available. Combination of intraventricular interferon plus oral isoprinosine is effective in halting the progression of the disease.
- Relapse is usually a problem even after good initial results.
- An effective measles vaccination is the only solution available to this fatal disease.

**AN ADULT PATIENT WITH SSPE: CASE REPORT**

A 33 year old previously healthy woman was admitted to the obstetrics ward complaining of blurring of vision during the 24th week of her first pregnancy. In the next three days behavioural changes and disorientation were observed, progressing to a drowsy state. She was transferred to the neurology ward. The patient's history was not suggestive of measles infection during early childhood.

General physical examination revealed pedal oedema and hypertension (160/94 mm Hg); a gynaecological examination disclosed a viable fetus consistent with gestational age. Her neurological evaluation revealed that the patient was drowsy, disoriented to time, place, and person, unable to answer simple questions properly, or count to 10. The patient was unable to perceive even hand movements or a beam of light. Examination of her optic disks revealed no abnormality. Pupils were of normal size and direct and consensual light reflexes were normal. Other cranial nerves were normal. Her gait was mildly ataxic, she had generalised hypertonia, all deep tendon reflexes were exaggerated, and both plantars were extensor. There was no sign of meningeal irritation.

Laboratory workup did not reveal any abnormality in blood and urine. Cranial computed tomography was normal. A possibility of eclamptic encephalopathy was considered and she was treated accordingly. She did not improve and became deeply comatose and developed left sided hemiparesis in the next few days. On careful observation the patient had periodic stereotyped left sided hemimyoclonic jerks involving her left shoulder, arm, and leg; she also had subtle hemifacial jerks with simultaneous closure of both the eyes. Brainstem reflexes were normal. She had frequent bouts of hyperpyrexia, tachycardia, hypertension, and irregular breathing. Electroencephalography was performed and revealed diffuse symmetrical slow wave activity. MRI revealed bilateral a symmetrical hyperintensity in T2-weighted images involving both occipital lobes (fig 3). Cerebrospinal fluid examination showed protein

0.6 g/l, glucose 3.2 mmol/l, and 3–4 cells, all mononuclear. Both serum and cerebrospinal fluid were strongly positive for antimeasles IgG antibodies. An assay of antimeasles IgM antibody assay by ELISA was also positive (value 1.857; positive >0.404, Novum kit).

In the next eight weeks the patient's condition remained unchanged. In the 32nd gestational week, spontaneous labour began and a dead fetus was delivered per vagina. Intrauterine death of the fetus was noted just before delivery. The patient's condition remained unchanged on symptomatic treatment. Eventually, decerebrate rigidity appeared, her autonomic instability worsened, she developed severe pulmonary infection, and died.

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