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Ravindra Kumar Garg

Subacute sclerosing panencephalitis

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Dr. Ravindra Kumar Garg (✉)
Dept. of Neurology
Chhatrapati Shahuji Maharaj Medical University
Uttar Pradesh
Lucknow – 226003, India
Tel.: +91-522/4003496
Fax: +91-522/2258852
E-Mail: garg50@yahoo.com

Abstract Subacute sclerosing panencephalitis (SSPE) is a subacute encephalopathy of childhood and young adolescence. Infrequently, SSPE can occur in adults and pregnant women. It is caused by an aberrant measles virus, known as the SSPE virus. SSPE virus differs from wild-type measles viruses in the form of several mutations affecting the viral genome. The matrix gene is most commonly affected by these mutations. The characteristic clinical manifestations of SSPE include behavioral changes, cognitive decline, myoclonic jerks, seizures, abnormalities in vision, bilateral pyramidal signs and coma. Ocular changes may occur in up to 50 % of patients. The most characteristic ophthalmological lesion is necrotizing retinitis. Cortical blindness can be the early feature of SSPE. The diagnosis of SSPE is often difficult in the early stages. In a typical case diagnosis is based on clinical, electroencephalographic, and cerebrospinal fluid findings. At present, there is no effective treatment to completely cure SSPE. Oral isoprinosine and intrathecal or intraventricular alpha-interferon may prolong survival to some extent. Immunization against measles is currently the most effective strategy against SSPE.

Key words subacute sclerosing panencephalitis · SPPE

Introduction

Subacute sclerosing panencephalitis (SSPE) is a devastating progressive neurodegenerative disorder of the central nervous system. It is caused by a persistent infection of the brain by an aberrant measles virus, known as SSPE virus. SSPE is a slow virus infection producing inflammatory changes of the brain and subsequently death of cortical neurons.

Epidemiology

In developed countries, SSPE is a rare disease because of widespread immunization against measles. The recently reported incidence of SSPE in one of the developed countries (Canada) was 0.06/million children/year [1]. However, the incidence of SSPE still remains high in Turkey and in some poor and developing countries like Papua New Guinea and India [2, 3]. A very high annual incidence of 56 per million population below the age of 20 years has been reported from Papua New Guinea. According to the estimate of the Global Advisory Committee on Vaccine Safety of World Health Organization, the true incidence of SSPE is approximately 4–11 cases per 100 000 cases of measles. If measles infection is acquired very early in life, the risk may be even higher (18 per 100 000 cases). A risk as high as 27.9 SSPE cases per 100 000 cases of measles has been noted. In several countries with good measles control, an increasing age at onset of SSPE has been observed [4].

Some concerns were raised that the measles vaccine itself might cause SSPE. Recent epidemiological data

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suggest that measles immunization protects against SSPE and the measles vaccine virus itself does not cause SSPE [4]. The administration of the measles vaccine does not alter the course of SSPE or trigger SSPE in an individual who would have developed the disease at a later time without immunization [5].

SSPE affects primarily children and young adults. Most patients with SSPE have a history of primary measles infection at an early age (< 2 years). 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 [6]. SSPE can occur from 2 to 10 years after the primary measles infection. The onset is generally between the ages of 5–15 years. SSPE is approximately twice as common in boys as in girls [7]. A statistically significant positive correlation has been observed between risk of SSPE and early measles infection, large family, overcrowding in the home, older age of the mother, higher birth order, fewer years of schooling of the parents, fewer cultural activities, and rural place of birth. All these factors if present increase the risk of SSPE [8]. The occurrence of multiple cases in a single family suggests a genetic predisposition to SSPE [9, 10]. Comparison of intrafamilial with sporadic cases of SSPE in a recent study revealed that latency of clinical manifestations in familial SSPE is significantly shorter than that in sporadic cases (median of 6.4 years versus median of 9.7 years) [9].

Pathogenesis

Mutated measles virus variants, also called SSPE virus, have been suggested as the pathogenetic agent for SSPE. Measles virus is a member of the genus *Morbillivirus.* Morbilliviruses belong to the paramyxovirus family. Measles virus is an enveloped virus and its genome contains six genes that encode for six corresponding proteins: nucleocapsid (N), phosphoprotein (P), matrix (M), fusion (F), haemagglutinin (H) and large (L) proteins. The inner capsid is composed of a non-segmented, negative-stranded ribonucleic acid (RNA) genome which is enveloped with nucleocapsid protein, RNA-dependent RNA polymerase complex consisting of the large protein and phosphoprotein. These together form a ribonucleoprotein complex [11, 12]. The matrix protein lines the inner surface of the envelope and plays an important role in virus budding and transcription regulation. Hemagglutinin protein is a surface glycoprotein which is responsible for the binding of measles virus to its host cell receptors. When a virus comes in contact with a cell the fusion protein changes shape and extends like a harpoon into the outer membrane of the target cell [11–13].

SSPE virus differs from wild-type viruses in the form of several mutations that mainly affect the matrix, hemagglutinin, nucleocapsid, and fusion genes. The matrix gene is the most commonly affected by these mutations. These genetic mutations in the SSPE virus result in poor expression of envelope proteins. Consequently, the SSPE virus is able to maintain a persistent infection in neuronal cells of the brain. The SSPE virus is neuropathogenic but unable to produce transmittable infectious viral particles [14]. Forcic et al. were able to detect and characterize measles virus strains in cases of SSPE by direct reverse transcriptase-polymerase chain reaction amplification of viral RNA extracted from brain tissue. In this case, phylogenetic analysis of the sequences of hemagglutinin and nucleocapsid genes led to identification of measles virus genotype D6 [15]. Studies have demonstrated that measles virus sequences obtained from brain tissues are homologous to the genotype circulating at the time of primary exposure to measles virus [16]. Recently, the whole wild-type measles virus in brain tissue of children with SSPE has been isolated. Nucleotide sequence analysis showed that the viruses detected in brain tissue belong to the wild-type measles virus D6 genotype [17]. In another case from South India, the measles virus with hypermutation in the M gene was isolated from the brain tissue of a patient of fulminant SSPE and phylogenetic analysis of the viral genome indicated that it belonged to D7 genotype. D7 genotype is considered rare in India [18, 19].

It is possible that all morbilliviruses transiently infect the central nervous system in their natural hosts, but development of SSPE is dependent on the efficiency of the immune system of the affected person. It has been suggested that a genetically determined immune dysfunction against the measles virus may be responsible for susceptibility to SSPE. A defective cell-mediated immunity and inflammatory cytokines are suggested in the pathogenesis of SSPE. Inoue et al. demonstrated that three candidate genes, MxA, interleukin-4, and interferon-1 genes were associated with SSPE susceptibility in Japanese patients. MxA protein is an antiviral protein induced by interferon-alpha and interferon-beta. This protein inhibits the replication of single-stranded RNA viruses including measles virus [20].

Measles virus possibly enters the nervous system at the time of the original systemic infection and enters the central nervous system either by direct infection of endothelial cells or in infected leukocytes. Neurons and oligodendrocytes are dominantly affected [21]. Because neuronal cells do not express known cellular receptors for measles virus in humans, the mechanism of virus entry to neural cells and spread within the central nervous system remains unclear. It has been suggested that interactions of measles virus with cellular receptors on neural and lymphoid cells are important elements in the pathogenesis of SSPE [22, 23]. The human CD46 molecule and signaling lymphocyte-activation molecule (SLAM) have been identified as cellular receptors for measles virus. In both humans and experimental ani-

mals once infection of neurons has been established, virus spreads transneuronally. The transneuronal spread to adjacent cells possibly occurs through the synapse and there is formation of a syncytium-like structure in the areas restricted to the synapse [24]. It has been suggested that apoptosis (either as a direct effect of viral infection or by cytokine-mediated responses) of various neuronal cells may contribute to the pathogenesis of measles virus infection in the human central nervous system [25].

Pathology

In the early stages, the disease chiefly affects the occipital areas, and then spreads to the anterior portion of the cortex. Subsequently, subcortical structures, brain stem, and spinal cord are involved [26]. SSPE results in widespread destruction of brain tissue, including both gray and white matter [27, 28]. In late stages, there may be marked atrophy of the cerebral cortex.

Histopathological findings in SSPE are characterized by inflammatory changes in brain parenchyma, white matter demyelination, numerous viral inclusions (in neurons, oligodendrocytes and astrocytes), neuronal loss, and astrogliosis.

In the early part of the illness, there are inflammatory changes in the meninges and cerebral parenchyma involving cortical and subcortical gray matter and white matter. There is marked inflammatory infiltrate around the vessels which contains macrophages, plasma cells, and lymphocytes; there is prominent perivascular cuffing by lymphocytes [29]. Ultrastructural study by electron microscopy in the autopsy material revealed that three types of inclusion bodies were present in brain tissues. Viral nucleocapsids were found in neurons and oligodendrocytes. Two other types of intranuclear inclusions – nuclear bodies and granulofilamentous inclusions – were present in astrocytic nuclei [30]. Massive argyrophilic and tau-positive glial fibrillary tangles were found in oligodendroglia in two autopsied cases of SSPE [31].

Clinical features

The characteristic clinical manifestations of SSPE include behavioral abnormalities, cognitive decline, myoclonic jerks, seizures and abnormalities in vision. Clinical manifestations of SSPE usually start with subtle intellectual deterioration of the affected child causing deterioration in school performance. Other cognitive impairment includes abnormal behavior, irritability, and forgetfulness. Later there is severe mental decline, poor comprehension and marked speech deterioration [6, 32].

One of the most characteristic manifestations of SSPE is periodic myoclonic jerks. Periodic myoclonus often leads to difficulty in walking and repeated falls. Typically the myoclonic jerks are generalized and involve the head, trunk and limbs (Video). Myoclonic jerks do not interfere with consciousness. Myoclonic jerks become exacerbated on excitement. In some patients myoclonus may be subtle in the form of periodic slow eye blinking and upwards rolling of the eyes. Myoclonus can be elicited by the patient standing with feet together and arms held forward and then watching for the periodic dropping of the head, neck, trunk, or arm. Myoclonus rarely can occur unilaterally in the early stages of the disease. In the late stage of disease the intensity of myoclonus diminishes [6, 33]. Patients frequently develop pyramidal and extrapyramidal signs. A few patients may develop ataxia, dystonia, and dyskinesia. There is progressive deterioration of sensorium to a stage of coma. In advanced stages of the disease, patients become quadriparetic, spasticity increases, and myoclonus may disappear.

In the terminal stages of the disease, patients may develop hypothalamic failure which manifests as intermittent hyperthermia, excessive sweating, and pulse and blood pressure abnormalities. Breathing at this stage becomes noisy and irregular. Decerebrate and decorticate rigidity appear. Ultimately the patient becomes vegetative.

Ocular changes occur in up to 50 % of SSPE cases [34]. Visual manifestations may precede the neurological manifestations by a few weeks or months [35–37]. Visual complaints may be because of involvement of the retina, optic nerve or visual cortex. The most characteristic ophthalmological lesion seen in SSPE is necrotizing retinitis. Retinitis affects the retina with secondary involvement of the retinal pigment epithelium and choroid. The retinitis usually manifests as a focal area of retinitis in the region of macula. Berker reported a case of SSPE in which the initial clinical presentations were optic atrophy and macular degeneration. Fundus examination in this patient revealed bilateral optic atrophy and macular degenerative changes including retinal pigment epithelial atrophy, macular scarring, and epiretinal membrane formation [36]. Optic nerve edema due to papilledema, papillitis and disc pallor, cortical blindness, nystagmus, gaze palsies, and ptosis are the other reported eye findings. It has been suggested that there is possibly measles virus-acquired virulent neurotropism in the retina before involvement of the central nervous system [38]. Ultrastructural examination of retina in a patient demonstrated numerous filamentous microtubular intranuclear viral inclusions in the nuclear layers of the retina consistent with the measles virus [39]. The diagnosis of SSPE should be considered in cases with acute vision loss resulting from cortical blindness even when other classical findings of SSPE are absent [40].

Visual-spatial agnosias and hallucinations can also be the early features of SSPE. There are several reports of Balint's syndrome and Anton's syndrome in patients with SSPE [41]. Takayama and co-workers, after reviewing the cases of fulminant SSPE, reported that more than half of the patients had blurred vision or visual agnosia as an initial symptom [42].

Diagnosis

The diagnosis is based on characteristic clinical features, periodic electroencephalographic complexes and elevated measles antibody titer in cerebrospinal fluid. After appearance of myoclonus the diagnosis of SSPE can reliably be established with the help of Dyken's diagnostic criteria (Table 1).

Table 1 Dyken's diagnostic criteria for subacute sclerosing panencephalitis [6, 27]

1. A typical clinical picture of progressive subacute mental deterioration with stereotyped generalized myoclonus
2. Characteristic electroencephalogram changes
3. Elevated cerebrospinal fluid globulin levels greater than 20% of total cerebrospinal fluid protein
4. Raised cerebrospinal fluid measles antibody titers
5. Typical histopathologic findings in brain biopsy or autopsy

Electroencephalography

Early in the course of SSPE, electroencephalography (EEG) may be normal or may have nonspecific generalized or focal slowing. The characteristic periodic EEG pattern, initially described by Cobb and Hill later by Cobb alone, consists of periodic EEG complexes [43, 44]. These complexes are pathognomonic features of SSPE. EEG shows stereotyped periodic complexes with high-voltage diphasic waves occurring synchronously throughout the recording. The complexes are usually associated with myoclonic jerks. Morphology of the complexes is highly stereotyped within an individual, but differs between patients. These EEG changes are usually apparent in the myoclonic phase of the disease [45] (Fig. 1). In one study three different types of EEG periodic complexes were described. Type-1 periodic giant delta waves, type-2 periodic giant delta waves intermixed with rapid spikes or fast activity, and type-3 long spike-wave discharges interrupted by giant delta waves [46]. Late in the course of illness the EEG appearance becomes increasingly disorganized and shows high amplitude random dysrhythmic slowing. The interval between the complexes shortened in all patients with progression of the illness [47].

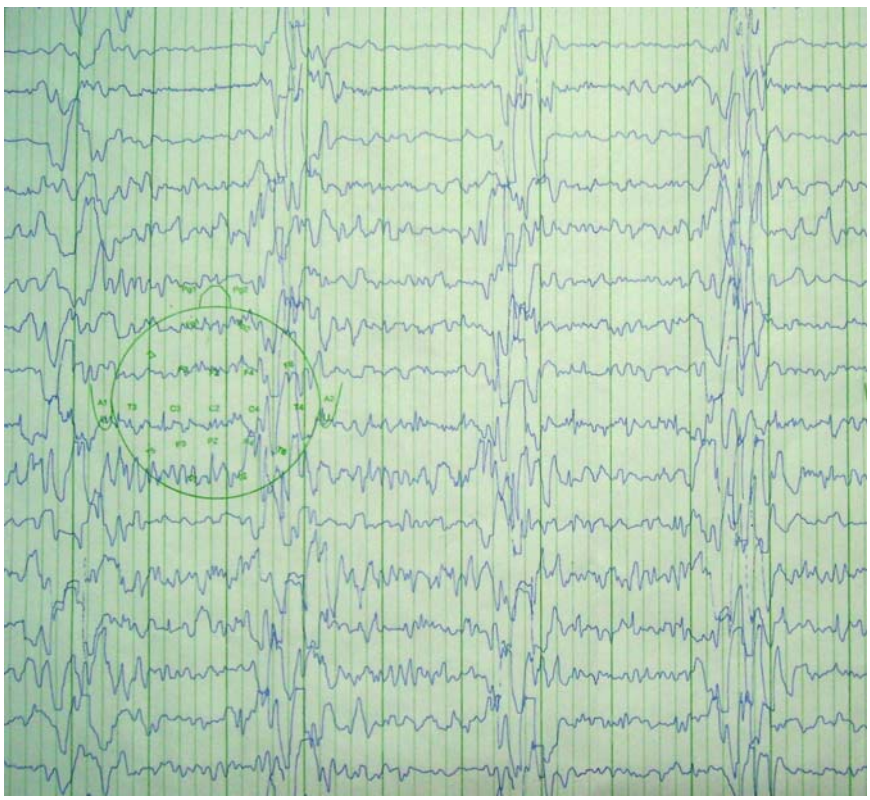

Fig. 1 An awake electroencephalogram showing slowing high voltage, generalized, stereotyped periodic complexes occurring synchronously throughout the recording (Record settings: paper speed = 30mm/s; sensitivity, 7mm = 50 μV; high filter = 70 Hz; low filter = 1Hz)

Cerebrospinal fluid examination

Cerebrospinal fluid examination often reveals normal pressure and normal routinely performed cellular and biochemical parameters. The cerebrospinal fluid globulin level is almost always elevated, constituting up to 20 to 60 % of the total protein in cerebrospinal fluid. Measles antibodies are often measured by using the indirect hemagglutination test, complement fixation test or enzyme linked immunosorbent assay. Measles antibody titers are usually lower by the indirect hemagglutination method than either by complement fixation test or enzyme linked immunosorbent assay. In the patients with SSPE anti-measles antibody titers of serum and CSF are always elevated. Raised antimeasles antibody titers 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 titer to serum titer ranges from 1:4 to 1:128 (below 200); this ratio is low compared with the normal ratio (1:200–1:500) [6]. In one study measles antibody titers, measured by an indirect immunofluorescent assay test, in serum ranged from 40–1280 and neat to 32 in cerebrospinal fluid. The serum and cerebrospinal fluid measles antibody titer ratio ranged from 5:1 to 40:1 in the majority (94 %) of patients, only 3 patients had a ratio of 80:1 [48].

A progressive increase in the ratio of cerebrospinal fluid to serum IgG with the advance of the disease suggests synthesis of IgG locally in the central nervous system [49, 50]. Measles virus-specific plasma cells are prominent in CSF of SSPE patients and clonal expansion is a prominent feature of the SSPE plasma cell repertoire. It was demonstrated that $CD138^+$ cells recovered from cerebrospinal fluid of a SSPE patient are primarily targeted against measles virus and three of four human IgG1 recombinant antibodies derived from expanded $CD138^+$ clones reacted to measles virus proteins. This important observation suggested a link between intrathecal synthesis of SSPE virus-specific IgG and the expansion and migration of antibody-secreting cells in the brain [51].

Neuroimaging

In the early stages of SSPE, the neuroimaging studies are often normal. The most frequently involved areas in SSPE are periventricular and subcortical white matter. The basal ganglia, cerebellum, spinal cord and corpus callosum are less commonly involved. Lesions of the deep nuclei may also be noted, frequently in the early and intermediate stages. Lentiform nuclei are more involved than the caudate nucleus. Magnetic resonance imaging was better than computed tomography in illustrating white matter and basal ganglia abnormalities [52]. In a recent study white matter demyelinating lesions, cerebral edema, cerebral atrophy and signal changes in basal ganglion and thalamus were common imaging abnormalities [53] (Figs. 2 a–d).

In later stages progressive hemispheric, cerebellar, and brainstem atrophy are seen. In the most advanced stage, when the patient is in a vegetative state, an almost total loss of white matter has usually taken place. At this stage, the corpus callosum is also thinner [54]. Even in advanced stages, grey matter is comparatively less affected. Severity of magnetic resonance imaging changes may not correlate well with the clinical findings [54].

Brain biopsy

In the absence of characteristic clinical and electroencephalographic manifestations brain biopsy may be required to confirm the diagnosis of SSPE [55]. Polymerase chain reaction provides a simple, rapid and highly sensitive means of detecting and identifying sequences of

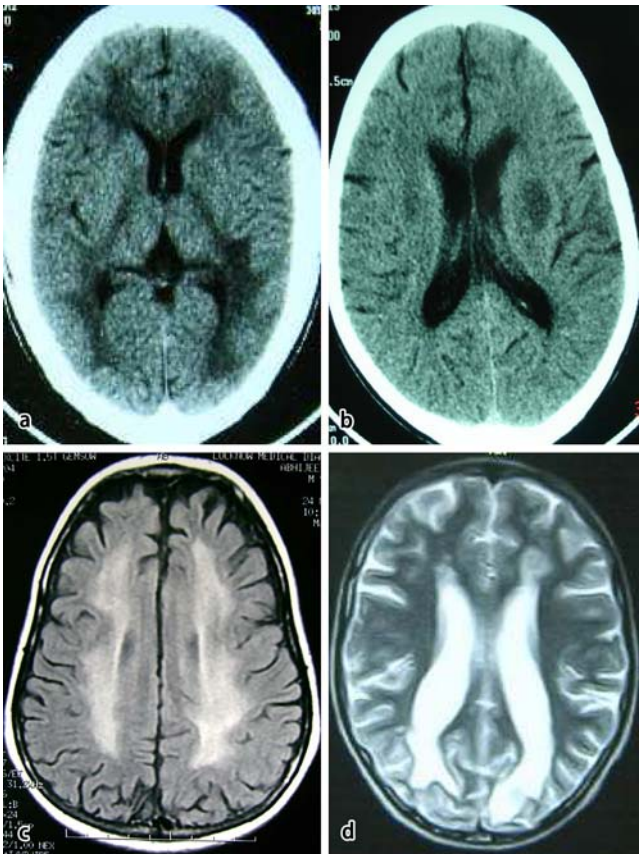

Fig. 2 **a** CT of brain showing white matter abnormalities in periventricular and subcortical regions of the cortex. **b** CT of brain showing involvement of basal ganglion. **c** Axial fluid attenuated inversion recovery MR image showing increased signal abnormalities in periventricular and subcortical white matter. **d** T2-weighted MR image showing increased signal abnormalities in white matter and gray matter of parieto-occipital regions

RNA genomes of measles virus extracted from brain tissue. In several studies the coding regions of the matrix, hemagglutinin and nucleoprotein genes of measles virus were sequenced following direct reverse-transcription polymerase chain reaction amplification of viral RNA. The measles virus genome was detected in SSPE brain tissues stored frozen for as long as 27 years and formalin-fixed paraffin-embedded SSPE brain tissues as old as 9 years [56, 57]. Nucleic acid hybridization techniques have also been used to demonstrate the measles virus genome.

Differential diagnosis

Clinical presentation in intial phases of SSPE may be non-specific and often pose great diagnostic difficulties. Diagnosis requires a high index of suspicion (Table 2). In a retrospective study including 307 patients it was observed that in 242 (78.8 %) patients the initial diagnoses were something other than SSPE. Some of these diagnoses included seizures, absence seizures, Lennox-Gastaut syndrome, metachromatic leukodystrophy, Schilder's disease, cerebral palsy, hemiparkinsonism, Wilson's disease, vasculitis, spinocerebellar ataxia, motor neuron disease, nutritional amblyopia, tapetoretinal degeneration, catatonic schizophrenia, and malingering [58].

Table 2 Differential diagnosis of subacute sclerosing panencephalitis

Pschychiatric manifestations
Depression
Schizophrenia
Malingering
Intracranial space occupying lesions
Peudotumor cerebri
Brain tumors
Other encephalopathies
Viral encephalitis
Cerebral venous thrombosis
Acute disseminated encephalomyelitis
Posterior leukoencephalopthy syndrome
Progressive rubella panencephalitis
Progressive myoclonic epilepsies
Unverrict Lundborg syndrome
Myoclonus epilepsy with ragged red fibers
Lafora's disease
Neuronal ceroid lipofuscinoses
Sialidoses
Seizure disorders
Absence seizures
Uncontrolled epilepsy with antiepileptic drug toxicity
Lennox-Gastaut syndrome
Movement disorders
Non-epileptic paroxysmal events
Rheumatic chorea
Wilson's disease
Cerebral palsy
In pregnancy
Cerebral venous thrombosis
Eclampsia

Several pschychiatric manifestations like malingering, emotional liability and depression have been reported as initial manifestations of SSPE. Because of delusions and hallucinations and nonspecific psychosis the clinical picture may simulate schizophrenia [59–62]. For example, in a 21-year-old man who, after extensive investigations by the general physicians and neurologists, was transferred to a psychiatric hospital with a diagnosis of functional illness. A diagnosis of SSPE was then made 9 months after disease onset [59].

Occasionally, patients with SSPE can present with dominant unilateral neurological signs, simple partial sensory and motor seizures, or papilloedema; these findings can lead to an erroneous diagnosis of an intracranial space occupying lesion. For example, SSPE was diagnosed in a 16-year-old girl with a more than 2-year history of right-sided simple partial sensory and motor seizures. In this girl after an initial response to antiepileptic medication, her seizures became intractable, and mild, right-hemispheric focal signs developed. Magnetic resonance imaging showed an extensive right-hemisphere infiltrative lesion, initially thought to be a neoplasm. Brain biopsy led to the possibility of SSPE, and diagnosis was confirmed by serological tests [63].

Abnormalities of vision, which appear in the early period of the disease as the only clinical symptom, also create diagnostic problems. The diagnosis of SSPE should be considered in cases with acute vision loss resulting from cortical blindness even when classical findings of the central nervous system do not exist [64]. SSPE should also be considered in any child or young adult who presents with vision loss because of unexplained retinal vasculitis, maculopathy or chorioretinitis. The macular lesions at the acute stage are likely to be confused with toxoplasmosis [39].

In developed countries the diagnosis of SSPE is often not considered by clinicians because of its rarity. Clinical manifestations of SSPE are often nonspecific at onset. Honarmand et al. described five cases of SSPE identified among 1000 cases registered in the California Encephalitis Project, but in none of the patients was the possibility of SSPE considered. SSPE was not suspected in the differential diagnosis of three of the cases until results of measles testing were known. In two patients leading diagnoses were mitochondrial cytopathy and acute disseminated encephalomyelitis [65]. Acute fulminant SSPE should always be included in the differential diagnosis of acute unexplained encephalopathic diseases.

The progressive rubella panencephalitis is an extremely rare condition; however the clinical and electro-

encephalographic features are almost indistinguishable from the SSPE. This condition is characterized by progressive dementia, ataxia, choreiform movements, myoclonic seizures, and fine perimacular retinal pigmentation. Microscopical study of biopsied brain tissue in a patient revealed a picture similar to SSPE, but with perivascular deposits and without inclusion bodies [66, 67].

SSPE also presents with various types of seizures, mainly myoclonic jerks, atonic and tonic-clonic seizures. The differential diagnosis, even non-epileptic paroxysmal events, may prove to be problematic [68]. Uncontrolled epilepsy with antiepileptic drug toxicity should be considered in the differential diagnosis of SSPE. SSPE needs to be distinguished from progressive myoclonic epilepsies which are a group of rare inherited neurodegenerative disorders. These diseases are clinically characterized with generalized epilepsy, myoclonus and a progressive neurological dysfunction. The five most prevalent progressive myoclonic epilepsy syndromes include Unverricht-Lundborg disease, myoclonus epilepsy with ragged red fibers (a mitochondrial cytopathy), Lafora's disease, neuronal ceroid lipofuscinoses, and sialidoses [69].

Treatment

Isoprinosine was first drug that had been reported effective against SSPE. It was suggested that immuno-modulatory effects of isoprinosine helped in stabilizing the course of disease [70–72]. On the contrary, in several studies the beneficial effect of isoprinosine was not evident. Because of the highly variable natural history, differences in clinical improvement between treated patients and controls were considered insignificant [73, 74].

Alpha-interferon was another drug that has been reported effective in SSPE [75]. Initially alpha-interferon was administered by intramuscular, intravenous or intrathecal routes. Panitch et al. used alpha-interferon by the intraventricular route in three patients for 6 months. All three patients improved to varying degrees and for different lengths of time. Clinical remissions were associated with decreased titers of antibody to measles virus in cerebrospinal fluid and with reduced rates of intrathecal IgG synthesis [76]. Intraventricular alpha-interferon is administered through a catheter inserted into the lateral ventricle and connected to an Ommaya reservoir placed under the scalp. Intrathecal alpha-interferon continuous infusion using a reservoir placed in the abdominal subcutaneous space was a method that was considered less invasive, allowing easy access to the intrathecal space with low risk of infection. Some unconfirmed reports suggested that even beta-interferon is effective if it is administered by the intraventricular route. Interferon-beta, if given along with isoprinosine, has also been suggested an effective treatment option in SSPE [77].

Ribavirin, another antiviral agent, has also been reported effective against SSPE. Ribavirin has inhibitory activity against several RNA viruses, including measles virus [78, 79]. By intraventricular administration, the ribavirin level in cerebrospinal fluid reaches a concentration at which ribavirin could completely inhibit the replication of SSPE virus. In a series of five patients treated with intraventricular ribavirin, four patients observed significant neurologic improvement along with a significant decrease in titers of hemagglutination inhibition antibodies against measles virus in cerebrospinal fluid [79].

Several reports suggested that combination of two or more than two drugs were more effective in stabilizing the course of the disease. Combination therapy appeared to prolong the survival time of patients. The intraventricular administration of alpha-interferon in combination with oral isoprinosine is currently the most effective treatment available [80]. Yalaz et al. treated 22 patients with a combination of intraventricular alpha-interferon and oral isoprinosine. Clinical improvement was observed in half of the patients. Of the remaining patients. five became stable, and the progression rate of the disease decreased in three [81].

Recently, the International Consortium on SSPE compared the efficacy of oral isoprinosine alone versus combined treatment of isoprinosine and intraventricular interferon-alpha2b in a randomized manner. The isoprinosine dosage was 100 mg/kg/d to a maximum of 3 g/d, taken orally in three divided doses for 6 months. Interferon-alpha2b was given with 100,000 unit/m^2 and escalated to 1,000,000 unit/m^2 over 5 days and then 1,000,000 unit/m^2 twice a week for 6 months. Authors could not observe any statistically significant difference between the two treatment groups [82].

Solomon et al. for the first time used a regimen comprising three drugs. A patient was started on a new regimen consisting of intraventricular interferon-alpha (starting at 100,000 unit/m^2/d, building up to 1 million unit/m^2/d), ribavirin (60 mg/kg/d intravenously), and isoprinosine (3 g/d) and observed a marked improvement [83]. In another three-drug regimen, Kurata et al. compared patients with SSPE who received treatment according to the three-drug protocol for at least 6 months (19 patients) with the patients who did not receive any treatment (13 patients). The treatment protocol consisted of oral isoprinosine (100 mg/kg/d), subcutaneous interferon alpha-2a (10 million unit/m^2/three times a week), and oral lamivudine (10 mg/kg/d). There were no statistical differences between the two groups according to neurological deficit index, clinical stage, and average age on admission and also on the final evaluation after treatment. The mortality rates of both groups were similar. The mean survival period of the treatment group

was significantly longer than that of the control group [84].

Recently, a recombinant adenovirus expressing the small interfering RNA was found to be a novel therapeutic measure against SSPE. In a study, Otaki et al. produced recombinant adenovirus expressing the small interfering RNA and demonstrated that this recombinant adenovirus efficiently inhibited replication of the measles virus and SSPE virus in a dose-dependent manner [85].

Symptomatic treatments like trihexyphenidyl, clonazepam, valproate and carbamazepine are often ineffective in controlling the myoclonus.

Adult-onset SSPE

Reports have suggested that adult-onset SSPE may have atypical features. Although the course of the disease was progressive and fatal in the majority of patients, there appeared to be a higher rate of spontaneous remission as compared with childhood-onset SSPE. Myoclonus, spastic hemiparesis, bradykinesia, and rigidity were the predominant motor manifestations. Visual symptomatology was very frequent, with 8 of the 13 cases reviewed having a purely ophthalmological presentation; only 2 patients presented with behavioral changes [86]. In a recent study from a developing country the clinical profile of adult-onset SSPE did not differ from that of pediatric patients, except for a longer interval between measles infection and symptom onset [87].

Pregnancy and SSPE

SSPE during pregnancy is very rare and is often fulminant [5]. Cortical blindness has been reported as the most common presenting manifestation during pregnancy. Characteristic myoclonus may not be apparent. The clinical picture may resemble that of eclampsia and diagnosis is frequently difficult. In several published reports, diagnosis of SSPE in pregnancy could only be confirmed after brain biopsy [29, 88]. It has been suggested that the relative older age of disease presentation and the unusually rapid neurological deterioration were partially due to immunologic and hormonal alterations of pregnancy [89].

SSPE is often associated with the death of the fetus in intrauterine life, or in the immediate peripartum period. There are several instances in the literature when a woman delivered a healthy infant either normally or by Cesarean section [90, 91]. Infants born to mothers with SSPE have not been subsequently diagnosed with SSPE themselves [5]. However, perinatal intrauterine measles infection may result in SSPE with a short onset latency and fulminant course. Dasopoulou and Covanis presented a newborn infected during pregnancy by the measles virus and developed SSPE within the first year of life after a short incubation period [92].

Table 3 Staging of subacute sclerosing panencephalitis [6,27]

1.	Stage 1	behavioral changes and cognitive decline
2.	Stage 2	myoclonus and motor deterioration
3.	Stage 3	pyramidal and extrapyramidal manifestations, disappearance of myoclonus, alteration in sensorium
4.	Stage 4	a vegetative state

Prognosis

The majority of patients have a progressive deterioration ultimately leading to death. Death typically occurs within 1 to 3 years (Table 3). Some patients have been reported to apparently have gone into remission for a variable period of time. In about 10 % of all cases, the disease progresses rapidly and leads to death within a few months. Recently, the clinical courses of 19 patients who survived beyond 3 years were reviewed. These patients had varied clinical courses. The majority observed stabilization of the disease in different stages for 6 months to 5 years. Some of the patients had remissions for 6 months to 9 years and even reversal of staging with functional recovery from being bed bound to ambulant [93].

Conclusion

SSPE is a devastating illness for families of the affected children. In a few, the disease can progress very rapidly and lead to death within a few months. So far available treatments are disappointing. In developing countries, the situation is grim. SSPE is still very frequently encountered. Combination of isoprinosine and intraventricular alpha-interferon is unaffordable. Novel therapies, like recombinant adenovirus expressing the small interfering RNA inhibiting replication of SSPE virus, do provide hope for the future. Vaccination against measles remains the most effective strategy against SSPE.

Conflict of interest The authors declare no conflict of interest.

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