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REVIEW

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Subacute sclerosing panencephalitis

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Summary

Subacute sclerosing panencephalitis (SSPE) is a slowly progressive brain disorder caused by mutant measles virus. SSPE affects younger age groups. SSPE incidence is proportional to that of measles. High-income countries have seen substantial decline in SSPE incidence following universal vaccination against measles. SSPE virus differs from wild measles virus. Measles virus genome recovered from the autopsied brain tissues demonstrates clustered mutations in virus genome particularly in the M gene. These mutations destroy the structure and functioning of the encoded proteins. Complete infectious virus particle has rarely been recovered from the brain. Human neurons lack required receptor for entry of measles virus inside the neurons. Recent in vitro studies suggest that mutations in F protein confer hyperfusogenic properties to measles virus facilitating transneuronal viral spread. The inflammatory response in the brain leads to extensive tissue damage. Clinically, SSPE is characterized by florid panencephalitis. Clinically, SSPE is characterized by cognitive decline, periodic myoclonus, gait abnormalities, vision loss, and ultimately to a vegetative state. Chorioretinitis is a common ocular abnormality. Electroencephalography (EEG) shows characteristic periodic discharges. Neuroimaging demonstrates periventricular white matter signal abnormalities. In advanced stages, there is marked cerebral atrophy. Definitive diagnosis requires demonstration of elevated measles antibody titers in cerebrospinal fluid (CSF). Many drugs have been used to stabilize the course of the disease but without evidence from randomized clinical trials. Six percent of patients may experience prolonged spontaneous remission. Fusion inhibitor peptide may, in the future, be exploited to treat SSPE. A universal vaccination against measles is the only proven way to tackle this menace currently.

KEYWORDS

chorioretinitis, encephalopathy, measles, myoclonus

Abbreviations: ADC, apparent diffusion coefficient; CF, complement fixation; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; EEG, electroencephalography; ELISA, enzyme-linked immunosorbent assay; FLAIR, fluid-attenuated inversion recovery; GABA, gamma-aminobutyric acid; HI, hemagglutination inhibition; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IgM, immunoglobulin M; IIF, indirect immunofluorescent assay; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron-emission tomography; RNA, ribonucleic acid; SLAM, signalling lymphocytic activation molecule; SSPE, subacute sclerosing panencephalitis; USA, United States of America; WHO, World Health Organization

1 | INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) is a progressive brain disorder caused by persistent mutant measles virus. The disease has a relentless deteriorating course, culminating in death. SSPE usually affects children and younger adults. Our review focuses on the epidemiology, pathogenesis and pathology, clinical features,

electroencephalography (EEG), neuroimaging, differential diagnosis, treatment, and prognosis of SSPE. We reviewed 2858 articles available in PubMed on 30 April 2019. PubMed search was done using the terms "subacute sclerosing panencephalitis" or "SSPE."

2 | EPIDEMIOLOGY

Measles is a highly infectious viral disease and spreads rapidly by airborne route. In the postvaccination era, measles-related deaths, in developed countries, have drastically gone down. However, in resource-constrained countries, the situation is still grim. In 2017, globally 173 330 measles cases were reported, and approximately 110 000 people died of it. In year 2000, estimated annual number of deaths were approximately 545 000. Asian and African countries still account for majority of measles-related deaths.[1]

The exact global burden of SSPE is unknown. Countries with a high incidence of measles encounter a high incidence of SSPE. A World Health Organization (WHO) expert group reported the global incidence as 4 to 11 SSPE patients per 100 000 measles cases. If measles occurs in early childhood, the risk of SSPE is much higher (approximately 18 per 100 000 measles cases).[2] In resource-constrained countries, incidence seems to be much higher (up to 27.9 SSPE patients per 100 000 cases of measles).[2] India, Pakistan, Papua New Guinea, and Turkey are the countries reporting the majority of global SSPE cases. Turkey, though a European country, continues to report a large number of SSPE cases. Between 1975 and 1987, a registry recorded 401 patients in Turkey.[3] Guler and colleagues, in 2015, presented data 64 patients that were seen between 2007 and 2013.[4] In Papua New Guinea, between 1988 and 1991, 87 confirmed cases were reported.[5] In 2007 to 2009, the incidence declined but still reported 22 cases in Madang province of Papua New Guinea with annual incidence of 54/million population aged <20 years. In four subdistricts of Madang province, the yearly incidence reached >100 per million population aged less than 20 years.[6] In India and Pakistan, annually a large number of new SSPE patients are seen. In North India, from a single tertiary care center, 114 confirmed cases were registered between 1992 and 2001.[7] In the postmeasles vaccination era, another north Indian tertiary care center registered 458 serologically confirmed SSPE cases over a 10-year period (1996 to 2005).[8] In Pakistan, from Karachi, 43 patients of SSPE were diagnosed between 2000 and 2012.[9] In both countries, a large number of SSPE cases are likely to remain unreported.

In high-income countries, there is a substantial decline in the incidence of SSPE. New cases now correlate with measles outbreaks. In Germany, 31 children with SSPE were identified between 2003 and 2009. The estimated risk of SSPE among younger children (less than 5 years) affected with measles was 1:1700 to 1:3300.[10] Wendorf and coworkers, in an epidemiological study (1998 to 2015), in the United States of America (USA), reported 17 patients with SSPE. The SSPE incidence if measles infection occurred before 5 years of age was 1:1367, and if measles occurred in infancy, it was 1:609.[11] In the prevaccination era, even developed countries witnessed an exceptionally high incidence of SSPE. In the USA, from 1988 to 1991, 3651 cases of measles, in children of <12 months of age, were recorded.[11] A study published in 1982 (in the prevaccination era) reported 634 (onset from 1956 to 1981) cases of suspected SSPE patients. Approximate risk of developing SSPE after measles infection was 8.5 cases per million cases during 1960 to 1974. The overall incidence of SSPE, in 1970, was 0.61 per million populations. It decreased to 0.35 in 1975 and 0.06 in 1980.[12] Earlier, between 1960 and 1976, a US SSPE registry collected data on 453 cases. The estimated yearly incidence of SSPE was 3.5 per 10 million persons younger than 20 years.[13] Similarly, in England and Wales, in the prevaccination era (1970 to 1989), 290 cases of SSPE were registered. The risk of SSPE following systemic measles infection was 4.0/100 000 measles cases. Measles infection, occurring under 1 year of age, carried a 16 times greater risk of SSPE compared with if measles occurring at age 5 years or later.[14]

Measles vaccine has a great protective effect against SSPE by protecting against measles. The countries having a high incidence of SSPE have high vaccination gap. Available epidemiological data do not suggest that measles vaccine causes SSPE. Measles vaccine neither accelerates the pace of the course of disease.[15,16] In children with SSPE, without definite evidence of prior measles infection, it is likely that these children either had the subclinical measles or undiagnosed measles in early childhood.[17] In a child with SSPE adequately covered with measles vaccine, wild measles infection is presumed to occur before vaccination.[18] Reemergence of SSPE cases in developed countries coincides with measles outbreaks.

The characteristic age of SSPE diagnosis is around 12 years (3-35 y). The median latency period, defined as onset of measles to onset of neurological symptoms, is 9.5 years (2.5 to 34 y).[11] Following improved measles control, higher age of onset is now noted.[2] The risk of SSPE is two times higher in males. Poor environmental conditions and a low socioeconomic status add to the risk for SSPE because poor environmental conditions add to the risk of acquiring early childhood measles infection.[17,19]

3 | VIROLOGY

Measles virus is a member of the genus *Morbillivirus* and belongs to the family Paramyxoviridae. Measles virus structurally consists of an envelope within which is a nucleocapsid covering a negative-sense single-stranded ribonucleic acid (RNA) genome. Measles virus genome encodes six structural proteins. The envelope contains two proteins: hemagglutinin (H) and fusion (F) proteins. The matrix (M) protein coats the internal surface of the envelope. In the inner nucleocapsid, there are three proteins: phosphoprotein (P), large protein (L), and nucleoprotein (N). L and P proteins are parts of the viral RNA-dependent RNA polymerase. These together form a RNA complex that is the infective part of measles virus. The interaction of M protein with the RNA complex and the cytoplasmic tails of the H and F proteins is crucial for the formation of the virus particle. Binding of H protein with cell receptor triggers F protein and facilitates viral entry into the target

cell. N, P, and L proteins vital for viral replication. The P gene encodes V and C proteins that are considered nonstructural proteins.[20]

Eight genetic clades (A-H) and 24 genotypes of wild-type measles virus are known to affect humans. No specific measles genotype is consistently associated with SSPE. Viral genomes of histopathologically recovered SSPE viruses often do not correspond to currently circulating wild measles virus. SSPE virus genotype resembles to a genotype that was in circulation when the patient acquired measles in childhood.[10,21,22]

4 | VIRAL ENTRY INTO THE BRAIN

Autopsy studies have demonstrated that measles virus gets entry in to the brain during the acute exanthematous phase.[23] EEG and cerebrospinal fluid (CSF) abnormalities are noted even in acute uncomplicated measles. Generally, signalling lymphocytic activation molecule (SLAM) and nectin-4 act as cell receptors for measles virus that facilitate viral entry inside the cell. CD46 acts as cell receptor for vaccine strain of measles virus but not for the wild strain of measles virus. Human neurons are generally devoid of SLAM or nectin-4; therefore, wild measles virus cannot enter neuronal cells.[24,25] There are three potential routes of entry into the brain: infected peripheral blood monocytes carrying the virus across the blood-brain barrier, viral replication within capillary endothelial cells releasing viral particles into the brain parenchyma, or through the olfactory bulb.[23,26,27]

5 | GENETIC DIFFERENCES BETWEEN SSPE VIRUSES AND WILD MEASLES VIRUS

Generally, no virus particle is recovered from the brain tissues of SSPE patient. A variety of genetic differences have been noted in the isolates recovered from the brain tissues of SSPE patients. In the brain, clustered mutations occur in the measles virus genome, which destroy the structure and functioning of the encoded proteins. The characteristic clustered mutation leading to uracil-to-cytosine transitions in the M gene is known as biased hypermutation. Mutated and defective measles viruses keep replicating in brain parenchyma. Measles virus undergoes genetic mutations only after entry into the brain. Cattaneo and coworkers studied changes in viral genome recovered from brain autopsies of SSPE patients demonstrated that 2% of the nucleotides got mutated during viral persistence in brain. This 2% of the nucleotide mutations produces approximately 35% change in amino acids.[28] Defects in the M protein results in the failure to form virus particle facilitating persistence of measles virus in neuronal cells. Failure to form virus particle also helps virus evading neutralizing antibodies.[29-31]

D6 measles isolate was recovered from a pregnant Canadian female patient who had a prior visit to India. The patient had a rapidly progressive course.[32] The isolated D6 measles Canadian strain had a different genome than other reported SSPE D6 strain. In isolated Canadian D6 strain, mutations were observed in whole of the viral genome. Most of the changes (17.6%) were present in the M gene. Total nucleotide variability, in the whole viral genome, was around 3%.[33]

6 | TRANSNEURONAL SPREAD IN THE BRAIN

Intact measles virus has no ability to spread within the brain. Instead, the viral ribonucleoprotein complex of mutated virus evolves to transmit across the neurons, through synapses. Recent investigations, done on human neuronal cell lines and the brains of animal models, have demonstrated that persisting measles virus has mutations in the F gene too. F gene mutations lead to amino acid substitutions and conformational changes in the F protein. Changes in F-protein ectodomain and cytoplasmic tail provide hyperfusogenic properties to the mutated measles virus. The hyperfusogenic properties facilitate the virus for cell-cell fusion with SLAM and nectin-4 deficient neuronal cells. H protein and its interaction with a specific neuronal receptor is also important for viral spread between neurons.[34-36] F protein–mediated transmission of the virus across synapse to another neuronal cell can potentially be inhibited by a fusion inhibitor peptide and antibodies against the measles virus H protein. Both hyperfusogenic F protein and the H protein are crucial for transneuronal spread of measles virus.[35]

7 | GENETIC SUSCEPTIBILITY

What makes measles infected human host susceptible to SSPE is not precisely known.

The probability to develop SSPE is genetically influenced. Variability in the global incidence of SSPE also indicates that genetic factors are involved. Many case-control studies (mostly done in Turkey and Japan) observed genetic defects in components of innate immunity, including Toll-like receptors and cytokines.[37-40]

8 | PATHOGENESIS

A persistent measles infection of brain clinically manifests several years after the acute measles infection. The brain infection leads to an exaggerated mononuclear inflammatory reaction to persisting measles virus; still, the virus evolves mechanisms to successfully evade host's immune defence. The mononuclear inflammatory response in the brain is mediated by $CD4^+$ and $CD8^+$ T cells along with monocytes and antibody-secreting B lymphocytes. The antibody response against measles virus is aggravated with high production of measles virus-specific antibody by plasma cells inhabiting inside the brain. Possibly, neurons and oligodendrocytes may die in the process of apoptosis.[41]

It has been hypothesized that in SSPE, cross-reactivity between viral and myelin antigens may result in autoimmune phenomenon–mediated demyelination.[42] Natural killer cells regulatory dysfunctions may promote autoimmunity in SSPE.[43]

9 | PATHOLOGY

The gross pathological changes in SSPE vary with the stage of the disease. Demyelination of white matter is an early finding. Temporal and parietal lobes are predominantly affected. In addition, basal ganglia, thalamus, brainstem, white matter of corona radiata, and cerebellar peduncles are variably affected. In cases with a long duration of illness, there is diffuse cortical atrophy, and the white matter reveals granular breakdown that corresponds to magnetic resonance imaging (MRI) abnormalities.

Histologically, SSPE is characterized by florid panencephalitis with leptomeningeal and parenchymal perivascular inflammation composed of lymphocytes and histiocytes. The cortex reveals microglial nodules and neuronophagia. Characteristic Cowdry type A intranuclear inclusions are evident within neurons and oligodendroglial cells in white matter (Figure 1). With chronicity, the inflammation reduces but destructive changes become more widespread and with extensive demyelination and widespread reactive astrocytosis (Figure 1). Intranuclear eosinophilic inclusions are easily detectable, and white matter becomes severely gliotic. The characteristic Cowdry type A inclusion bodies are demonstrated inside of both nucleus and cytoplasm of neuronal and glial cells. Another type of inclusion bodies, Cowdry type B inclusion bodies, is exclusively demonstrated in neuronal tissues of the brainstem. The parieto-occipital cortex is most dominantly affected. Anterior parts of the cerebral cortex, periventricular white matter, thalamus, brainstem, and spinal cord are less severely involved.[32,44-49] Studies in rats suggest that measles virus preferentially infects GABAergic and glutaminergic neurons while cholinergic neurons are resistant to viral infection. Dissemination of virus along glutaminergic and GABAergic pathways explains the involvement of motor, somatosensory, auditory and visual cortex, basal ganglia and thalamus sparing the hippocampus and cerebellum.[50] In the later stages of SSPE, cortical atrophy ensues with neuronal loss and neurofibrillary tangles. In SSPE, tau protein is abnormally hyperphosphorylated and accumulates in the form of bundles of filaments. The neuronal cells containing neurofibrillary tangles also demonstrate measles virus genome inside.[51,52] At advanced stages, inflammation becomes scarce, and the inclusion bodies are difficult to detect.[45]

10 | IMMUNOHISTOCHEMISTRY

Immunohistochemistry reveals that, in SSPE, brain tissue lymphohistiocytic infiltrates are predominantly consisting of $CD68^+$ macrophages and activated microglia. $CD3^+$ T lymphocytes and $CD20^+$ B lymphocytes are comparatively less obvious. Measles virus protein and RNA, in neurons, oligodendrocyte, astrocyte, and lymphocyte, can be detected by immunohistochemistry or by in situ hybridization technique. Intracytoplasmic inclusion bodies, in fact, provide

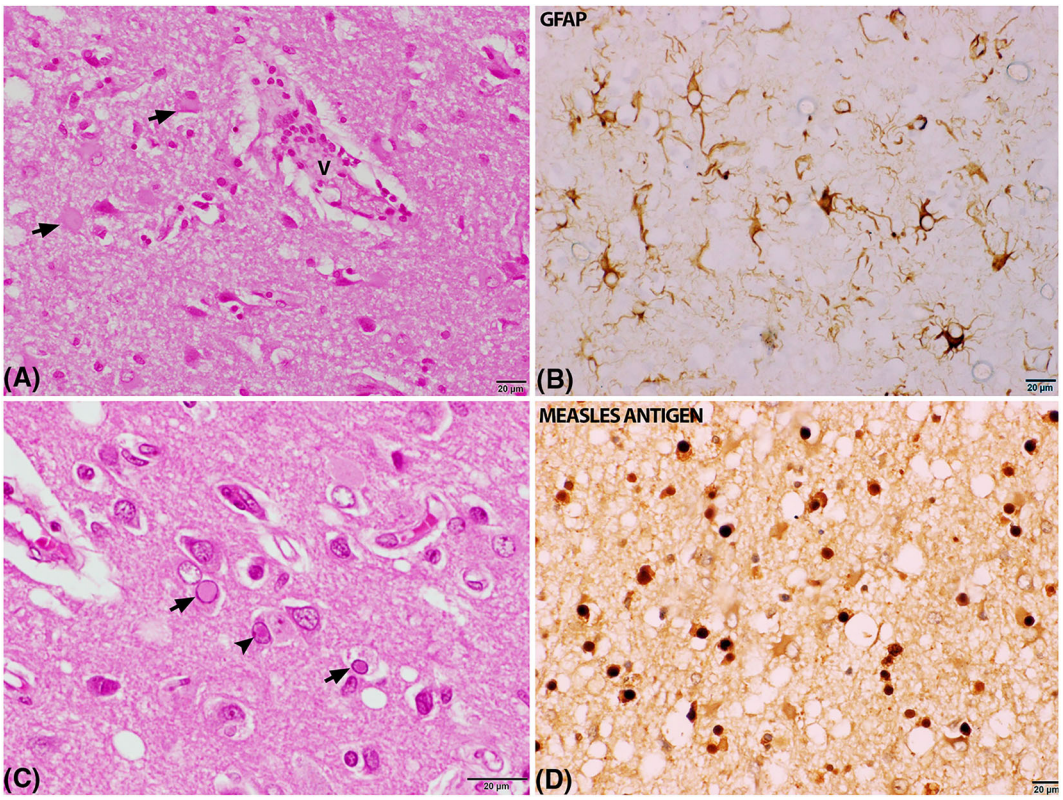

FIGURE 1 Histopathology reveals florid encephalitis (A) in frontal cortex with perivascular inflammation (v) and several hypertrophic reactive astrocytes (arrows, A) that are highlighted by glial fibrillary acidic protein (GFAP) stain (B). Several intranuclear eosinophilic inclusions are detectable within neurons (open arrows) and oligodendroglia (arrow, C). Immunohistochemistry for measles viral antigen within several oligodendroglia and neurons throughout the cortex (D)

platform for effective viral transcription and replication. The measles viral antigen is distributed rostrocaudally in the brain labeling both oligodendroglia and neurons, paralleling the sequential changes on MRI and the clinical stage (Figure 1). Lack of viral budding from the infected cell suggests that the virus is defective. The complete measles virus particle is rarely recovered from the brain.[53] Immunohistochemistry consistently demonstrated expression of N and P proteins. Envelope proteins were never demonstrated.[54-56]

11 | ELECTRON MICROSCOPY

Electron microscopy demonstrates that the intraneuronal intranuclear inclusion bodies consisting of viral nucleocapsid, consistent with a paramyxovirus. Reverse transcription polymerase chain reaction technique strongly demonstrates measles virus genome.[33] Ultrastructural studies highlight "smooth" nucleocapsids within intranuclear inclusions reflecting lack of L and P proteins necessary for viral replication while cytoplasm is filled with replication competent nucleocapsids (fuzzy) spreading along dendritic processes.[53,57] Electron microscopy demonstrated inclusion bodies in the retinal neuronal cells and also demonstrated measles virus particles in the retinal lesions.[58-60]

12 | CLINICAL FEATURES

SSPE in children, typically, starts with subtle cognitive decline, resulting in poor scholastic performance. In addition, patients have forgetfulness, behavioral changes (like hypersexuality and inattention), and gait abnormalities. Verbal output progressively keeps decreasing. Patients develop progressive difficulty in walking. The patients become akinetic and mute. Florid pyramidal signs are present. In terminal stages, the patients are in the vegetative state. The patients develop autonomic instability manifesting as pyrexia and marked generalized sweating.[61] Ultimately, death is inevitable (Table 1). Myoclonus, in early stages, is subtle and hardly discernible, unless it is specifically looked for. Objects may drop spontaneously, or the children may have recurrent falls. Subtle myoclonus may be made apparent by observing the patient with outstretched upper limbs and while doing the finger-to-nose test. Tandem walking can also demonstrate subtle myoclonus. The myoclonus is classically periodic and stereotyped. Myoclonus is usually generalized. Infrequently myoclonus is subtle and localized.[62]

TABLE 1 Clinical staging of subacute sclerosing panencephalitis (SSPE)

Stage	Clinical Features	Disability Status
Stage 1	Subtle decline in mental and scholastic performance	No or mild disability, no or mild impairment to walking
Stage 2	Periodic myoclonus and severe mental decline	Moderate disability with significant impairment to walking
Stage 3	Akinetic mutism with generalized spasticity	Confined to bed and totally dependent
Stage 4	Vegetative state	Impaired consciousness and requires 24-h nursing care

13 | OPHTHALMOLOGICAL MANIFESTATIONS

Ophthalmological involvement was seen in up to 42% (25/49) of the SSPE cases. Each and every component of the visual system, starting from retina to visual cortex, can be involved. In 75% (14/20), ophthalmoscopic findings were present.[63] Ophthalmological findings may precede neurological manifestations for a few weeks to a few years.[64] Chorioretinitis with macular involvement is characteristic of SSPE. Necrotizing chorioretinitis is characterized by dilated tortuous veins, retinal hemorrhages with subretinal exudates and retinal and macular pigmentary changes. The healed retinal scar, with well-defined borders around the central retinal atrophy, is seen in long-standing cases.[65] Chorioretinitis occurs as a result of measles viral invasion[66] (Figure 2 and Table 2).

Vision loss in SSPE may be because of bilateral involvement of visual cortex.[67,68] Other infrequent ocular complications include

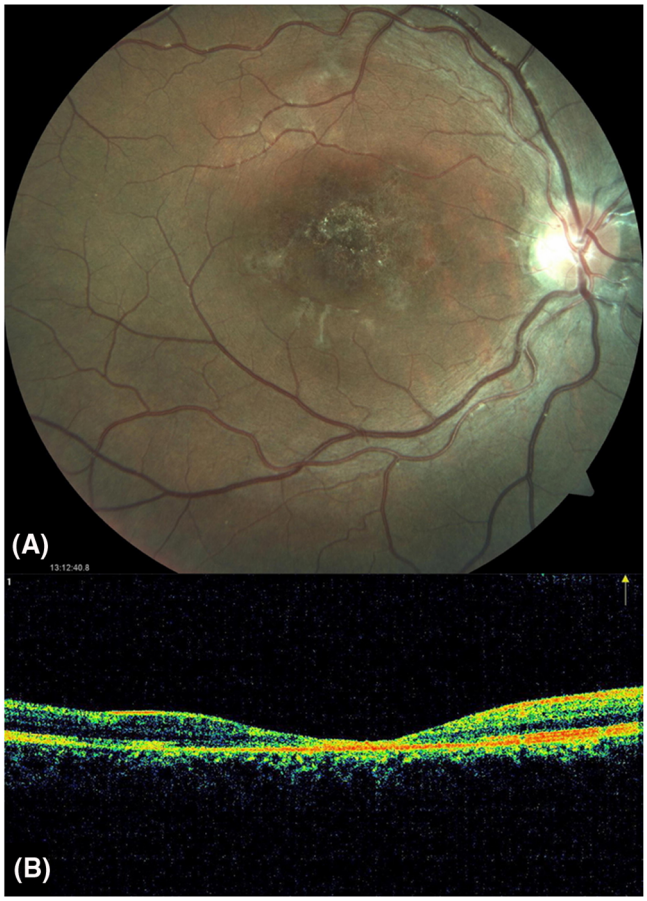

FIGURE 2 Retinal pigmentation and scarring are evident in the right eye (A) extending from the perimacular area to the peripheral fundus. The left eye (B) shows mild perivascular sheathing

TABLE 2 Ophthalmological complications in subacute sclerosing panencephalitis

Choroid and retina
Chorioretinitis
Subretinal fluid and retinal vasculopathy
Necrotizing retinitis
Macular degeneration
Macular edema
Multifocal placoid pigment epitheliopathy
Optic nerve
Papillitis
Optic neuritis
Retrobulbar neuritis
Papilledema
Optic atrophy or temporal pallor
Cortex
Cortical blindness
Anton syndrome
Balint syndrome

serous macular detachment, retinal vasculitis, subretinal fluid, papillitis, disc hemorrhages with venous engorgement, and macular star. Fluorescein angiography often reveals occlusive vasculitis. Optical coherence tomography demonstrates focal necrotic areas in the ganglion cell and nuclear layers of retina.[69-73] Papillitis, optic neuritis, optic atrophy, and papilledema are infrequently reported. Papilledema, in SSPE, simulates intracranial space-occupying lesion, and many patients are diagnosed with pseudotumor cerebri. Neuroimaging may reveal chinked ventricles and effacement of the subarachnoid space.[73,74]

14 | CSF EXAMINATION

CSF examination is, typically, normal. Mildly elevated protein is noted in some.[75] Markedly raised CSF immune-globulin, despite normal CSF protein, is a hallmark abnormality. In SSPE, CSF immunoglobulins constitute more than 20% of total CSF protein. A high titer of measles immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, in the CSF and serum, is the gold standard for the diagnosis of SSPE.[76] The antimeasles IgM antibodies titers are higher in CSF than titers in serum. This phenomenon suggests that measles IgM antibodies are produced within central nervous system (CNS).[76,77] CSF oligoclonal bands are demonstrated in approximately 90% of SSPE patients. The rate of antimeasles IgG synthesis is higher and constitutes more than 20% of the total intrathecal IgG production.[78] In SSPE, CSF IgG production increases substantially, and a substantial amount is against measles virus.[79-81] Plasma cells recovered from CSF of SSPE patients target measles antigens.[82]

Immunoassays, enzyme-linked immunosorbent assay (ELISA), complement fixation (CF), and hemagglutination inhibition (HI), are used for the detection of measles antibody in serum and CSF. ELISA for measles antibody is superior to CF and HI.[83] ELISA is better test for the diagnosis of SSPE, with a sensitivity of 100%, a specificity of 93.3%, and 100% positive predictive value.[84] An elevated HI measles antibody titers of 1:256 or higher in serum and 1:4 or higher in HI measles antibody titers in CSF confirm SSPE.[85] The ratio of serum titer to CSF titer is lower.[86,87] In many laboratories, measles IgG is measured with the help of standard indirect immunofluorescent assay (IIF) antibody assay technique. In a series of 49 SSPE patients, measles antibody titers (by IIF antibody assay) in serum ranged from 40 to 1280 and in CSF varied from 0 to 32. The serum: CSF ratios ranged from 5:1 to 40:1.[88]

The ratio of measles antibodies in the CSF and the serum versus the ratio of total IgG or total albumin in the CSF and the serum (CSQrel) is now employed for the estimation of measles antibody production within the CNS. The CSQrel in SSPE is typically greater than 4.0 (range 5:1 to 80:1).[89]

15 | ELECTROENCEPHALOGRAPHY

EEG in SSPE is characterized by generalized periodic complexes or discharges. Periodic EEG complexes consist of generalized and synchronous bursts of sharp-slow wave discharges. A typical discharge is polyphasic with duration varying from 0.5 to 2 seconds, high voltage (300-1500 mV), and repetitive (occurring every 4 to 15 s). The repetitive nature or periodicity of the complexes is fairly regular. These complexes are stereotyped and superimposable on each other. Periodic discharges persist during sleep.[90-93] The EEG periodic complexes can variably consists of large delta waves, large delta waves and rapid spikes, or fast activity or spikes with large delta wave discharges[90] (Figure 3).

16 | NEUROIMAGING

Computed tomography (CT), early in the course of the disease, is normal. CT abnormalities are observed in later stages that include focal white matter hypodensities. Abnormalities dominantly affect parieto-occipital areas. Brain atrophy is seen in terminal stages.[94] MRI is a far better imaging modality for depicting brain abnormalities of SSPE. MRI is normal in initial stage of SSPE.[95] At later stages, abnormalities are usually located in subcortical, periventricular, and cortical gray matter. Corpus callosum, basal ganglia, cerebellum, and brainstem are less frequently affected.[96] A typical neuroimaging picture demonstrates bilateral asymmetric periventricular and subcortical white matter hyperintensity. Classical T2-weighted images or fluid-attenuated inversion recovery (FLAIR) images show hyperintense signals. In the advanced stages, there is a progressive loss of cortical volume, leading to cerebral atrophy[97,98] (Figure 4).

Diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) map, and diffusion tensor imaging (DTI) imaging sequences are supplemental imaging techniques to routine MRI. These imaging sequences are helpful in the detection of smaller lesions, and lesions

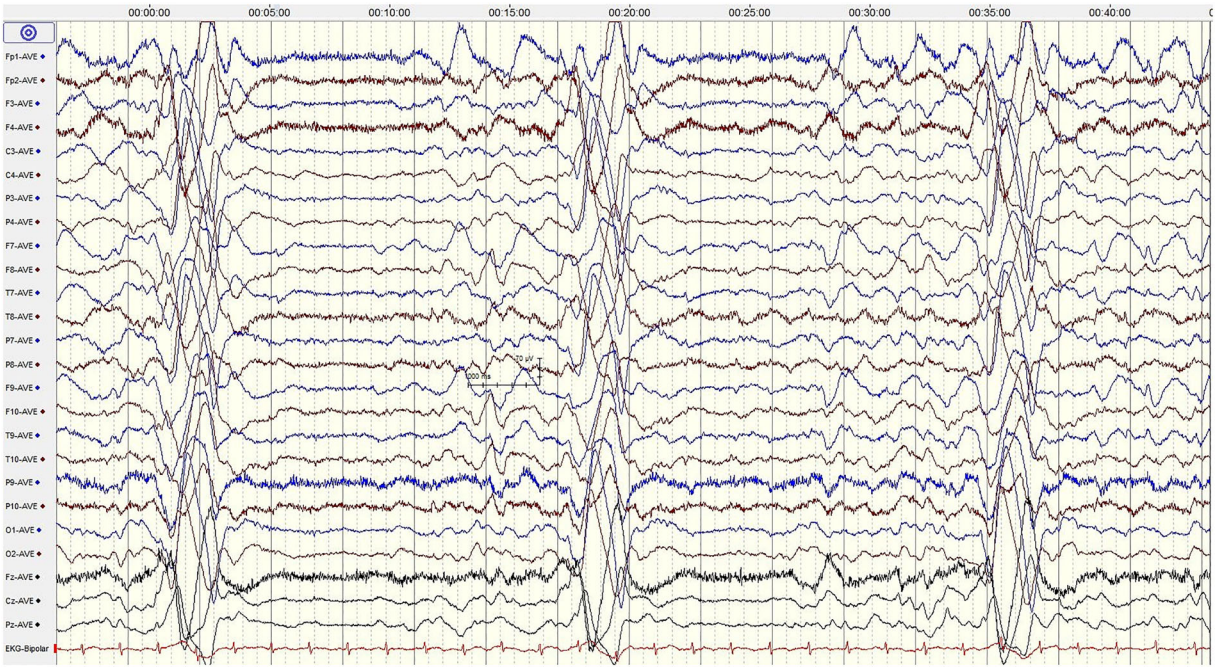

FIGURE 3 Electroencephalography (EEG) of a SSPE patient depicts the periodic stereotypical discharges occurring at an interval of 4 to 5 seconds (EEG machine setting–sweep: 15 mm/s; amplitude:10 μV/mm; filters: 1, 70; notch: 50 Hz).

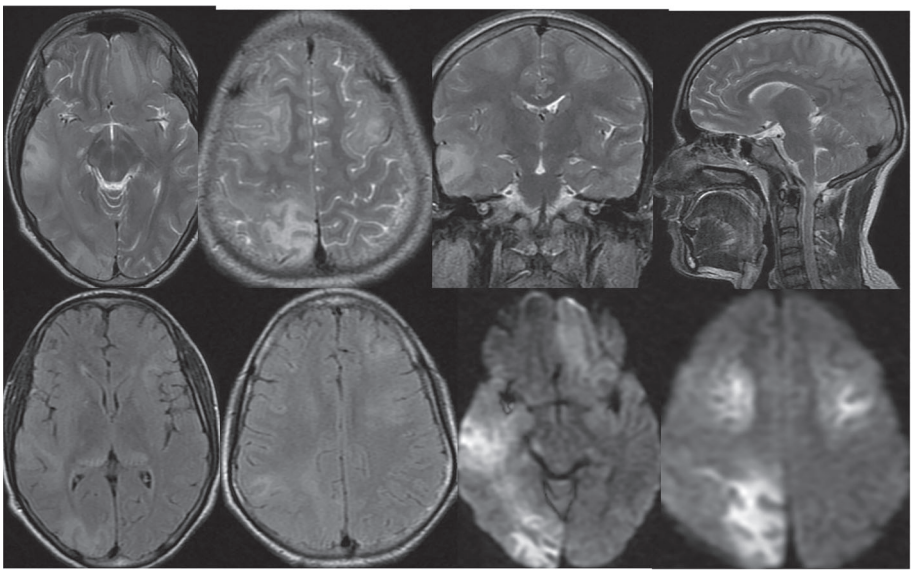

FIGURE 4 Magnetic resonance imaging (MRI) of the brain of a patient with subacute sclerosing panencephalitis (SSPE) reveals multiple hyperintensities, on axial T2-weighted (A, B), coronal T2-weighted (C, D), axial fluid-attenuated inversion recovery (FLAIR) (E, F), and diffusion-weighted (G, H) MRI sequences, predominantly involving the white matter in nearly pan-lobar distribution. The note is made of the involvement of substantia nigra as well as posterior thalami

can be demonstrated even when conventional MRI is normal. Periventricular and subcortical white matter signal changes were seen in 63.6% of patients with stage 2 and in all the patients with stage 3.[99,100] Magnetic resonance spectroscopy (MRS) demonstrates metabolic abnormalities of the brain. Low *N*-acetyl aspartate and elevated myoinositol MRS values are characteristic in SSPE. Spectroscopic changes correlate with clinical severity.[101] DTI and MRS collectively help in quantifying the neuronal loss.[102] positron-emission tomography (PET) demonstrates focal metabolic abnormalities when conventional imaging reports normal findings.[103]

17 | DIFFERENTIAL DIAGNOSIS

Diagnostic confusion is frequently encountered in early stages or in countries where there is less familiarity with SSPE (Table 3). In many cases, there are primary psychiatric manifestations, like schizophrenia, and patients are treated by a psychiatrist.[104] Many children are considered to have malingering or conversion reaction.

In many countries, SSPE is an important cause of progressive cognitive decline. Other differential diagnosis includes autoimmune encephalopathies, vitamin B12 deficiency, herpes simplex encephalitis, neurosyphilis, and progressive multifocal leukoencephalopathy in human immunodeficiency virus (HIV)–infected patients.[105] Autoimmune encephalitis has a close resemblance with acute fulminant SSPE. Encephalopathy with chorea or orofacial and limb dyskinesias may simulate SSPE.[106] Young pregnant women presenting with cortical blindness may initially be considered to have eclampsia.[107] Papilledema, focal neurological deficits, and focal seizures can mislead to an erroneous diagnosis of brain tumor.[108] Neuroimaging characteristics, T2, and FLAIR signal changes in the white matter seen in SSPE are similar to those in acute disseminated encephalomyelitis. Many such patients receive inadvertent immunotherapy.[109]

18 | BRAINSTEM INVOLVEMENT

There are reports indicating neuroimaging abnormalities dominantly or exclusively affect brainstem structures. Sole brainstem involvement can be a heralding manifestation of SSPE. Diffuse involvement of pons and middle cerebellar peduncles gives a distinctive "moustache" like picture on MRI. The pontine tegmentum is usually spared. Midbrain, another brainstem, is also affected in SSPE but much less frequent. Substantia nigra and inferior colliculus may show signal changes, and other brain areas may still be normal. This entity may be misdiagnosed as clinically isolated demyelinating syndrome.[110-115]

19 | PREGNANCY

SSPE in pregnancy is often an acute and fulminant disease that very quickly culminates into a vegetative state. Immunologic and hormonal alterations of pregnancy are hypothesized to be responsible for the rapid course of the disease.[32,47,49,116,117] Visual loss simulates eclampsia with an inadvertent treatment with magnesium sulfate. Good obstetric care and timely cesarean section may enable the delivery of a healthy child.[116]

TABLE 3 Dyken criteria for the diagnosis of SSPE

Clinical	Progressive mental decline Generalized myoclonus
Electroencephalography	Periodic EEG discharges
Cerebrospinal fluid	Elevated gamma-globulin or oligoclonal pattern
Antimeasles antibody	Elevated titers in CSF
Brain biopsy	Intranuclear and cytoplasmic inclusion bodies Measles virus RNA or antigen

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

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; RNA, ribonucleic acid; SSPE, subacute sclerosing panencephalitis.

20 | ACUTE-FULMINANT SSPE

Acute-fulminant SSPE is characterized by a rapid course of disease culminating in death, within 6 months. Fulminant SSPE has been reported in pregnancy or in the immediate postpartum period.[118] Cognitive and behavioral disturbances are common. In some, cortical blindness brought patients to medical attention. Patients may have generalized EEG slowing. The minimum reported time to death after diagnosis was 19 days.[119]

21 | TREATMENT

SSPE has a relentless deteriorating course. Many drugs have been suggested to stabilize the course and retard progression, but no evidence is available from double-blind, randomized clinical trials. Treatment is given for a long period, probably, life-long.

22 | ANTIVIRAL AGENTS

Isoprinosine (inosine pranobex) is the first antiviral agent that has been used in the treatment of SSPE. Antiviral effect of isoprinosine is possibly because of its immune-stimulant properties. Isoprinosine is given orally in a dosage of 100 mg per kg (maximum of 3000 mg) per day, usually in three to five divided doses. There are no major side effects, except for mild hyperuricemia. Isoprinosine is an expensive drug and not readily available in countries where SSPE is common.[120-123]

Interferon-α has an immunomodulatory effect against many viral illnesses. Interferon-α is usually administered subcutaneously, 10 million units/m^2 three times a week. Interferon-α is also administered intrathecally and via the intraventricular route. Intraventricular interferon-α dose ranges from 100 000 to 1 000 000 U/m^2, usually given for 2 to 5 days a week. Interferon-β is manufactured from virus-infected fibroblasts. Interferon-β also has an immunomodulatory effect. Parenteral interferon-β treatment is usually combined with oral inosiplex.[124-129]

Ribavirin is a nucleoside analogue with antiviral properties. Ribavirin is considered to have inhibitory properties against RNA viruses. Ribavirin, in SSPE, has been used with either intrathecal or intraventricular route (40 to 60 mg/kg/day), frequently, in combination with interferon-α and isoprinosine.[125,130] In a report, four patients of SSPE were treated with mesenchymal stem cells, but in all patients, no benefit was demonstrated.[131]

23 | SYMPTOMATIC TREATMENT

Carbamazepine, levetiracetam, and clobazam are anticonvulsants that have been tried to control myoclonic jerks. Carbamazepine received maximum attention as antiepileptic, but it did not affect neurological deterioration.[132-135]

24 | FUSION INHIBITOR PEPTIDE

Transneuronal measles virus spread is mediated by hyperfusogenic F protein. A fusion inhibitor peptide (compound AS-48) has recently been developed. Fusion inhibitor peptide binds at the region that connects the head and stalk of F protein. In this particular region, single amino acid substitutions in measles virus isolates from SSPE are located. Fusion inhibitor peptide suppresses membrane fusion mediated by hyperfusogenic measles virus. Fusion inhibitor peptide might in future be exploited to treat SSPE.[31,36,136]

25 | PROGNOSIS

Death is inevitable within 1 to 3 years after diagnosis.[137] Risk and Haddad noted that only 41% of the patients survive up to 2 years.[138] Approximately 5% of SSPE patients have spontaneous remission. Many patients experience a prolonged remission.[139] There are instances when patients survived for 8 years. Increasing CSF measles antibody titer facilitates a long survival. In an isolated case, it was claimed that interferon-α led to a survival up to 18 years.[140]

26 | CONCLUSION

The only hope against SSPE, currently, lies in its prevention. In countries with effective measles control, SSPE is virtually an extinct disease. A universal measles vaccination is of paramount importance to wipe out this devastating disease from the face of the earth.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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