Subacute sclerosing panencephalitis – current perspectives

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Abstract: Subacute sclerosing panencephalitis is a progressive neurodegenerative disease. It usually occurs 7–10 years after measles infection. The clinical course is characterized by progressive cognitive decline and behavior changes followed by focal or generalized seizures as well as myoclonus, ataxia, visual disturbance, and later vegetative state, eventually leading to death. It is diagnosed on the basis of Dyken’s criteria. There is no known cure for subacute sclerosing panencephalitis to date, but it is preventable by ensuring that an effective vaccine program for measles is made compulsory for all children younger than 5 years in endemic countries.

Keywords: SSPE, progressive, vaccine, preventable

Introduction
Subacute sclerosing panencephalitis, commonly known as SSPE, is a progressive neurodegenerative disease caused by the persistence of measles infection commonly seen in children and young adults.1 SSPE was previously known as Dawson’s inclusion body encephalitis as Dawson in 1933 and 1934 reported cellular inclusions in the cerebral lesions of patients with SSPE, thus resulting in this disease being labeled as Dawson inclusion body encephalitis.2 Ten years later, Brain et al3 reported similar conditions with further case reports, and later, the term SSPE was coined. Electron microscopic evidence of paramyxovirus was established between 1967 and 1969.4

Measles is a highly contagious RNA virus of the paramyxoviridae family and the genus morbillivirus. It is an airborne disease and transmitted via nasopharyngeal droplets. The virus is highly lymphotropic, affecting dendritic cells, alveolar macrophages, and subsets of B and T cells in the lymphoid tissue of the lower respiratory tract, and later, it infiltrates the epithelium of the upper respiratory tract. Acute complications include otitis media, pneumonia, diarrhea, and postinfectious encephalitis.5 Neurological complications of measles involve post-measles encephalitis, measles inclusion body encephalitis, transverse myelitis, and SSPE.6 The risk of serious complications and death is increased in children younger than 5 years and adults older than 20 years.7 This disease is preventable, and immunization against measles via live attenuated vaccine has been available for more than 45 years.8

SSPE usually occurs 7–10 years after measles infection, but the latency varies from 1 month to 27 years.9 A shorter latency has been reported in intrafamilial cases of SSPE as well as in children who were affected at an earlier (<2 years) age such that the incidence was 18/100,000 in children younger than 5 years and 1.1/100,000 in those children with measles after 5 years.10,11 It is caused by the cerebral involvement of the...
measles virus, which causes destruction of the neurons. The
pathogenesis of SSPE is yet to be elucidated, but it has been
shown to be caused by the wild strains and not by the vac-
cine strains, which has been supported by genetic studies.12
The strains of measles virus causing SSPE have multiple
point mutations in their genomes, especially in the gene
encoding for the matrix protein gene.13 Studies have shown
that the capacity of wild-type measles virus strains to cause
SSPE results from their increased capacity to spread and
that this is partially due to a tri-residue motif, P64, E89, and
A209 (PEA), in their M proteins, which is absent in vaccine
and lab-adapted strains.14 Mutations in M proteins result in
interference with the assembly of new viral particles and their
budding, which form viral particles that are transmitted via
ribonucleic protein with a trans-synaptic spread.15 Immaturity
of the cellular immunity mechanism has been critical as sug-
gested by earlier age of acquiring measles infection resulting
in higher incidences of SSPE.11 Although other viruses have
been studied in association with SSPE, there is no data to
support their role in causation of the disease.13

The worldwide prevalence of SSPE has declined to 1
per 100,000 cases of measles due to better immunization
coverage in developed countries.7 There is not only geo-
ographical variation in the prevalence of SSPE but economic
development also contributes to the falling trends. Developed
countries such as USA have reported an incidence of 6.5–11
cases per 100,000 acute measles infections.12 European
countries like Turkey have reported an incidence of 2.2 cases
per million in their population.16 Developing countries like
Pakistan have reported an estimated incidence of 10 cases
per million in their population.17 The highest rate that has
ever been reported is from Papua New Guinea, which is 51
cases per one million during 2007–2009.18 Although there is
no gender predisposition, but SSPE has been seen more
commonly in boys.19 The risk of SSPE is higher if the onset
of measles is at a younger age, in low socioeconomic class,
in cases with low parental education and large family size.4

The clinical course is characterized by progressive
cognitive decline and behavior changes followed by focal
or generalized seizures as well as myoclonus, ataxia, visual
disturbance, and later vegetative state.20,21 Patients suffer-
ing from SSPE die within few years of initial clinical presenta-
tion although there have been rare case reports of spontane-
ous remission.22 Epilepsy has been reported in one-third of
the patients with SSPE.22

Jabbour et al23 have divided the clinical manifestations
into four stages. Stage I is characterized by irritability,
dementia, social withdrawal, lethargy, and regression of
speech; stage II is characterized by various types of move-
ment disorders such as dyskinesia, dystonia, and myoclo-
nus. Stage III is consistent with extrapyramidal symptoms,
decerebrate posturing, and spasticity, while the stage IV is
characterized by loss of function of cerebral cortex with signs
of vegetative state, autonomic failure, and akinet mutism.
Atypical presentations have been described including isolated
psychiatric manifestations, poorly controlled seizures, and
isolated extrapyramidal symptoms, such as dystonia, chorea,
emi-parkinsonism, etc. Occasionally, a stroke-like onset has
also been described. There may be a transient plateau period
or slight improvement in some patients, but classically it has
a relentless pattern associated with high mortality.24 Differen-
tial diagnoses include epilepsy and psychiatric illnesses
in early stages along with other viral encephalitides, atypical
multiple sclerosis, leukodystrophies, variant Creutzfeldt–
Jakob disease, and neurometabolic encephalopathies.25 The
diagnosis of SSPE is often considered late in developed
countries owing to its rare occurrence and the nonspecific
clinical manifestations at onset.26

Visual loss as an initial presentation has also been
described.27 Ocular findings are seen in almost 50% of cases.
A variety of neuro-ophthalmological and retinal findings are
associated with SSPE, and the classic lesion is focal necro-
tizing macular retinitis. There may be retinal hemorrhages,
edema, and detachment. Vitrreal inflammation is not seen in
SSPE. Optic disc changes include papillitis, papilledema, and
disc pallor. Retinal involvement may settle with time or
eventually lead to scarring. Ophthalmic symptoms may
precede the neurological symptoms of SSPE. Other symp-
toms that may occur include cortical blindness, gaze palsies,
ptosis, and nystagmus.28

The diagnosis is based on the Dyken’s criteria, which
include two major and four minor criteria. Major criteria
include 1) raised anti-measles antibody titers in cerebrospi-
nal fluid (CSF) greater than or equal to 1:4 or ratio greater
than or equal to 1:256 in serum, and 2) typical or atypical
clinical history (typical includes acute or rapidly progres-
sive, subacute progressive, chronic progressive, and chronic
relapsing–remitting, while atypical includes seizures, pro-
longed stage I, and unusual age of presentation that is either
in infancy or adulthood). Minor criteria include the following:
1) characteristic electroencephalographic findings that include
periodic, generalized, bilaterally synchronous and symmetri-
cal high-amplitude slow waves that recur at regular intervals
of 5–15 seconds called periodic slow-wave complexes also
known as “Radermecker” complexes (Figure 1). The interval
between complexes is generally fixed, but variation in the
interval between periodic discharges may also be seen, also known as pseudo-periodic or quasi-periodic discharges.29,30 2) CSF globulin levels greater than 20% of the total CSF protein. 3) Characteristic histopathological findings on brain biopsy including inflammatory changes in the meninges and cerebral parenchyma necrotizing leukoencephalitis with diffuse demyelination; viral inclusion bodies in neurons; oligodendrocytes and astrocytes; neuronal loss; and astrogliosis. 4) Specialized molecular diagnostic test to identify wild-type measles virus mutated genome. Usually two major criteria plus one minor criterion are required, but if the features are atypical, then histopathological or molecular evidence may be required.29,30 Interestingly, histopathological studies carried out after autopsy of individuals without SSPE showed approximately 20% having detectable measles virus in the brain.31 However, just the presence of RNA without satisfaction of Dyken’s criteria would not mean that the person has SSPE. Neuroimaging may be helpful but is not characteristic of SSPE. During the early stages, magnetic resonance (MR) imaging of the brain may show decreased gray matter volume, especially within the frontotemporal cortex, amygdala, and cingulate gyrus. As the disease progresses, hyperintensities on T2-weighted images in the cerebral cortex, periventricular white matter, basal ganglia, and brainstem may develop (Figure 2A–C). Eventually, the MR images will reveal diffuse cortical atrophy, as evidenced by enlarged sulci and ventriculomegaly. MR spectroscopy findings range from increased choline-to-creatine ratio and inositol-to-creatine ratios along with normal N-acetyl aspartate-to-creatine ratios to decreased N-acetyl aspartate-to-choline and N-acetyl aspartate-to-creatine ratio correlating to loss of brain volume (Figure 3A and B).19,32–36 Currently, there is no cure for SSPE, and eradication by effective vaccination program is considered to be more beneficial and cost-effective than any other high-level forms of control.6 Measles-containing vaccines are a part of the childhood vaccination schedule in all countries. Current World Health Organization (WHO) policy is that “Reaching all children with 2 doses of measles vaccine should be standard for all national immunization programs”.37 Despite this, global coverage with the first dose of measles vaccine has largely stagnated since 2004. Six WHO regions have measles elimination goals for the year 2020, but the World Health Assembly has still not endorsed the eradication of this disease. In 2012, Measles and Rubella Initiative published a Global Measles and Rubella Strategic Plan 2012–2020, which aimed to achieve elimination of these two diseases in 5 WHO regions by 2020. By the end of 2015, none of these milestones had been met. Although the number of countries with measles vaccine 1 coverage of >90% has risen between 2010 and 2015, we are still a long way from a global measles eradication.37
Supportive treatment including management of seizures and other complications is the mainstay.11 Divalproate sodium is one of the common antiepileptics employed.38 There are no standard treatment protocols for the treatment of SSPE. Anti-viral drugs and immunomodulators are used in the treatment of SSPE. Even though there are many drugs that have been tried in the treatment of SSPE, inosine pranobex, interferon alfa, ribavirin, and lamivudine are the most commonly used drugs in routine clinical practice. These have been used either singly or in combinations. Inosine pranobex (Isoprinosine, Inosiplex) is an antiviral drug with immunomodulatory effects. It is a synthetic compound. It is given orally in doses of 100 mg/kg/day (with a maximum dose of 3,000 mg/day) in three divided doses to patients with SSPE. Abnormalities in serum and urinary uric acid and occasional nausea have been reported with Isoprinosine.39 Interferon alfa is an immunomodulator drug. It is preferably given via the intraventricular route as it has very poor penetration of the blood–brain barrier. Ribavarin and lamivudine have also been tried with no great success.

Ketogenic diet has also been tried; it was found to temporarily reduce the myoclonic jerks.40 Steroids and intravenous immunoglobulin are no longer recommended for the treatment of SSPE.

Future therapies are incorporating antiapoptotic agents, and RNAi is being experimented upon and may be beneficial in future.41

The prognosis for SSPE remains guarded. Mortality has been reported in 95% of the patients.42 The average life span of a patient suffering from SSPE is 3.8 years (45 days–12 years).16 Another study has proposed that the mean survival in children is about 1 year 9 months to 3 years.11

**Conclusion**

In short, SSPE is a potentially lethal disease and causes a huge burden both emotionally and financially, affecting not only the family but the country as whole. Furthermore, as this is seen more in the underdeveloped countries, the economic burden to these nations is huge. There is a strong need to improve the vaccination status of countries where the incidence of measles is high as it may be the only way to eradicate this devastating condition. This requires a global and political will and ownership by the individual countries.

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The ethical review committee of the Aga Khan University agreed that no patient consent for the use of the figures was needed as patient data was kept anonymous.

**Disclosure**

The authors report no conflicts of interest in this work.

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