Measles-Associated CNS Complications: A Review

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Abstract

Measles virus infection is a common infectious disease of childhood, incidence of which is still high in developing countries. Other than the morbidity associated with the acute systemic infection, the measles virus can cause serious fatal neural complications. It can either enter the brain leading to acute encephalitis like primary measles encephalitis and acute post infectious measles encephalomyelitis or it may persist in brain cells (as mutated virus) leading to long-term neurodegenerative diseases like measles inclusion body encephalitis and subacute sclerosing pan encephalitis. The patho-clinical features, treatment, and the outcomes of these complications are different and should be identified in time for early diagnosis and management.

Introduction

Measles is a highly contagious infection caused by measles virus, which belong to paramyxoviridae family. The virus enters the human body (its sole reservoir) via respiratory system in air droplets form. It targets the macrophages and dendritic cells in lungs which express SLAM receptors. These cells then migrate to lymph nodes and transmit the infection to lymphocytes expressing SLAM receptors, hence causing viremia. In later stage, the infected cells transmit the infection to nectin 4 expressing epithelial cells in respiratory tract, from where virions are shed in mucus and spread air drop infection through coughing. Patient develops various symptoms during acute phase of measles infection like fever, cough, coryza, conjunctivitis, nasal congestion followed by a morbilliform rash, and koplik spots over buccal mucosa (in 70% cases). Measles virus infection also causes immunocompromised state in the host, making the host susceptible for secondary infections. Other than this, measles infection can lead to several complications including diarrhea, otitis media, pneumonia, CNS infections and sequelae, blindness and hearing loss. The morbidity and mortality related to measles is higher in developing countries owing to under nutrition, large populations, inaccessibility of health care and vaccination. This review is undertaken to highlight the CNS measles infections and associated morbidity.

Measles virus affects the CNS either during active infection or after the infection has become inactive. The CNS complications are: (1) primary measles encephalitis (PME), (2) acute post infectious measles encephalomyelitis (APME), (3) measles inclusion body encephalitis (MIBE), and (4) subacute sclerosing pan encephalitis (SSPE). The neuropathogenesis, host immune status, and clinical settings are different, but all involves brain-virus and immune interactions that lead to severe morbidity and mortality as discussed ahead.

Current Epidemiology

Measles is one of the most contagious vaccine preventable disease. The global incidence of measles infection decreased...
Table 1 Incidence of measles related CNS complications after natural measles infection and after vaccination\(^9,21^\)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence after measles infection</th>
<th>Incidence after vaccination</th>
<th>Morbidity and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PME</td>
<td>1-3/1,000</td>
<td>&lt;1 per 10,000,000 less fulminant</td>
<td>Mortality: 10 to 15%, permanent neurological sequelae in 25%, with epilepsy and intellectual disability</td>
</tr>
<tr>
<td>APME</td>
<td>1/1,000</td>
<td>1–2/10,000,000 less fulminant</td>
<td>Some have a full recovery, while few are left with substantial neurological sequelae</td>
</tr>
<tr>
<td>MIBE</td>
<td>RARE (only in immunocompromised patients)</td>
<td>&lt;1 per 10,000,000</td>
<td>Mortality: 75%</td>
</tr>
<tr>
<td>SSPE</td>
<td>4-11/1,000,000</td>
<td>0</td>
<td>Mortality: 100%</td>
</tr>
</tbody>
</table>

Abbreviations: APME, acute post infectious measles encephalomyelitis; MIBE, measles inclusion body encephalitis; PME, primary measles encephalitis; SSPE, sclerosing pan encephalitis.

significantly with immunization. As observed from 2000 till 2017, there was 83% decline in measles infection. In 2017, around 1,73,330 measles cases were reported worldwide, and approximately 1,10,000 people died of it, majority of which were in Asian and African countries.\(^8,9^\) Unfortunately, rise in number of measles cases in developing countries and frequent outbreaks in industrialized countries have been reported in past 3 years. A 300% rise in measles cases was observed in many developed countries (United States and France) during year 2019\(^9,10^\). Decreased immunization due to vaccination hesitancy is considered to be the most important factor leading to this reemergence.\(^11^\) Measles infection leading to CNS complications is rare, but often detrimental. Neurological complications of measles are reported to occur in around 4 per 1,000 measles cases, out of which one per 1,000 were encephalitis and behavioral changes each and two per 1,000 cases had motor disturbances.\(^12^\) The four different types of measles-associated encephalitis have been reported to have different epidemiological profiles (\(\rightarrow\) Table 1). PME and APME occur approximately in 1 to 3/1,000 measles-infected patients. MIBE is rare, confined to immunocompromised hosts and may be considered as an opportunistic infection.\(^13^\) The reported incidence for SSPE is 1:10,000 to 20,000 measles cases, it generally occurs after a long latent period of measles infection and is associated with 100% mortality.\(^13^\)

How Does Measles Virus Enter the Brain?

The entry of measles virus in brain still remains unclear, however, different models have shown different mechanisms for measles-related CNS infection:

1. Via receptors: SLAM receptor is the main receptor for morbilliform virus infection including both canine distemper virus (CDV) and measles virus. This receptor is expressed on dendritic cells, thymocytes, lymphocytes, and macrophages in humans. In CDV-infected dogs SLAM receptor expression increases in epithelium of many organs like lungs, gastrointestinal and urinary tracts, however, these detected SLAM positive cells are immune or inflammatory cells. The brain cells are negative for SLAM expression, still various brain cells are infected with CDV, suggesting other receptors role for viral spread in CNS.\(^14,15^\) The nectin-4 receptor expression has been reported in various CNS cells (purkinje cells, neurons, ependymal cells, and choroid plexus cells) in dogs suggesting it contributes to CDV neuropathogenicity, while it is hardly detected in human brain cells. Astrocytes in dog’s brain were found to be infected by CDV leading to demyelination, although they do not express nectin-4. These findings further suggest the role of an unknown receptor in neuropathogenicity of CDV.\(^14,15^\) Recently nectin 1 receptors have been suggested to play a role in CDV and measles neuroinvasion. It has been postulated that viral RNP enters the nectin 1 expressing neuronal cells (olfactory bulb/brain parenchyma) via transcellular endocytosis from nectin four positive cells in nasal turbinate or meninges.\(^14–17^\)

2. Mutations in virus: It has been hypothesized that various mutations of measles virus may help in neuroinvasion without any need of receptors. These mutated virus particles have been isolated from either autopsy or biopsy of brain tissue of patients of complicated measles infection\(^17–19^\) (\(\rightarrow\) Table 2).

3. Measles virus tropism via hematogenous route: via infecting the endocytes at blood–brain barrier and then passing in CNS or via virus-infected lymphocytes entering brain through BBB.\(^17,20^\)

Measles-Associated Different CNS Complications; Associated Morbidity and Mortality

There has been a considerable controversy regarding the mechanism of measles encephalitis. Whether it is due to direct CNS infection or immune mediated? It has been suggested that early CNS symptoms (within a week of measles infection) can only be explained with direct neuroinvasion of virus and the late symptoms with autoimmune mechanism.\(^21,22^\) Some investigators failed to demonstrate viral proteins or RNA in the brain of measles encephalitis patients while,\(^23^\) others recovered measles virus from brain parenchyma and CSF of such patients.\(^24,25^\)
The clinical profile and characteristics of measles virus in each disease are discussed below and summarized in Table 3.

**Primary Measles Encephalitis (PME)**
The measles virus directly infects CNS during acute measles infection in a previously healthy child, leading to measles encephalitis. The virus replicates in brain cells and leads to injury of neurons, which further causes lymphocytic infiltration in brain parenchyma, meninges, and CSF, hence, the infectious measles virus can be detected from brain cells and CSF. It occurs in immunocompetent, unvaccinated or partially vaccinated measles-infected patients (more common in children than adults) with a frequency of 1 to 3 per 1,000 cases. The symptoms of encephalitis generally develop during the exanthema phase or within a week of measles prodrome. The child presents with fever, headache, irritability encephalopathy (altered mental status), seizures and involuntary movements or motor deficits (hemiplegia/paraplegia), and coma. Child may have features of raised ICT due to brain edema. It occurs in immunocompetent, unvaccinated or partially vaccinated measles-infected patients (more common in children than adults) with a frequency of 1 to 3 per 1,000 cases. The symptoms of encephalitis generally develop during the exanthema phase or within a week of measles prodrome. The child presents with fever, headache, irritability encephalopathy (altered mental status), seizures and involuntary movements or motor deficits (hemiplegia/paraplegia), and coma. Child may have features of raised ICT due to brain edema.

The long-term neurological sequelae leads to hemi or para-plegia, intellectual disability, recurrent seizures, and deafness. The diagnosis of PME is mostly clinical. CSF examination shows marked lymphocytic pleocytosis and mildly elevated protein. Neuroimaging shows edema and/or focal signal changes in white matter, putamen, caudate nucleus, and thalamus. The viral RNA can be detected in CSF via real time PCR.

The treatment of PME is mainly supportive including continuous vitals monitoring, anticonvulsants, measures for raised ICT (mannitol or hypertonic saline), antipyretics and fluids and electrolytes management. Ribavirin has shown anti-measles properties in vitro and has been given in complicated measles cases via intravenous or aerosol routes. However, it has not been approved for measles encephalitis by U.S. FDA. Controlled trials need to be done to prove the efficacy of ribavirin in measles. Mortality is observed in around 10 to 15% of patients and long-term neurological sequel in 25% of patients.

**Acute Post Measles Encephalitis**
It is also referred to as acute measles encephalitis (AME), acute demyelinating encephalomyelitis (ADEM), or post infectious encephalitis (PIE) or acute disseminated encephalomyelitis. The encephalitis is immune mediated unlike PME which is due to direct viral invasion. The molecular mimicry has been suggested as the mechanism for the development of APME. Circulating antibodies react with the myelin basic protein of oligodendrocytes, causing inflammation and dysfunction in CNS. APME causes lesions in both grey and white matter, leading to perivenular inflammation and demyelination. Immunoglobulin titers in CSF as compared to that in the serum do not increase, suggesting less synthesis of antibodies in CSF. Myelin basic protein concentrations are increased in CSF and nearly 50% of the patients show lymphocyte proliferative responses to myelin basic protein. It is primarily an immune-mediated demyelinating disease, however, the role of myelin reactive antibodies is still unclear. Any rise in myelin reactive antibodies was not detected by either ELISA or RIA in patients with APME, while in animal models a rise in myelin reactive antibodies along with pathology similar to that seen in human cases has been observed.

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**Table 2** Mutations of measles virus reported to cause neuroinvasion

<table>
<thead>
<tr>
<th>Protein</th>
<th>Mutation</th>
<th>Effect</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>M protein</td>
<td>Biased hypermutation of M protein (uridine to cysteine substitution)</td>
<td>More fusogenic phenotype without budding making it more suitable for CNS infection</td>
<td>SSPE and MIBE</td>
</tr>
<tr>
<td></td>
<td>RNA mutation causing low expression of M protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F protein</td>
<td>HRC domain (T461I, A440P, N462S, N465S) HRN domain (G168R/E170G), (S262G), cytoplasmic tail domain (R520C, L550P), F2 subunit of F protein. F extracellular domain (T461I,S103I/N462S/N465S)</td>
<td>Hyperfusogenic F protein which allows entry in brain without receptors</td>
<td>SSPE</td>
</tr>
<tr>
<td></td>
<td>HRC domain L454W</td>
<td>Highly unstable and hyperfusogenic F protein, not requiring receptor for invasion</td>
<td>MIBE</td>
</tr>
<tr>
<td>H protein</td>
<td>Substitution mutations cytoplasmic tail (R7Q) stalk domain (R62Q), and five blade of the head domain (D530E) C-terminus elongation of the H protein due to single-point mutation at the stop codon</td>
<td>Contributes neurovirulence impact binding, targeting</td>
<td>SSPE</td>
</tr>
<tr>
<td></td>
<td>Mutations in H gene of MIBE</td>
<td>Less frequently documented</td>
<td>MIBE</td>
</tr>
<tr>
<td></td>
<td>N, P, and L proteins</td>
<td></td>
<td>SSPE and MIBE</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous symptom; MIBE, Measles Inclusion Body Encephalitis; RNA, ribonucleic acid; SSPE, sclerosing pan encephalitis.
Table 3 Differentiating features of measles associated CNS complications

<table>
<thead>
<tr>
<th></th>
<th>PME</th>
<th>APME</th>
<th>MIBE</th>
<th>SSPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles infection (active/passive)</td>
<td>Active measles infection</td>
<td>Post infectious</td>
<td>Active measles infection in patients who are immunosuppressed</td>
<td>Measles infection early childhood, no active infection now.</td>
</tr>
<tr>
<td>Temporal relation of onset with measles infection</td>
<td>During acute exanthem phase</td>
<td>During resolution phase or weeks/months after measles infection or vaccination?</td>
<td>Onset within a year of infection or measles vaccination?</td>
<td>Occurs after 3-20 years of infection although shorter latency periods reported recently</td>
</tr>
<tr>
<td>Mechanism of disease</td>
<td>Measles virus enters the brain causing lymphocytic infiltration</td>
<td>Molecular mimicry mediated immune response</td>
<td>Persistence of primary measles infection</td>
<td>Persistence of mutated measles virus</td>
</tr>
<tr>
<td>Age group</td>
<td>More common in children than in adults</td>
<td>Most common in children and adolescents, rare in adults</td>
<td>Any age, More common in children and young adults</td>
<td>Usually 8-11 years, can be seen in toddlers and adults</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Fever, headache, irritability, encephalopathy, seizures, involuntary movements, or motor deficits and coma</td>
<td>Encephalitis (seizures, altered sensorium, raised ICT), myelitis (back pain and bladder and bowel dysfunction, hyporeflexia), ataxia, optic neuritis</td>
<td>No rash, encephalopathy, refractory seizures, motor deficits</td>
<td>Behavioral problems, motor dysfunction, spasticity, myoclonic jerks, ocular involvement</td>
</tr>
<tr>
<td>EEG</td>
<td>Focal or generalized epileptiform discharges or diffuse slowing</td>
<td>Either normal or non-symmetric changes</td>
<td>Focal or generalized epileptiform discharges or diffuse slowing</td>
<td>Burst suppression, diffuse slowing</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Focal signal changes on T2 images and edema</td>
<td>Multifocal hyperintensities in brain and spinal cord, brain edema, demyelination</td>
<td>Initially normal, later edema, atrophy or ventriculomegaly can be seen</td>
<td>Hyperintensities in cerebral cortex, periventricular white matter, brainstem, cortical atrophy and ventriculomegaly</td>
</tr>
<tr>
<td>Neuropathology</td>
<td>Lymphocytic infiltration, inflammation, raised intracranial tension</td>
<td>Perivascular demyelination and inflammation</td>
<td>Inclusion bodies in neurons and glial cells, focal necrosis without inflammation</td>
<td>Cellular inclusion bodies, demyelination, neuronal loss</td>
</tr>
<tr>
<td>CSF picture</td>
<td>Marked lymphocytosis with elevated proteins, normal glucose levels</td>
<td>Mild to moderate lymphocytosis with elevated proteins, normal glucose levels</td>
<td>Usually normal, later can show mild pleocytosis or raised proteins</td>
<td>normal</td>
</tr>
<tr>
<td>Isolation of measles virus from brain cells</td>
<td>Can be isolated from brain cells and CSF</td>
<td>Cannot be isolated</td>
<td>Can be isolated</td>
<td>Mutated virus can be isolated</td>
</tr>
<tr>
<td>Serology</td>
<td>Measles specific antibodies may or may not be detected in serum and CSF</td>
<td>Myelin basic protein (MBP) is raised in CSF</td>
<td>Rising titers of measles specific antibodies in serum and CSF</td>
<td>Markedly raised measles antibodies in serum and CSF</td>
</tr>
<tr>
<td>Treatment</td>
<td>Symptomatic treatment, anticonvulsants, ribavirin</td>
<td>Symptomatic treatment and Immunosuppression with steroids, plasmapheresis and IVIG</td>
<td>Symptomatic, ribavirin, interferon alpha</td>
<td>Symptomatic, ribavirin, interferon alpha</td>
</tr>
</tbody>
</table>

Abbreviations: APME, acute post infectious measles encephalomyelitis; IVIG, intravenous immunoglobulin; MIBE, measles inclusion body encephalitis; PME, primary measles encephalitis; SSPE, sclerosing pan encephalitis.

To APME was observed after myelin injection. Recently, confirmation sensitive myelin reactive antibodies have been detected in some patients with ADEM. Infectious measles virus is not isolated from brain or CSF of APME patients because the disease pathology is post-infectious.

As EAE is a good model to study autoimmune mechanism in multiple sclerosis (MS), similarly, the autoimmune response induced by measles virus against MBP explains myelin reactive antibodies in APME. In recent EAE model, autoreactive T cells in EAE and MS are induced by peripheral immunization with an adjuvant emulsified antigen and by unknown pathogen, respectively. These T cells then recognize their antigens on APCs in spleen and activate inflammation in CNS. The tissue debris is then drained from CNS via CSF to the cervical, lumbar lymph nodes, and spleen, where it leads to generation of new autoreactive T cells, further exacerbating the autoimmune reaction.

Encephalitis in Lewis rats following measles infection was found to be associated with cell-mediated T-cell response against MBP. Further, it was suggested that CNS susceptibility to autoimmune T-cell autoimmune reaction increases following CNS infection with measles virus. It occurs in 1 per 1,000 measles infection which makes measles the most common cause of post infectious ADEM. The highest number of cases are of children 5 years and above, symptoms onset after resolution of rash, even weeks or months later, rarely, it can also predate the rash. The signs and symptoms include abrupt onset of fever, encephalitis (headache, seizures, altered sensorium, raised ICT, and multifocal neurological signs), myelitis (back pain and bladder and bowel dysfunction, and hyporeflexia), ataxia, optic neuritis, and cranial nerve involvement. It has been reported that APME relapses in one-third patients and these patients are at increased risk of developing MS.
diagnosis is based on history with clinical examination and it is confirmed with the aid of lab findings – presence of serum IgM/IgG anti-measles antibodies (not in CSF), MRI findings (multifocal hyperintensities in brain and spinal cord on T2 and FLAIR images, brain edema and demyelination) and mild to moderate CSF pleocytosis with elevated protein. Unlike PME the measles virus RNA cannot be detected in CSF or brain cells of APME patients. The treatment is based on the mechanism of disease which is considered to be immune mediated and post infectious. Hence, the goal of treatment is to temper the immune response and not the use of antivirals. Corticosteroids (intravenous followed by oral), intravenous immunoglobulin (IVIG), and plasmapheresis, along with the supportive measures are the recommended treatment options. The prognosis is better than PME and some patients show full recovery, while, some patients showed permanent neurological sequelae along with attention and behavioral issues when evaluated more than 3 years after the episode. Mortality is 5% in children and 25% in adults.

Even with so many differences in pathology, it is sometimes difficult to differentiate whether the patient has PME or APME, because the symptoms of both can occur soon after measles. There may be both factors contributing to the clinical picture including acute viral infection as well as ongoing inflammatory response. However, if the brain imaging shows more edema then patient is treated with steroids.

**Difference between APME and other ADEM:** There are some variations in the ADEM phenotype caused due to measles or other organisms (usually virus). The clinical course of APME is more rapid and severe than other types of ADEM. Cerebellar ataxia most commonly occurs in varicella patients and has better prognosis. The incidence of varicella and rubella-associated ADEM is reported to be much lesser than APME, i.e., 1/10,000 and 1/20,000 cases, respectively. ADEM following an acute pharyngitis (group A beta hemolytic streptococcal infection) shows intracytoplasmic or intranuclear inclusion bodies and has been reported with prominent extrapyramidal and behavioral symptoms.

**APME prevention with measles vaccination:** The incidence of APME or ADEM after measles live vaccine reduction to one to two cases per million vaccinations, which is significantly lower than among unvaccinated population (Table 1). It will make only 5% of cases amongst all measles-associated ADEM. Also, the clinical phenotype is typically less severe and better recovery than PIE occurs after primary measles infection. However, it has also been suggested that single dose of measles vaccination is not effective in preventing measles and APME. In a study from Vietnam, APME after measles infection was reported in 15 patients (age 20 to 24 year) who had received single dose measles vaccination in infancy. The IgG antibodies titers were raised in all vaccinated patients, and the avidity showed a decreasing trend with an increasing age. Again, it emphasized on the need of second dose of vaccination.

**Measles Inclusion Body Encephalitis**

It is also known as immunosuppressive measles encephalitis and subacute measles encephalitis. MIBE is rare, occurs only in immunocompromised children and adults of any age, with symptoms onset within days to months after measles infection or vaccination. Multiple reports from Texas have described MIBE in total of 33 patients (mean age 6 years) with various immunodeficiency conditions. A report of measles outbreak in South Africa (2009 to 2010) has described eight HIV positive patients (median age 28 years) with MIBE, out of which six patients died and only two survived. Largely, the cases of MIBE have been reported in patients with acute lympholastic leukemia and few cases in various malignancies, post transplantation patients, autoimmune disease, HIV infection and recently in stem cell transplantation patient.

The onset of MIBE can occur days to months (within a year) after measles infection or measles vaccination. T-cell function is impaired in immunocompromised patients, hence the typical morbiliform rash (exanthem) as seen in immunocompetent patients is not observed in these patients. Although some have shown a mild rash but without any koplisk spots or any other clinical symptoms of primary measles infection. Patients presented with altered sensorium and seizures. Focal seizures along with Todd’s paralysis are the most common types of seizures reported. Epilepsia partialis continua, focal motor deficits (hemiplegia, hemiparesis), aphasia, dysarthria, dysphagia, ataxia, and visual problems can also occur. Headache, vomiting, emotional lability, and autonomic dysfunction have been reported in few cases. It is a rapidly progressive encephalitis leading to coma and death in majority cases.

The neuropathological findings show inclusion bodies in neurons and glial cells, focal necrosis without inflammation. Initial CSF picture is either normal or may show mildly elevated proteins and pleocytosis. However, a four-fold rise in measles antibody in CSF from baseline is observed, as the disease progresses. MRI brain is usually normal but may show edema, enlarged ventricles, and atrophy. In absence of definitive evidence of measles infection, the diagnosis can be confirmed on brain biopsy, by detecting measles virus RNA using reverse transcription polymerase chain reaction or detecting measles hemagglutinin and matrix protein via immunohistochemistry. The brain biopsy tissue of patients shows intracytoplasmic or intranuclear inclusion bodies and hence, the name encephalitis. The treatment of MIBE includes mainly the supportive measures, although a few cases have shown some improvement in symptoms and imaging with ribavirin antiviral therapy, while, interferon-alpha has not shown any efficacy. The prognosis of MIBE is poor, causing mortality in 75% cases and rest are left with neurological sequel.

**Characteristics of MIBE Virus**

The measles virus isolated from brain cells of MIBE patients has shown many mutations in intracytoplasmic domain of F protein. The mutation in L454W of HRC domain has been reported previously which leads to highly unstable F protein with hyper-fusogenicity and thermal labiality. Also, measles virus with this mutation does not require H binding to enter the brain cells. The emergence of virus with L454W mutated
F protein under the selective pressure of fusion inhibitors, raised the question if this neuropathogenic measles virus can be found outside the CNS and lead to spread via natural route. A recent study on mice model has shown respiratory epithelial infection with this measles strain suggesting the possibility of infecting a new host. On the contrary, sequence analysis of measles virus from 4 MIBE patients has shown similarity with epidemic virus (genotype B3) unlike the typical hypermutation of the matrix and fusion as previously reported. They showed N, M, F, and H genes mutations in unique patterns. Mutation rates in brain were similar to the epidemic virus, although, these mutations were mostly non-synonymous. The function of nucleoprotein gene of measles virus remains same, as this protein helps the virus to move from cell to cell in the brain. Similar mutations of N gene have been reported in SSPE and MIBE patients, suggesting similarity in two diseases, except the rapid development of MIBE in immunocompromised patients.

**MIBE Association and Prevention with Measles Vaccination**

MIBE following vaccination has been documented in few cases with ALL and CD8 deficiency, implicated to be caused by vaccine strain with fatal outcomes. Immunosuppressed patients are at higher risk of developing MIBE, but vaccination should not be avoided in all such patients. Children living with lymphoblastic leukemia (remission phase) and post allogeneic bone marrow transplantation patients have been successfully vaccinated for measles without any adverse events. Measles vaccine can be safely given to patients have been successfully vaccinated for measles without any adverse events. Measles vaccine can be safely given to asymptomatic HIV patients and can be considered in symptomatic HIV patients who are not immunosuppressed. How- ever, it should not be given to severely immunosuppressed HIV patients. Also, vaccination schedule should be updated for the patients before starting immunosuppressive treatments. The reduction in measles-associated morbidity and mortality following vaccination outweighs the rare risk of serious disease following measles vaccination in immunocompromised patients. Post exposure prophylaxis (within 6 days) with polyvalent human immunoglobulin should be considered in all immunocompromised patient, even if one has been vaccinated. Lack in the vaccination coverage and non-administration of second dose of vaccine are the two factors contributing to measles infection and its CNS complications in immunocompromised patients.

**Subacute Sclerosing Pan Encephalitis**

Subacute sclerosing pan encephalitis (SSPE) is a slowly progressive panencephalitis, that is caused by persistence of measles virus which mutates and leads to neurovirulence. The estimated global incidence of SSPE is 4 to 11 cases per lac measles cases, but lesser number of cases are being reported. The incidence is much higher (approximately 18/1,00,000), if measles infection occurs in early childhood. Higher incidence (28 cases per 1,00,000 measles cases) has been reported from developing countries like India and Pakistan. The new cases of SSPE in developed countries now correlate with measles outbreaks. In a recent report of United States, the incidence of SSPE is reported higher (1/609) if measles infection occurs in first year of life while, it decreases (1/1,367) for children under 5 years. The risk of developing SSPE is 16 times higher if measles occurs in infancy as compared to occurring at 5 years or later.

The usual age of presentation ranges from 8 to 11 years but a few cases of SSPE have been reported in toddlers in association with congenital measles. A latent period of 1 to 15 years following primary measles infection has been defined, only recently few cases with shorter latency period have been reported without any evidence of congenital measles. Hence, implicating the need for high index of suspicion for SSPE cases with shorter latency period and presentation at early age. SSPE is often diagnosed late because of the non-specific symptoms at the onset, including behavioral problems like inattention, forgetfulness, temper tantrums, and decline in scholastic performance. It is much later that the motor dysfunction and intellectual dysfunction become apparent. Patients typically has myoclonic jerks (typically periodic, generalized, and stereotype), dyskinesia, and ataxia. Later, expressive speech decreases progressively along with difficulty in walking and tone abnormalities, finally leading to vegetative state.

In nearly half of the SSPE patients, ocular manifestations have been reported, most common being necrotizing chorioretinitis. However, macular edema/ degeneration, optic neuritis/atrophy, papillitis/papilledema, and cortical blindness can also occur. The neuropathological findings in SSPE depend on the course of the disease. During early disease, edema is the predominant finding, followed by oxidative damage of DNA and RNA in infected cells along with lipid peroxidation in areas of demyelination. Perivascular infiltration of inflammatory cells and demyelination in cortical and subcortical are found in acute phase followed by neuronal loss later. The inflammation starts from the posterior brain with medial thalamus and deep structures involvement followed by anterior brain involvement.

CSF examination is generally normal but sometimes may show mildly elevated proteins. The gold standard for diagnosing SSPE has raised IgM and IgG anti-measles antibodies in CSF and serum, higher titers in CSF EEG generally shows specific burst suppression pattern which deteriorates to diffuse slow waves with the progression of disease. MRI brain picture can vary from decreased grey matter volume to hyperintensities in cerebral cortex, periventricular white matter, and brainstem leading to cortical atrophy and enlarged ventricles in last stage.

Supportive care and symptomatic management are the mainstays of treatment for SSPE which include anticonvulsants and spasticity reducing drugs. Trials with few drugs like isoprinosine and interferon alpha have shown some benefits of therapy in terms of slower progression, temporary stabilization and prolonged survival. While, ribavirin and immunoglobulin have shown little effects, mesenchymal stem cell treatment has demonstrated no benefit in SSPE patients.
Atypical Presentation of SSPE

There are few reported cases of SSPE with largely or exclusively involving brainstem and presenting with symptoms like cerebellar ataxia, blindness, choreathetoid movements of extremities. The neuroimaging of these patients showed pons, middle cerebellar peduncles, midbrain, substantia nigra, and inferior colliculus involvement while other areas still spared. These cases may be misdiagnosed as isolated demyelinating syndrome.73–75 Rarely SSPE may present with an acute-fulminant disease with rapid course of disease leading to death, within 6 months. It is difficult to differentiate acute fulminant SSPE from ADEM and diagnose early.76 It has also been reported during pregnancy and postpartum, with least reported time to death after diagnosis to be 19 days.77

Characteristics of SSPE Virus

A variety of genetic mutations have been reported in measles virus isolated from SSPE patients brain tissue. It has been suggested that genetic mutations occur only after virus enters the brain. The characteristic clustered mutation is biased hypermutation, leading to uracil to cytosine transitions in M gene. Another study reported mutation in 2% of nucleotides in SSPE virus, which led to 35% changes in amino acids.78 Defects in M proteins help the virus for replication and persistence in neuronal cells while evading the neutralizing antibodies. Genetic mutation in F gene leads to hyperfusogenic F protein, which enables measles virus for neuronal spread.18,79,80 Many mutations have been reported (►Table 2) which facilitate cell to cell fusion without SLAM or nectin 4 receptors. Similarly, many mutations reported in H protein help in virus spread among neurons (►Table 2).

SSPE Prevention with Measles Vaccination

Since the introduction of measles vaccination, number of SSPE cases have reduced drastically, but in developing countries like India, due to lower vaccination coverage, number of SSPE cases are still high. None of the studies or epidemiological surveys have shown SSPE due to vaccine strain measles virus.81 It is suggested that, SSPE patients who do not have history of prior measles infection, might have had subclinical or undiagnosed measles in early childhood. In a child with SSPE, who has received measles vaccine, wild measles infection is presumed to occur before vaccination.82 Re-emergence of SSPE cases in developed countries coincides with measles outbreaks. In a study from California, higher rates of SSPE were reported in unvaccinated children, mainly those who acquired infection during first year of life.59

Association of Measles Vaccine Virus with CNS-Related Measles Complications

There have been concerns regarding measles vaccine virus causing measles-related CNS complications. Few cases of encephalitis in healthy individuals,83–85 a couple of MIBE case reports in immunocompromised patients (ALL and HIV),48,54,55 and some cases of SSPE86 have been attributed to vaccination, in whom there was no history of prior clinical measles infection. However, the possibility of wild type measles virus infection cannot be ruled out in these cases.

Some authors have implicated the vaccine virus to cause acute encephalitis in many cases solely on the basis of temporal association (onset of symptoms within 6 to 15 days of vaccination).83,84 In one of these cases, measles virus was isolated from CSF on nineth day of vaccination.83 On the basis of infectivity titer, tissue culture sensitivity, and plaquing, it was indicated that the isolate was vaccine like virus, however, genetic sequencing was not performed. Epidemiological data demonstrate that the rate of acute encephalitis within 15 to 30 days of measles vaccination is comparable to the expected background encephalitis rate.85 However, a clustering of cases on days 8 and 9 post vaccination suggested a possible causal relationship.84 To date, there have been no reports of genetic sequences characteristic of measles vaccine strains in cases of acute encephalitis.

Amongst reported cases of vaccine-associated MIBE, vaccine like virus was isolated from the brain tissue of a 21-month-old boy, who had primary immunodeficiency. The nucleotide sequence of isolated virus was identical to that of the Moraten and Schwarz vaccine strains in the nucleoprotein and fusion gene regions while, the fusion gene was different from wild-type genotype A virus, implicating vaccine virus as the cause of MIBE. However, authors also suggested that such an adverse event is very rare and the report should not lead to changes in current immunization practice.48

According to the report of GACVS (Global Advisory Committee On Vaccine Safety) meeting 2005, the available epidemiological and measles virus genotyping data, do not suggest that measles vaccine virus can cause SSPE. Furthermore, measles vaccine can neither trigger/accelerate the course of SSPE in an unvaccinated individual nor can lead to the development of SSPE in a person who had benign persistent wild measles infection at the time of vaccination. Also, the available evidence points to natural subclinical measles infection as the cause of SSPE in vaccinated individuals, who had no previous history of prior measles infection.87 In a report on 81 children with confirmed SSPE, 17 children did not report past history of measles infection or vaccination. This suggests the phenomenon of subclinical measles leading to SSPE.88 Till date, no genetic similarity of the defective measles virus in the brain tissue of SSPE cases has been shown with the attenuated measles vaccine virus, hence, there is no evidence to believe that measles vaccine may cause SSPE.89

Summary

Measles is a vaccine preventable disease, still the measles infection rates are high amongst developing countries leading to significant morbidity and mortality. The neurological complications of measles infection can occur within days, months, or years later. The varied presentation and pathology of these complications sometimes pose difficulties in diagnosis and
management as well. Many mutations have been detected in various genes of measles virus which are implicated for the persistence and tropism of virus in the brain. The newer therapeutic options are based on these mutations and are currently under research. Timely diagnosis and supportive treatment still remain the first line of treatment. Adequate vaccination of population with two doses of measles vaccine is the only preventive measure and should be undertaken.

Conflict of Interest
None declared.

References
10 World Health Organization. Immunization, vaccines and biologicals: new measles surveillance data for 2019
19 Laksono BM, de Vries RD, McQuaid S, Duprex WP, de Swart RL. Measles virus host invasion and pathogenesis. Viruses 2016;8(08):210
20 Bechmann I, Galea I, Perry VH. What is the blood-brain barrier (not)? Trends Immunol 2007;28(01):5–11
22 Cherry JD, Harrison GJ, Kaplan SL, Hotzet PJ, Steinbach WJ, Feigin and Cherry’s Textbook of Pediatric Infectious Diseases. 2014
26 Hosoya M. Measles encephalitis: direct viral invasion or autoimmune-mediated inflammation? Intern Med 2006;45(14):841–842
34 Mayer MC, Meinel E. Glycoproteins as targets of autoantibodies in CNS inflammation: MOG and more. Ther Adv Neurol Disord 2012;5(03):147–159
Bellini WJ, Rota JS, Lowe LE, et al. Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than was previously recognized. J Infect Dis 2005;192(10):1686–1693


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