



# Subacute Sclerosing Panencephalitis in Perspective

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Three different forms of infections in the central nervous system have been associated with the measles virus: acute postinfectious encephalitis, acute progressive infectious encephalitis (also known as measles inclusion body encephalitis or MIBE) and subacute sclerosing panencephalitis (SSPE).<sup>1</sup> The postinfectious encephalitis is considered an autoimmune reaction, MIBE appears as a direct attack by the virus on the brain cells, while SSPE is a slow viral infection of the central nervous system, usually resulting in death within months or years.<sup>2</sup>

## Can measles vaccine cause MIBE?

From 1995 to 1998, no definite cases of SSPE were reported through the Canadian Paediatric Surveillance Program (CPSP). In 1999, however, two definite cases, as defined by very high serum and CSF IgG ratios in the presence of typical clinical manifestations, were identified through the CPSP.<sup>3</sup>

There also was a Canadian case report on MIBE caused by the vaccine strain of the measles virus, published in 1999.<sup>4</sup> An apparently healthy male infant with no history of measles received measles-mumps-rubella vaccine at about age one. Eight and a half months later he was diagnosed with MIBE and died 51 days after hospitalization. This disease is associated with immunodeficiency and usually develops within one to seven months after infection with the measles virus. On brain biopsy, measles antigens were detected by immunohistochemical staining and confirmed by reverse transcription polymerase chain reaction. They were identified as belonging to the Moraten and Schwarz vaccine strains, and not to known genotype A wild-type viruses. On further investigation it was found that the child had an abnormality in the humoral arm of the immune system in the form of a profound deficiency of CD8 cells as well as dysgammaglobulinemia.

The authors concluded that: "Most significant primary immunodeficiency states in children will be detected before the age of MMR vaccination, and for such children live virus vaccines should be avoided. Clearly, a serious outcome such as occurred for this patient is an exceedingly rare event, and this report should not lead to changes in current immunization practices."<sup>2</sup>

RESOURCES



### Is SSPE still current?

SSPE manifests itself as progressive mental deterioration, myoclonia, motor disabilities, coma, and death.<sup>5</sup> The average period between exposure and onset of SSPE ranges from seven to twelve years, while the average age of onset is nine years. Both laboratory findings and epidemiologic data have linked SSPE with exposure to the measles virus. Before measles immunization, SSPE was a rare complication of measles infection at 1 per 100,000 cases.<sup>5</sup> Since the introduction of immunization programs, the incidence of SSPE following measles infection has declined drastically to 0.06 per 1,000,000 in the U.S.<sup>2</sup>

A case-control study in Israel comparing Sephardic Jews and Arabs versus Ashkenazic Jews identified the following risk factors for SSPE: 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.<sup>6</sup>

Because SSPE is only one of a number of degenerative neurological diseases, it requires a high level of diagnostic suspicion. It is very important that all suspect cases be followed up with laboratory investigations to determine a definite case of SSPE. Serum and CSF measles IgG antibody levels should be determined. Actual titre values are preferred over more general terms such as positive or negative. With the elimination of indigenous measles disease in Canada, due to widespread measles immunization programs, it is essential that brain tissue specimens be collected post-humously on all suspect cases of SSPE for virus detection.

Brain biopsy material can be examined for measles virus RNA by reverse transcription polymerase chain reaction. Subsequent DNA sequencing of the viral nucleoprotein or hemagglutinin genes allows differentiation of vaccine and wild-type measles strains.<sup>7</sup> In Canada, the Viral Exanthemata Lab at the Bureau of Microbiology performs vaccine versus wild-type strain differentiation for measles, rubella and varicella-zoster viruses.

The following summary on SSPE was modified from the Pediatric Database (PEDBASE) website,<sup>8</sup> although for a definite IMPACT case of SSPE it is essential to have detected measles virus antigen on a brain tissue biopsy.

### What is needed to confirm a case of SSPE (PEDBASE)?

#### *Pathogenesis:*

1. Background
  - a. pathogenesis involves the accumulation of incomplete measles virus that cannot be cleared by B or T cell mechanisms
  - b. measles genomes in SSPE are larger and contain multiple mutations



### ***Subacute sclerosing panencephalitis in perspective (continued)***

- c. begins in cortical grey matter, progresses to subcortical grey and white matter, then to lower structures

#### *Pathology:*

2. Intranuclear Inclusion Bodies
  - a. inflammation, necrosis, gliosis, and repair
  - b. panencephalitis involves cortical and subcortical grey and white matter and blood vessels with an increasing number of glial cells

#### *Clinical Features:*

3. Clinical Course
  - a. First clinical stage – Behavioural changes
    - insidious onset
    - subtle changes in behaviour and declining school work:
      - aggression
      - withdrawal
    - followed by overtly bizarre behaviour and dementia
    - occasional headaches
  - b. Second clinical stage – Neurological changes
    - seizures
      - myoclonic - symmetrical involving axial muscles
      - generalized tonic-clonic develop later
    - movement disorders
      - cerebellar ataxia, chorea, choreoathetosis, dystonia, progressive bulbar palsy, spasticity
    - optic changes
      - chorioretinitis, macular pigmentation, optic atrophy, papilledema, retinopathy
    - dementia progresses to stupor and coma in either flaccid or spastic decorticate postures

#### *Investigations:*

4. Serology
  - a. IgG and IgM to measles virus
5. Cerebral Spinal Fluid
  - a. elevated IgG and IgM fractions to measles virus on oligoclonal electrophoresis
  - b. normal cell count
  - c. normal or elevated total protein
6. Brain Biopsy
  - a. measles virus antigen
7. EEG
  - a. First Stage – moderate nonspecific slowing
  - b. Second Stage – episodes of “suppression-burst;” high amplitude slow and sharp waves recur at intervals of 3-5 seconds on a slow background



8. Imaging Studies

a. CT/MRI

- variable cortical atrophy and ventricular enlargement
- normal study or single or multiple focal low-density lesions in the white matter

**Selected Literature Abstracts from Medline**

TI: Adult-onset subacute sclerosing panencephalitis: case reports and review of the literature.

AU: Singer C, Lang AE, Suchowersky-O

AD: Department of Neurology, University of Miami School of Medicine, FL 33136, USA.

SO: *Mov Disord* 1997 May; 12(3): 342-53

AB: Subacute sclerosing panencephalitis (SSPE) is mainly thought of as a disorder of childhood and adolescence and may not be readily recognized when presenting later in life. Prior reports have suggested that adult-onset SSPE may have atypical features. We have added two cases to the existing literature on adult-onset SSPE, compared them with a more classic juvenile presentation, and extensively reviewed those reports that were published after the etiological link with the measles virus had been established. Adult-onset SSPE patients present at a mean age of 25.4 years (range 20-35 years). They have a higher proportion of either negative history of measles exposure or undocumented history by the reporting authors. Those with available history of measles exposure tend to have it either earlier (younger than 3 years old) or later (after 9 years) than the usual childhood measles infection. Where the primary infection is known, unusually long measles-to-SSPE intervals have been documented, ranging from 14 to 22 years. None of the cases followed measles vaccination. Visual symptomatology was very frequent, with 8 of the 13 cases reviewed having a purely ophthalmological presentation; only 2 patients presented with behavioral changes. Although the course of the disease was progressive and fatal in the majority, 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. Neuropathology revealed cortical and subcortical gray matter involvement preferentially of the occipital lobes, thalamus, and putamen. The importance of recognizing the spectrum of potential presentations of SSPE and providing an early diagnosis will increase as more effective treatments become available.

TI: Measles virus in the brain.

AU: Norrby E, Kristensson K

AD: Microbiology and Tumorbiology Center, Karolinska Institute, Stockholm, Sweden.

***Subacute sclerosing panencephalitis in perspective (continued)***

SO: *Brain Res Bull* 1997; 44(3): 213-20

AB: Measles virus can give three different forms of infections in the central nervous system. These are acute postinfectious encephalitis, acute progressive infectious encephalitis, and subacute sclerosing panencephalitis (SSPE). The postinfectious acute disease is interpreted to reflect an autoimmune reaction. The acute progressive form of brain disease, also referred to as inclusion body encephalitis, reflects a direct attack by the virus under conditions of yielding cell-mediated immunity. The late progressive form of encephalitis (SSPE) has been extensively analyzed. Recent molecular genetic studies have unravelled a range of mechanisms by which a defective expression of either the matrix, the fusion, or the hemagglutinin proteins may lead to viral persistence in brain cells under conditions not allowing identification by immune surveillance mechanisms. Many aspects of virus-cell interactions have been examined by use of explant cultures of neuronal cells of human and animal origin. Some of the findings are reviewed. Experimental animals, in particular rodents, have been used to establish systems in which phenomena, pivotal to the evolution of acute as well as persistent measles virus infections in the brain, can be studied. A wide range of potentially important mechanisms has been highlighted and is discussed. More recently, mice with genetic defects in immune functions were used to evaluate consequences as to initiation and dissemination of virus infection in the brain.

TI: Fulminating subacute sclerosing panencephalitis: case report and literature review.

AU: PeBenito R, Naqvi SH, Arca MM, Schubert R

AD: Department of Pediatrics, Brookdale University Hospital and Medical Center, Brooklyn, NY 11212-3198, USA.

SO: *Clin Pediatr (Phila)* 1997 Mar; 36(3): 149-54

AB: We describe a young urban boy with atypically fulminant subacute sclerosing panencephalitis (SSPE). He had measles at 3 years of age despite receiving measles immunization in infancy. The literature describing acute SSPE is reviewed and summarized. This report reiterates the need to include SSPE as a diagnostic possibility in acute encephalopathic processes. The dismal prognosis of SSPE further emphasizes the need for measles vaccination and revaccination of all children who are initially immunized at an age of less than 15 months.

TI: Subacute sclerosing panencephalitis.

AU: Gascon GG

AD: Department of Neurology, Brown University, Rhode Island Hospital, Providence, USA.

SO: *Semin Pediatr Neurol* 1996 Dec; 3(4): 260-9



AB: Subacute sclerosing panencephalitis (SSPE), a neurodegenerative disease caused by a persistent “slow virus infection” with a mutated measles virus, is endemic in much of the developing world. Its incidence will increase in the USA, not only in immigrants, but also because of the 1988-1990 measles epidemic. This report reviews the pathogenesis, clinical and laboratory diagnosis, and future perspectives in treatment and prevention.

### References

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8. <http://www.icndata.com/health/pedbase/files/SUBACUTE.HTM>