Subacute Sclerosing Panencephalitis: The Foothold in Undervaccination

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Subacute sclerosing panencephalitis (SSPE) is a fatal complication of measles infection. We present a case of a fully vaccinated 3-year-old boy who was diagnosed with and treated for autoimmune encephalitis before arriving at a diagnosis of SSPE. We discuss the challenges of diagnosing SSPE in developed countries. *(J Pediatr 2016;179:259-62).*

Subacute sclerosing panencephalitis (SSPE) is a rare form of encephalitis that occurs years after infection with the measles virus, causing widespread demyelination and neuronal loss in the central nervous system. This fatal sequelae occurs in children who are immunocompetent infected with measles virus at a young age because of undervaccination or infection before 1 year of age.[1,2] The risk of developing SSPE after childhood measles is estimated to be 1 in 25 000 in the general pediatric population and 1 5500 in children infected before 1 year of age.[2-5] Age at presentation is usually 6-11 years after measles infection, ranging from 10 months of age to decades into adulthood.[1] Early symptoms include intellectual deterioration, personality changes, and behavioral abnormalities. Subsequent weakness, rigidity, myoclonus, and autonomic failure ensue, typically progressing to death within 1-3 years.[1,2] No treatment is known to be curative. The incidence of SSPE is inversely related to the local measles vaccination coverage,[6] and vaccination offers the only means of protection against this devastating illness.

In the developed world, the incidence of SSPE has decreased markedly since the introduction of the measles vaccine in 1963,[1] such that few pediatricians and pediatric neurologists have encountered a single case. This is not true worldwide, where vaccination rates are lower and measles infection is more prevalent.[1] Measles was verified as eliminated from the US in the year 2000, with sustained elimination verified in 2011.[7] Outbreaks occurring after elimination have been traced to imported sources of the virus.[8] Although the nation's vaccination coverage remains high compared with other countries, vaccination rates in some communities have recently fallen below the necessary threshold to sustain herd immunity.[9] It is likely that SSPE will continue to occur at very low levels in the US from exposure to imported cases, travel to measles-endemic countries, and among US residents born in measles-endemic countries. The clinical presentation of SSPE mimics more common neurologic conditions, including autoimmune encephalitis and some genetic conditions.[1,10,11] Clinicians continue to require an increased level of awareness and knowledge of acute measles infection and SSPE to recognize and diagnose this fatal condition.

CSF	Cerebrospinal fluid
EEG	Electroencephalogram
MMR	Measles, mumps, and rubella
SSPE	Subacute sclerosing panencephalitis

Case

A 3-year-old white male with a history of speech delay presented with a 1-week history of confusion, somnolence, and unsteady gait. He had no history of infectious symptoms. His immunizations were up-to-date. Findings of a neurologic examination was notable for hypotonia and ataxic gait. Initial serum laboratory evaluation was unremarkable. Analysis of cerebrospinal fluid (CSF) showed a white blood cell count of 5 cells/μL (87% lymphocytes), red blood cell count of <1 cell/μL, protein of 40 mg/dL, and glucose of 60 mg/dL. Initial testing for infectious etiologies was negative, including bacterial culture, polymerase chain reaction for herpes simplex virus, enterovirus, and Epstein-Barr virus, *Borrelia* antibodies, West Nile virus antibodies, and *Bartonella* antibodies. Electroencephalogram (EEG) showed frontal-central slowing but no seizures or epileptiform activity. Magnetic resonance imaging of the brain demonstrated nonspecific bilateral frontal, left temporal, and parietal cortical and subcortical T2 hyperintensities (**Figure 1**). The patient received intravenous immunoglobulin 2 g/kg and pulse intravenous methylprednisolone 30 mg/kg/day for 3 days without clinical improvement.

Over the following 4 weeks, the patient's symptoms progressed to severe encephalopathy, increased tone, myoclonus, and atonic seizures. Repeat EEG showed diffuse slowing, multifocal epileptiform discharges, and frequent myoclonic seizures. Repeat magnetic resonance imaging of the brain showed no change from the previous study. Testing for autoimmune, paraneoplastic, metabolic, and genetic etiologies was unrevealing, including skin biopsy and genetic testing for neuronal ceroid lipofuscinosis. Brain biopsy was pursued and demonstrated nonspecific perivascular lymphocytic and histiocytic inflammation and neuronophagia, with a notable absence of viral inclusions.

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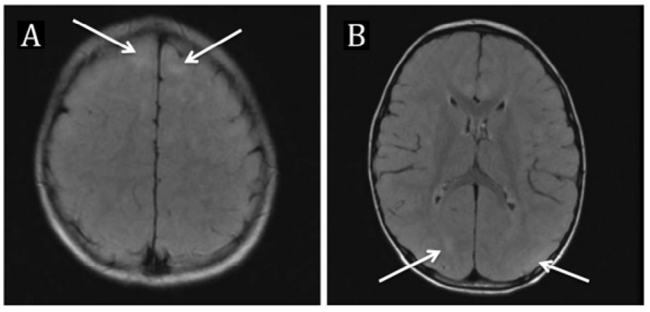

Figure 1. Brain magnetic resonance imaging 1 week after patient presentation. Axial T2 fluid-attenuated inversion recovery image shows **A,** bifrontal hyperintensities in the cortex and subcortical white matter (*arrows*) and **B,** hyperintensity in the left parietal cortex and occipital subcortical white matter (*arrows*).

Given the patient's rapid clinical deterioration over the course of weeks, with evidence of inflammation on brain biopsy in the setting of negative infectious studies, the decision was made to treat for presumed autoimmune encephalitis. He received pulse intravenous methylprednisolone 30 mg/kg/day for 3 days, followed by monthly doses of cyclophosphamide up to 900 mg/m^2. His symptoms progressed to minimal responsiveness, near-constant myoclonic seizures, and autonomic instability. Repeat EEG showed discontinuity, with periods of relative suppression alternating with high-amplitude bursts of multifocal epileptiform discharges (**Figure 2**).

The evolution of the patient's EEG findings, in addition to his clinical course, led the care team to consider testing for SSPE. Measles serum and CSF antibodies were positive with a serum measles IgG index >8 and CSF measles IgG titer of 1:640 (normal range <1:5). Because the patient had previously received intravenous immunoglobulin, parallel testing of the CSF was performed and revealed a negative mumps titer. Further interrogation of the history revealed a febrile infection at 5 months of age, soon after the patient traveled to Germany and Egypt in 2011, where measles was known to be endemic.[12,13] Approximately 1 week after returning from his trip abroad, he was admitted to the hospital with fever, cough, rhinorrhea, and rash involving his face, trunk, and extremities. Laboratory investigations excluded a bacterial infection, and he was diagnosed with a nonspecific viral infection, without measles testing. He received his first routine measles, mumps, and rubella (MMR) vaccination 9 months later, at 14 months of age.

With this additional history and positive measles antibody testing, the patient's brain biopsy specimen was sent to the Centers for Disease Control and Prevention for confirmatory testing. Measles RNA was detected from RNA extracted from 2 samples of fixed brain tissue. After genotyping and comparison with the global measles sequence database (Measles Nucleotide Surveillance [ie, MeaNS]),[14] the RNA sequence was a representative of measles genotype D4. This sequence was closely related (1 nucleotide difference in N-450) to sequences of wild-type measles viruses from genotype D4 that were circulating in Europe during 2011, which had previously documented importations to numerous other countries.[15,16]

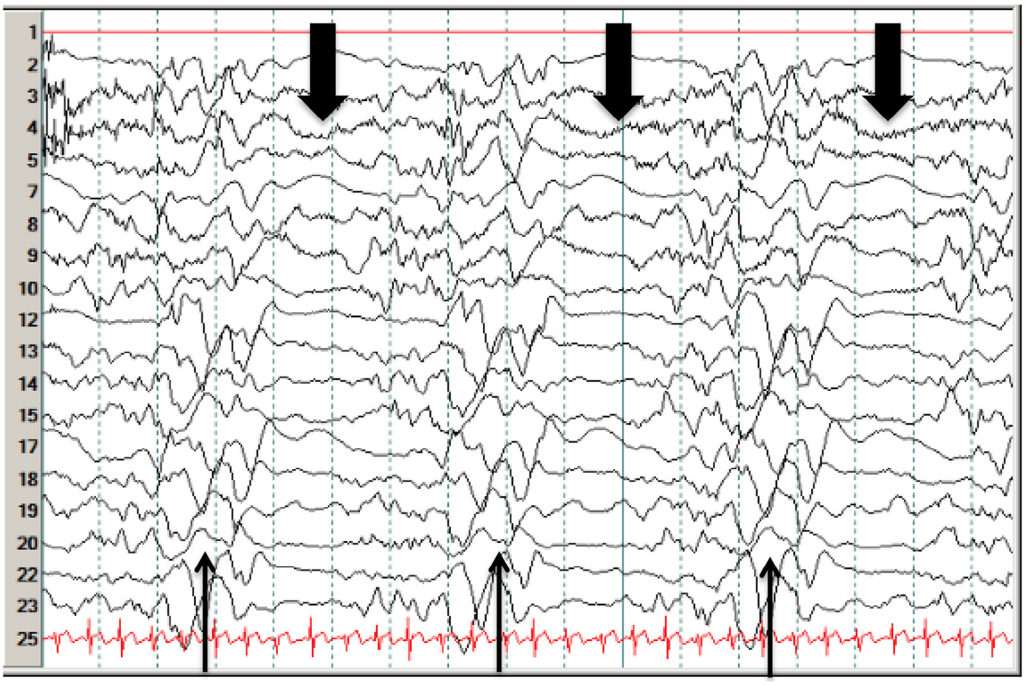

Figure 2. EEG 3 months after symptom onset showing discontinuous background with periods of relative suppression lasting seconds (*thick arrows*) alternating with high-amplitude bursts of multifocal epileptiform activity (*thin arrows*). Displayed at 20 seconds per page and sensitivity of 10 μV.