Case Report

Subacute Sclerosing Panencephalitis in Immunized Thai Children

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Subacute sclerosing panencephalitis (SSPE) is a progressive neurodegenerative disease with high mortality and poor prognosis. This is caused by persistent defective measles virus infection. Clinical presentations are variable including behavioral-cognitive change, myoclonic seizure, visual problem, spasticity or abnormal movement. The authors report a case of 10 year-old boy, previously healthy with complete immunization, presenting with frequent myoclonic jerks, abnormal movements, spasticity and altered mental status. Electroencephalographic (EEG), magnetic resonance imaging (MRI), and laboratory findings are typical for SSPE.

Keyword: *SSPE, Measles, Vaccine, Subclinical infection*

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Subacute sclerosing panencephalitis (SSPE) is a neurodegenerative disease caused by persistent slow virus infection; defective measles virus. This was first described in 1934 by Dawson and originally called "Subacute inclusion body encephalitis or Dawson's encephalitis". Subsequently, Van Bogaert used the name "subacute sclerosing leukoencephalitis" due to presence of dominant white matter change. In 1969, the name was changed to "subacute sclerosing panencephalitis" after measles virus was found from brain biopsy and involvement of gray and white matters were identified[1-3]. Prevalence of SSPE is 1 per million children in the United States, from 1960-1970, while the annual incidence is 2.4 per million in the Middle East and 21 per million in India[4]. Children usually are affected with measles virus infection at an early age, mostly before the age of 2 years.

The age of symptom onset usually ranges from 5-15 years and male is more affected than female with a ratio of 2-4:1[2]. The time from onset of first symptom to death ranges from 1 month to 6 months with a median of 2 months in cases of fulminant SSPE and a median of 1.8 years for all SSPE[5].

The pathogenesis is not entirely clear. It is thought that incomplete elimination of virus from infected cells by failure of cellular response is the main pathogenesis of SSPE. Genetic polymorphism may be responsible for developing SSPE by producing low level of interferon, interleukin 2 (IL-2), IL-10 and IL-12. The measles virus can remain in neurons for years as chronic intracellular infection before triggering an inflammatory response against these infected cells leading to cell death and neurodegeneration[6,7].

The authors report a case of 10 year-old boy, previously healthy with complete immunization presenting with typical clinical features of SSPE such as myoclonic jerks, mental deterioration, laboratory, magnetic resonance imaging (MRI) and electroencephalographic (EEG) findings.

Case Report

A 10-year-old boy was referred from regional hospital to pediatric department, faculty of medicine, Siriraj hospital in August, 2007 with provisional diagnosis of intractable seizure and psychiatric symptoms. His symptoms began in April, 2007 while his father has recognized progressive personality

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change and poor school performance. One month later, he developed brief jerking movement of extremities and also complex partial seizures with secondarily generalized tonic-clonic seizures. He was subsequently hospitalized at the regional hospital. Several investigations including routine blood work, EEG, computer tomography (CT) of the brain, and cerebrospinal fluid (CSF) analysis were performed and findings were unremarkable. Phenytoin was given 5 mg/kg/day for seizure control. One month before referring to Siriraj hospital, he has progressive cognitive decline, memory problems, confusion and inability to conduct activities of daily living. Myoclonic seizures and abnormal movement were still frequent. Several medications including valproic acid, topiramate and risperidol were provided but his symptoms persisted.

Past medical and family histories were unremarkable for neurological disorder except for history of hospitalization for viral exanthem when he was 3-year-old. His immunization program is complete and up to date.

At our hospital (4 months after symptom onset), physical examination revealed cloudy consciousness and repetitive myoclonic jerks occurring every few seconds. Abnormal movements such as chorea, ballism, and tardive dyskinesia were noted as well. Motor powers are at least grade III. He had upper motor neuron signs such as hypertonia and hyperreflexia. Routine hematologic and blood chemistry test were within normal limit. CSF showed clear and colorless appearance, 4 white blood cells/cumm, protein 18 mg/dl and glucose 65 mg/dl. The CSF measles antibody titers were 1:64 and > 1:512 for serum measles antibody titer by neutralization test. EEG showed absence of sleep architecture and posterior dominant rhythm. The background consisted of high voltage delta-theta activities intermixed with bursts of high voltage, bilaterally synchronous sharp waves lasting for 0.5-2 seconds. These periodic, stereotypic bursts occurred every 3-5 seconds and 1:1 relationship with myoclonic jerks as shown in Fig. 1. These EEG findings appeared to be present both during wakefulness and sleep. MRI of the brain showed well-defined, oval shape, hypersignal intensity on T_2-W FLAIR and hyposignal intensity on T_1-W without enhancement at right lentiform nucleus as shown in Fig. 2.

Supportive treatment was given. Phenytoin was discontinued due to aggravation of myoclonic seizures and valproic acid was continued. Other medications prescribed from the regional hospital were withdrawn. Clinical myoclonic seizures slightly

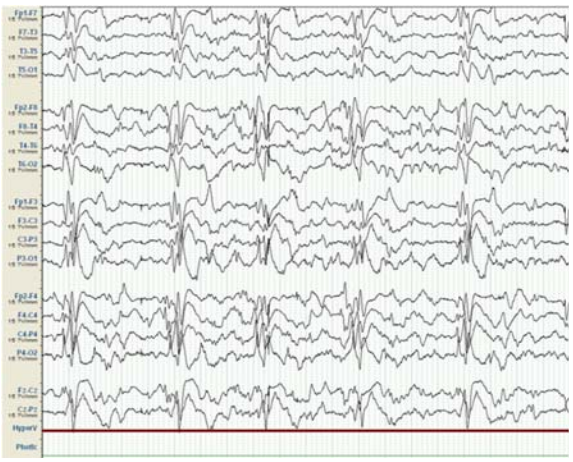

Fig. 1 Anterior-posterior bipolar montage EEG shows periodic, diffuse high voltage bursts occurred every 3-4 seconds. (Low frequency filter, 1Hz; High frequency filter, 70 Hz; Notch filter, 50 Hz; speed, 20 seconds per page)

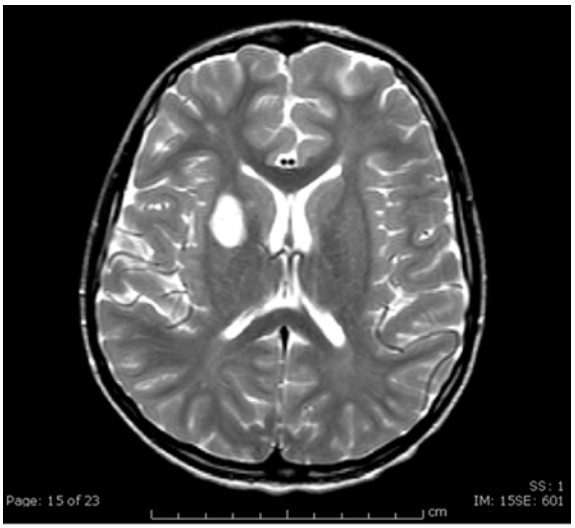

Fig. 2 Axial T_2-W MRI shows well-defined, oval shape, hypersignal intensity at the right lentiform nucleus

decreased after valproic acid administration with additional clonazepam.

After discharge from the hospital, his clinical symptoms deteriorated into vegetative state with progressive myoclonic seizures and severe spasticity until he died in January, 2008.

Discussion

The author's patient was diagnosed as SSPE based on diagnostic criteria which are shown in Table

Table 1. Diagnosis criteria of SSPE

Major criteria	(1) Typical or atypical clinical history
	Typical: acute progressive, subacute progressive, subacute remitting and relapsing, chronic progressive, and chronic remitting and relapsing
	Atypical: early seizures, prolonged stage 1, and unusual age of presentation (infancy or adult)
	(2) Increased measles antibody titers in CSF ($\geq$ 1:4)
Minor criteria	(3) Increased CSF IgG
	(4) Typical EEG: periodic slow wave complexes in stage 2
	(5) Brain biopsy or postmortem: typical pathology and/or culturing the altered measles virus
	(6) Molecular diagnostic test: identified mutations of wild-type measles virus

Two major criteria plus one minor criterion are usually required; the more atypical the SSPE, the more criteria 5 and/or 6 are needed.
CSF: cerebrospinal fluid, EEG: electroencephalography, IgG: immunoglobulin G

Adapted from references 2 and 7

1[2,7]. His clinical course was subacute progressive over the period of 4-6 months and his CSF measles antibody was greater than cut off titer (1:4). He also had typical periodic EEG complexes every 3-5 seconds as a minor criteria.

Clinical manifestation of SSPE was categorized into 4 stages: 1) personality change, poor school performance, abnormal behavior; 2) massive, repetitive, and frequent myoclonic jerks, seizures, dementia; 3) rigidity, extrapyramidal symptoms, progressive unresponsiveness and 4) coma, vegetative stage, autonomic failure, akinetic mutism[7]. At the time of presentation at the author's hospital, his clinical symptoms were likely already in stage 3 due to his frequent myoclonic jerks, abnormal movements, spasticity and altered mental status. The EEG finding of shortened interburst interval and marked background slowing was also consistent with clinical stage 3[8].

The author's patient was initially not diagnosed as SSPE until referring to the author's hospital with clinical stage 3. Primary physicians are usually reluctant to diagnose and would refer to higher medical center for further investigation and management. Prashanth et al[9] revealed the percentage of patients who had a correct referral diagnosis is 21.2%, most of them (82%) were evaluated by neurophysician. Due to variable clinical symptoms, patient with atypical manifestation of SSPE such as generalized seizure, atonic event, visual impairment, autonomic dysfunction or psychiatric manifestation may have an incorrect initial diagnosis[9-12]. Possible differential diagnosis in patient with SSPE included seizure disorder, subacute measles encephalitis, measles inclusion body encephalitis, late infantile or juvenile lipidoses, various degenerative white matter/gray matter disease, head trauma and other psychiatric disorders[1,13].

MRI finding of abnormal signal intensity on basal ganglia is usually found in later stage. Initially, MRI brain may be normal or shows asymmetrical hypersignal intensity in T_2-w imaging over cerebral cortex and subcortical white matter, which is more dominant over posterior head regions[14,15]. The basal ganglia, thalamus, and corpus callosum are usually involved after the cortical and subcortical areas are affected[16]. Finally, periventricular white matter abnormalities and cortical atrophy may be observed[15]. However, these data do not show good correlation between abnormal MRI finding and clinical manifestation.

Measles vaccine has demonstrated its effectiveness in preventing SSPE for years[17]. But there were several reports which showed occurrence of SSPE despite immunization against measles. Nunes et al reported 48 cases of SSPE, 14% of them had been immunized for measles[18]. Of 40 patients with SSPE in Bulgaria, two (5%) had history of measles vaccination[19]. In Asia, Ip et al reported 3 out of 10 cases with SSPE who were previously immunization against measles[4]. A large study in India showed 307 patients diagnosed as SSPE at tertiary care hospital, two of them were immunized against measles[20]. Of 57 patients with SSPE in Pakistan, Malik et al reported a considerable number of patients (71%) being

vaccinated against measles at about 9 months of age. This could be due to poor nutritional status and poor immune response[21]. The author's patient had received measles vaccine at the age of 9 months and one booster dose at 4 years of age as in the authors nationwide immunization program. He still developed SSPE at the age of 10 years. One of the possible explanations is subclinical measles infection prior to first vaccination[22]. A wide-type measles infection, not covered in regular vaccine, can be a culprit infection causing SSPE[22]. Persistent infection with the attenuated measles virus in the vaccine or vaccine failure is another hypothesis[2]. However, the current data suggests that measles vaccine does not cause SSPE[17]. The author's patient had a history of viral infection and rashes at the age of 3 years which was non-specific and unlikely to be measles infection. Most of the SSPE patients had a history of measles infection before the age of 2 years. Bojinova et al found 95% of their SSPE patients had an early measles infection (mean age 16 months) and no immunization against measles[19].

In Thailand, the immunization program against measles was fully organized nationwide in 1996. Annual reports of measles infection showed high number of cases every 4-6 years. Case rates per 100,000 population in 1998, 2002 and 2008 were 20.1, 16.5 and 11.8 respectively. Total numbers of measles infection during the year 2006-2010 were demonstrated and categorized by age group as shown in Fig. 3[23]. About 12-17% of cases occurred before the age of 1 year. Annual epidemiological surveillance report in 2008 showed only 82% coverage with first dose of measles vaccine at the age between 9-12 months[24]. These evidences support the possibility of early measles infection before receiving the vaccine. Base on the authors knowledge, few cases of SSPE had been reported in Thailand. This could be due to unreported cases or misdiagnosis of SSPE.

Currently, there is no specific effective treatment for SSPE. Different combination regimens of antiviral and immunomodulating therapy have been reported and may prolong survival such as intraventricular interferon-alpha, ribavirin and Isoprinosine[25] or oral Isoprinosine, subcutaneous interferon alpha 2a and oral lamivudine[26]. The main treatment for the SSPE patient is supportive and symptomatic, especially seizure management. Several antiepileptic drugs had been challenged to the authors patient but there was only minimal response in seizure control. Antiviral or immunomodulating agent was not introduced to the authors patient. Due to the late stage at time of diagnosis, progressive deterioration, and poor response to symptomatic treatment, he subsequently died at 9 months after the onset.

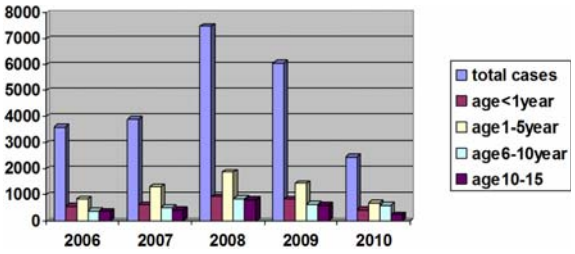

Fig. 3 Number of measles cases by age from National Disease Surveillance (Report 506); Bareau of epidermiology, DDC, MOPH[23]

Conclusion

SSPE is a rare disease but still persists, although the incidence currently is low due to worldwide immunization program against measles. In developing countries, the incidence of measles can be high due to ineffective immunization or increasing number of immigrated population from the low immunization coverage regions. SSPE has high morbidity and mortality with variable clinical presentation. Early recognition and comprehensive investigations are required for the correct diagnosis. History of complete immunization cannot totally exclude the diagnosis of SSPE because of the possibility of early measles infection, especially before the age of 1 year.

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Potential conflicts of interest

None.

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รายงานผู้ป่วย subacute sclerosing panencephalitis ในเด็กไทยที่ได้รับการฉีดวัคซีนหัด

ขนิษฐา คูศิวิไลส์, สรวิศ วีรวรรณ

Subacute sclerosing panencephalitis (SSPE) เป็นโรคทางระบบประสาทที่มีความเสื่อมเพิ่มขึ้นเรื่อยๆ ตั้งแต่มีอาการ โดยมีการพยากรณ์โรคไม่ดีและมีอัตราตายสูง สาเหตุของโรคนี้เกิดจากความผิดปกติภายหลังจากการติดเชื้อไวรัสหัด (measles) อาการแสดงมีหลายรูปแบบ เช่น สติปัญญาถดถอย พฤติกรรมเปลี่ยนแปลง ชักแบบกระตุก ปัญหาการมองเห็น ความผิดปกติของกล้ามเนื้อและการเคลื่อนไหว ในรายงานผู้ป่วยอายุ 10 ปี ได้รับการวินิจฉัยเป็น SSPE โดยที่มีประวัติได้รับการฉีดวัคซีนครบตามกำหนด มีอาการพฤติกรรมเปลี่ยนแปลง ชักแบบกระตุก การเคลื่อนไหวและความตึงตัวของกล้ามเนื้อผิดปกติ ร่วมกับมีผลการตรวจวินิจฉัยทางห้องปฏิบัติการ การตรวจคลื่นไฟฟ้าสมอง และการตรวจภาพถ่ายคลื่นแม่เหล็กไฟฟ้าสมอง ที่เข้าได้กับโรคนี้