DOI:10.4274/tnd.03789
Turk J Neurol 2015;21:112-6

Process from Diagnosis to Treatment of 3 Patients with Late-onset Subacute Sclerosing Panencephalitis

Geç Yaşta Presente Olan 3 Subakut Slerozan Panensefalit Olgusunun Tanıdan Tedaviye Süreci

Aylin Bican, İbrahim Bora

Uludağ University Faculty of Medicine, Department of Neurology, Bursa, Turkey

Summary

Subacute sclerosing panencephalitis (SSPE) is diagnosed with clinical evaluation including history and physical evaluation along with electroencephalogram (EEG), magnetic resonance imaging of the brain and cerebrospinal fluid (CSF) analysis. A total of 3 patients with SSPE (mean age=25.3 years) who were admitted to the Department of Neurology at Uludağ University Faculty of Medicine, were evaluated retrospectively. Clinical staging was performed using Risk and Haddad's classification. Time to SSPE diagnosis from initial symptoms ranged from 10 days to 3 months; the patients presented to a physician two months after their symptoms were recognized; weakening of mental capacities attracted the attention of members of their families. EEG examinations revealed slow baseline activity and penetrating slow discharges with regular high amplitudes every 8-10 seconds. Although immunoglobulin (Ig) M for measles was negative, IgG was positive in the cerebrospinal fluid and serum samples of all patients. All patients received isoprinosine, and various doses of valproic acid and clonazepam during their treatment. One patient died 13 months after the diagnosis, the other two continue to be followed up. SSPE infection should be considered in central nervous system-involved rapidly-progressing late-onset adult diseases because there has recently been a rapid increase in the number of reported cases of SSPE.

Keywords: Subacute sclerosing panencephalitis, prognosis, late presentation

Öz

Subakut slerozan panensefalit (SSPE) elektroensefalografi (EEG), kranyal manyetik rezonans (MR) görüntüleme ve klinik belirtileri değerlendirip, hikayeleri, fizik muayenedeki değişikliği ve EEG ve beyin omurilik sıvısı (BOS) incelemeleri ile tanı konur. Uludağ Üniversitesi Tıp Fakültesi, Nöroloji Kliniği'nde toplam 3 SSPE'li (yaş ortalaması=25,3) hasta retrospektif olarak değerlendirildi. SSPE tanısı semptomların başlangıcından 10 gün ile 3 ay arasında konuldu. EEG incelemelerinde 8-10 saniye süreli yüksek amplitüdlü yavaş dalgalar ve temel aktivitede yavaşlama gözlendi. BOS örneklerinde kızamık IgM negatif iken IgG pozitif, serumda hepsi pozitif idi. Valproik asit ve klonazepam değişik dozlarda ve sürede kullanıldı tüm olgulara Isoprinosine verildi. Bir olgu 13 ay sonra kaybedildi, diğer olgular takip edilmektedir. SSPE enfeksiyonu santral sinir sistemini tutup hızlıca progrese olmaktadır ve son zamanlarda geç yaşta görülen SSPE olgularının sunumları hızla artmaktadır.

Anahtar kelimeler: Subakut slerozan panensefalit, prognoz, geç başlangıç

Introduction

Subacute sclerosing panencephalitis (SSPE) was defined in 1933 by Dawson. SSPE is a subacute or chronic progressive degenerative disease of the central nervous system (CNS), which results from slow infection with a defective measles virus. This is a rare complication of measles with an incidence of 1/100.000 cases. The incidence of SSPE in developed countries is 1-4/1.000.000 and incidence exceeds 21/1.000.000 in developing countries. Defective matrix (M) protein has been implicated in the etiopathogenesis of SSPE. Although SSPE affects individuals at a wide range of ages, with a range of 2 to

Address for Correspondence/Yazışma Adresi: Aylin Bican MD, Uludağ University Faculty of Medicine, Department of Neurology, Bursa, Turkey
Phone: +90 224 295 17 40 E-mail: aylinbican@mynet.com
Received/Geliş Tarihi: 28.05.2014 **Accepted/Kabul Tarihi:** 16.01.2015

32 years reported in the literature, it is most often observed in those aged between 5 and 15 years (1). Nearly 50% of patients were reported to have had early measles infections, especially before 2 years of age, or measles vaccinations (2,3,4,5). The disease rapidly progresses; patients typically die 6-24 months after symptom onset (2).

In this study, we discuss the disease process in patients with late-onset SSPE. We obtained cranial imaging, clinical and EEG data for patients diagnosed as having SSPE and analyzed their medical histories, physical examination findings, and results of cerebrospinal fluid (CSF) analyses.

Materials and Methods

In the present study, 1 male and 2 female patients (mean age=25.3 years; range, 24-28 years) were diagnosed as having SSPE through their medical history, physical examination signs, EEG results, measles antibody levels in serum, and CSF analyses, and were evaluated at the Department of Neurology Clinic at the Medical School of Uludağ University; these patients' data were evaluated retrospectively. The study was approved by the Ethics Committee of Uludağ University. In all cases, electroencephalograph (EEG) recordings were made both before and after diazepam administration using a 32-channel EEG device (Figure 1). Cranial magnetic resonance imaging (MRI) was performed on all three patients (Figure 2). Initial symptoms, the time of symptom onset, the time of diagnosis, measles history, vaccination status, EEG and MRI signs, and treatment responses were evaluated. The clinical staging of all cases was performed according to the signs at presentation using the Risk and Haddad scale (3):

Stage I: Progression of psycho-intellectual changes and/or development of nonspecific neurologic symptoms
Stage II: Stereotypic attacks of recurrent myoclonus
IIA: Without falling attacks
IIB: With falling attacks
IIC: Confined to bed
Stage III: Vegetative state
IIIA: Aimless but spontaneous movements
IIIB: Motor response to painful stimuli
IIIC: Deep coma and death

Results

The mean age of the 3 patients (2 female and 1 male) was 25.3 years (range, 24-28 years). All three patients sought treatment for SSPE very late. Patients' initial symptoms were decreased academic success, forgetfulness and distraction, deterioration of speech, loss of balance, and 2 of the patients had jerky muscle movements (Table 1). The time from symptom onset to SSPE diagnosis ranged from 10 days to 3 months. The patients' decreasing abilities and mental capacities in particular, were causes of concern for their families. Vaccination data was not available. According to information obtained from the patients' parents, one patient had measles infection despite being vaccinated. The physician had said that there may have been a problem with the vaccine. The other two patients had had measles vaccinations.

Two of the patients were at stage 2B at the time of hospitalization, and one was at stage 1; the latter case was followed up as stage 2 because myoclonus occurred during the investigations. Our late-onset patients were symptomatic and their disease progressed rapidly during clinical monitoring, despite treatment with isoprinosine.

In EEG examinations, all patients had slowed baseline activity and sharp slow-wave discharges with regular high amplitudes, every 8-10 seconds.

Although all patients' samples were negative for immunoglobulin (Ig) M antibodies against measles, all serum and CSF samples were positive for IgG antibodies against measles.

No intracranial pathology was found in the cranial MRI examinations of 2 patients, but significant hemispheric atrophy was found in the third patient.

Treatment plans were developed for all 3 patients; valproic acid (VA) and clonazepam were administered at different doses, and all patients were started on isoprinosine treatment. One patient died 13 months after diagnosis. The symptoms observed in these patients are summarized in Tables 1 and 2.

Table 1. Information about age, sex, initial symptoms, neurologic examination, clinical stages, time of measles infection, and vaccination

Patients	Age/Sex	Initial symptoms	Neurological examination at application	Stage	Age of measles infecion	Measles vaccination
Patient 1	24/F	Decrease in academic success; deterioration in speech	Speaking was slow; comprehension was good; reaction time was prolonged; MMSE 24/30	Stage I	2.5 yrs	None
Patient 2	29/M	Forgetfullnes; behavioral changes	Speaking and understanding are limited; myoclonus all over body; MMSE 19/30	Stage IIb	2-3 yrs	Vaccinated but had measles infection
Patient 3	32/F (Exitus)	Distracted; imbalance; falling	Orientation was deteriorated; extensive myoclonus; MMSE 14/30	Stage IIb	1-2 yrs	None

F: Female, M: Male, MMSE: Minimental test

Discussion

Subacute sclerosing panencephalitis generally occurs in people aged between 5 and 15 years, but cases have been reported when symptoms first appeared in the third or fourth decades of life. The first symptoms of SSPE appear 6-8 years after infection, at ages of 5-18 years in females and 4-24 years in males. In this study, the symptoms first appeared in the second decade in all patients.

It has been suggested in previous case reports in the literature that SSPE can occur in adults. Frings et al. (4) reported a Turkish female patient aged 38 years who presented with clinically progressive dementia. A patient with SSPE aged 34 years has also been reported (5). The age at clinical presentation can vary because SSPE may occur at earlier ages in children who had measles infections before the age of 1 year. An insufficient immune response against measles at earlier ages may play a role in the pathogenesis of SSPE (6).

In a study by Prashanth et al. (6) conducted in South India, 32 out of 307 patients with SSPE were late-onset cases. Moreover,

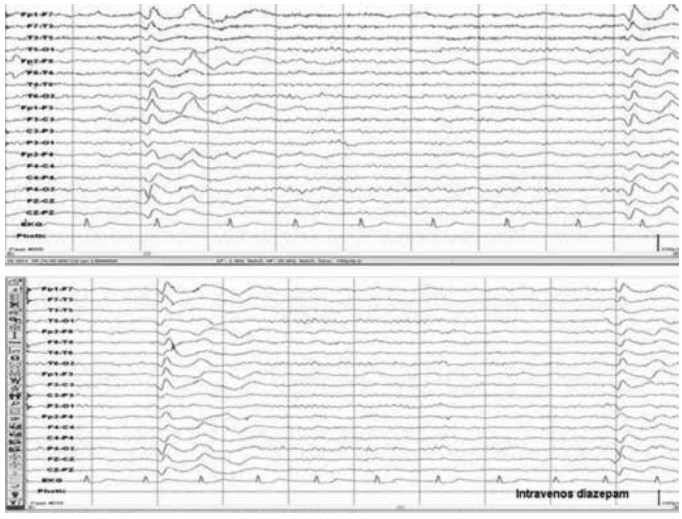

Figure 1. All patients exhibited similar electroencephalograph features; a representative recording is shown

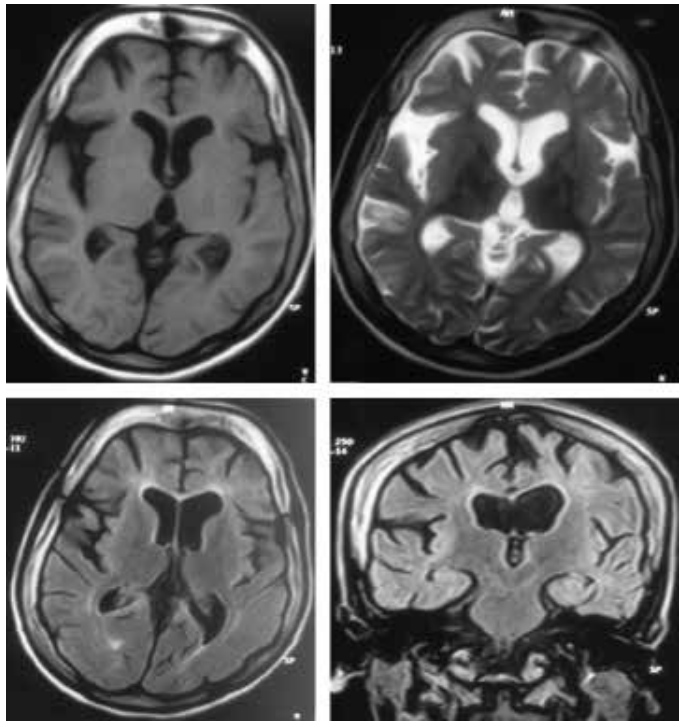

Figure 2. Cranial magnetic resonance imagining

Table 2. Information about, cranial magnetic resonance imaging, cerebrospinal fluid findings with antibody in serum and cerebrospinal fluid

Patients	EEG	Cranial MRI	CSF findings	Measles antibody (CSF)	Measles antibody (serum)
Patient 1	PGC	No intracranial pathology	Cell: None Glucose: 50 (85) Na: 142 Cl: 131 Protein: 32	IgM (-) IgG (+) 24.53 IU/ml	IgM (-) IgG 1/80 (+)
Patient 2	PGC	Intracranial cortical atrophy	Cell: None Glucose: 45(80) Na; 134 Cl: 121 Protein: 35	IgM (-) IgG (+) 1/80 (+)	IgM (-) IgG (+)
Patient 3	PGC	No specific finding other than cerebellar arachnoid cyst	Cell: None Glucose: 60 (106) Na: 130 Cl: 114 Protein: 42	IgM (-) IgG 6.0 (<0.5)	IgM (-) IgG 1/80 (+)

MRI: Magnetic resonance imagining, Na: Sodium, Cl: Chloride, IgM: Immunoglobulin M, IgG: Immunoglobulin G, PGC: Periodic generalized complex, CSF: Cerebrospinal fluid, EEG: Electroencephalograph

these 32 cases have been compared with 13 late-onset cases of SSPE reported by Singer et al. (7) in 1997, and 8 cases of late-onset SSPE reported by Tan et al. (8) in 1991. Prashanth et al. (6) found that late-onset cases progressed rapidly and had poor prognoses. In this present study, we report 3 cases of late-onset SSPE and our patients had similar prognoses (8).

Behavioral changes and decreased intellectual abilities can be observed in the absence of other neurologic signs and symptoms in the early phase of SSPE. Progressive deterioration in the academic performance of an affected child is usually reported by parents or teachers. These patients generally receive treatments at psychiatric clinics during this initial period. One of our patients was initially referred to us for consultation while he was an inpatient at a psychiatry clinic because of behavioral changes.

The most common symptoms of our patients were amnesia, behavioral changes, difficulty walking, loss of balance, difficulty holding up the head, and involuntary movements of the extremities. Although the most common presenting symptom reported in literature is behavioral changes, mild psycho-intellectual and behavioral changes might not always draw the attention of parents. Thus, patients generally seek treatment because of myoclonus. Two of our patienst had episodes of myoclonus from the time they presented to our clinic, whereas myoclonus developed during our investigations in the third case. Myoclonus was reportedly observed in 57.9% of patients by Cece et al. (9), whereas it was reported in 89.4% by Eroglu et al. (10).

A typical EEG pattern is usually present in the myoclonic phase and is almost sufficient for diagnosis. The EEG is characterized by bilateral, symmetrical, periodic, synchronized, high-voltage (200-500 mV) polyphasic bursts and stereotypical delta waves. It should also be noted that atypical EEG findings can be observed in SSPE, and it has been reported that typical patterns can be seen in EEG recordings made when such patients are given diazepam. This finding suggests that EEG recordings may be more sensitive for SSPE diagnosis when patients are taking diazepam (11).

MRI is a more sensitive method for detecting abnormalities in the white matter. Previous studies have reported that the clinical stage of SSPE is not correlated with MRI findings. Thus, it has been reported that cranial imaging methods cannot be employed to define the severity or prognosis of disease. However, Cece et al. (9) reported that in 50 out of 76 patients, MRI data revealed increased hyperintensity in the subcortex, periventricular areas, and the cortex; brain atrophy; and volume losses in the corpus callosum, basal ganglia and brainstem at different stages of SSPE.

The pathogenesis of SSPE remains unclear. Recent studies indicate that after the measles virus enters the human body, the structure of the virus begins to change. Structural changes in the M protein, which is formed as a result of a long-lasting latent period; glycoprotein (F), which causes membrane fusion; and hemagglutinin (H) have been observed in virus particles in the CNS (1,4). It has been demonstrated that the mutant virus develops as a result of these structural changes and can replicate in brain tissue via protein synthesis; it can then infect the brain, which lacks an immune system. Moreover, it has also been shown that the presence of antibodies against the virus before infection plays a role in SSPE. The prevalence of SSPE is higher in the following group of patients: patients who had measles infections before 2 years of age (maternal antibodies were present), patients who were vaccinated early, and patients who received intravenous immunoglobulins during infection (12). These data support the hypothesis that encountering antibodies against measles before encountering the virus itself may also play a role in the pathogenesis of SSPE. Two of our patients had measles infections before the age of 2 years. Mutant measles virus infects neurons primarily in the CNS. Secondary demyelination is then believed to occur as a result of oligodendroglial cells being affected; however, it is unknown how these cells are affected. The measles virus is believed to play a similar role in the etiology of multiple sclerosis (13). No definitive treatment is available for SSPE, but a variety of drugs and treatment methods have been used for many years. Isoprinosine and interferons in particular, have been demonstrated to prolong survival if they are administered long term. Spontaneous recovery is observed in 5-10% of cases and is reported very rarely in the literature (14).

Eroglu et al. (10) reported the results of their long-term follow-up of 19 adult patients with SSPE: among 9 patients treated with isoprinosine, 1 patient (11.1%) was stable, 1 (11.1%) was progressing, and 7 (77.7%) patients died. The other 10 patients were given both isoprinosine and intraventricular interferon; 2 (20%) of these patients were stable, 1 (10%) was progressing, and 7 (70%) patients died (10). All of our patients received isoprinosine treatment; 1 patient died 13 months after diagnosis, while still receiving the drug. One patient is still under follow-up at 20 months, and the third is in the 3rd month of follow-up.

SSPE should be considered when CNS involvement is present in rapidly-progressive, late-onset disease in adults that may be attributable to diseases of childhood and early adulthood because the number of reported cases of SSPE has recently exhibited an increasing trend.

Informed Consent: Aylin Bican Demir, İbrahim Bora, **Concept:** Aylin Bican Demir, **Design:** Aylin Bican Demir, **Data Collection or Processing:** Aylin Bican Demir, İbrahim Bora, **Analysis or Interpretation:** Aylin Bican Demir, İbrahim Bora, **Literature Search:** Aylin Bican Demir, **Writing:** Aylin Bican Demir, **Peer-review:** Externally peer-reviewed, **Conflict of Interest:** No conflict of interest was declared by the authors, **Financial Disclosure:** The authors declared that this study has received no financial support.

References

1. Erturk O, Karslıgil B, Cokar O, Yapici Z, Demirbilek V, Gurses C, Yalcinkaya C, Gokyigit A, Direskeneli GS, Yentur S,Onal E, Yilmaz G, Dervent A. Challenges in diagnosing SSPE. Childs Nerv Syst 2011;27;2041-2044.
2. Mahadevan A, Vaidya SR, Wairagkar NS, Khedekar D, Kovoor JM, Santosh V, Yasha TC, Satishchandra P, Ravi V,Shankar SK. Case of fulminant-SSPE associated with measles genotype D7 from India: an autopsy study. Neuropathology 2008;28;621-626.
3. Risk WS, Haddad FS. The variable natural history of subacutes clerosing panencephalitis: a study of 118 cases from the Middle East. Arch Neurol 1979;36;610-614.
4. Frings M, Blaeser I, Kastrup O. Adult-onset subacute sclerosing panencephalitis presenting as a degenerative dementia syndrome. J Neurol 2002;249:942-943.

5. Zilber N, Rannon L, Alter M, Kahana E. Measles, measles vaccination, and risk of subacute sclerosing panencephalites (SSPE). Neurology 1983;33;1558-1564.
6. Prashanth LK, Taly AB, Ravi V, Sinha S, Arunodaya GR. Adult onset subacute sclerosingpanencephalitis: clinical profile of 39 patients from a tertiary care centre. J Neurol Neurosurg Psychiatry 2006;77;630-633.
7. Singer C, Lang AE, Suchowersky O. Adult-onset subacute sclerosing panencephalitis: case reports and review of the literature. Mov Disord 1997;12;342-353.
8. Tan E, Namer IJ, Ciger A, Zileli T, Kucukali T. The prognosis of subacute sclerosingpanencephalitis in adults. Report of 8 cases and review of the literature. Clin Neurol Neurosurg 1991;93;205-209.
9. Cece H, Tokay L, Yildiz S, Karakas O, Karakas E, Iscan A. Epidemiological findings and clinical and magnetic resonance presentations in subacute sclerosing panencephalitis. J Int Med Res 2011;39;594-602.
10. Eroglu E, Gokcil Z, Bek S, Ulas UH, Ozdag MF, Odabasi Z. Long-term follow-up of patients with adult-onset subacute sclerosing panencephalitis. J NeurolSci 2008;15;275:113-116.
11. Praveen-kumar S, Sinha S, Taly AB, Jayasree S, Ravi V, Vijayan J, Ravishankar S. Electroencephalographic and imaging profile in a subacute sclerosing panencephalitis (SSPE) cohort: a correlative study. Clin Neurophysiol 2007;118;1947-1954.
12. Seki F, Yamada K, Nakatsu Y, Okamura K, Yanagi Y, Nakayama T, Komase K, Takeda M . The SI strain of measles virus derived from a patient with subacuteC sclerosing panencephalitis possesses typical genome alterations and unique amino acid changes that modulate receptor specificity and reduce membrane fusion activity. Virol 2011;85;11871-11882.
13. Owens GP, Gilden D, Burgoon MP, Yu X, Bennett JL. Viruses and multiple sclerosis. Neuroscientist 2011;17; 659-676.
14. Imataka G, Nakagawa E, Yamanouchi H, Arisaka O. Drug-indiced aseptic meningitis: development of subacute sclerosing panencephalitis following repeated intraventricular infusion therapy with interferon alpha/beta. Cell Biochem Biophys 2011;61;699-701.