

Atypical presentations of SSPE: a clinical study in four cases

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Subacute sclerosing panencephalitis (SSPE) is a progressive, fatal disease of the central nervous system caused by a persistent measles virus. It is clinically characterized by insidious onset of intellectual deterioration and behavioral changes followed by myoclonias and eventually complete neurologic deterioration. The diagnosis is based on characteristic clinical features, periodic electroencephalography (EEG) complexes of high slow waves and increased antibody titer against measles in cerebrospinal fluid. Here, we report four SSPE cases, two of whom manifested with hemiparesis; in the third and fourth cases, cerebellar ataxia and acute encephalopathy with focal seizures were the presenting symptoms at the onset of disease, respectively. The typical periodic EEG complexes in our patients led to the diagnosis of SSPE. Our findings show that SSPE should be considered in the differential diagnosis of hemiparesis, cerebellar ataxia and acute encephalopathy, and highlight the diagnostic significance of EEG in unidentified cases.

Key words: subacute sclerosing panencephalitis, hemiparesis, ataxia, encephalopathy.

Subacute sclerosing panencephalitis (SSPE) is a progressive inflammatory and degenerative disorder of the central nervous system¹⁻³. It is caused by mutant measles virus with altered M protein, probably leading to persistent viral infection⁴. An initial subtle mental deterioration and behavioral changes followed by myoclonic jerks and eventual significant motor and mental disability constitute the characteristic clinical picture of SSPE. However, it may show variability, and SSPE can also present with unusual features like visual loss, signs of increased intracranial pressure, epileptic seizures, or focal neurologic deficits¹⁻³. The typical electroencephalography (EEG) pattern is characterized by periodic complexes of bi-, tri-, or polyphasic high amplitude delta waves that are not suppressed by intravenous diazepam. They can often be demonstrated only after diazepam administration in awake EEG. A high titer of anti-measles IgG in cerebrospinal fluid (CSF) is diagnostic for SSPE¹⁻³. Here, we present four cases of SSPE presenting with unusual features. Clinical features, EEG and cranial magnetic resonance imaging (MRI) findings are discussed.

Case Reports

Case 1

A five-year-old boy was brought to our hospital because of progressive right-sided weakness, slurred speech and diminished alertness during the preceding one month. He had normal mental and motor developmental milestones. He experienced measles infection at the age of three years. Neurological examination showed confusion, left-sided hemiparesis with increased deep tendon reflexes, increased muscle tone in the left upper and lower extremities and left extensor plantar response. Cranial MRI was normal. Laboratory investigations including tandem mass screening, blood lactate and ammonia revealed no abnormality. CSF examination showed no cells, and normal protein (34 mg/dl) and glucose (53 mg/dl). Awake EEG exhibited abnormal background activity with medium voltage-slow waves in the left fronto-central regions, theta waves in bilateral occipital regions and periodic high voltage slow waves with higher amplitude in the left brain regions (Fig.1a). EEG after diazepam injection showed similar periodic

complexes of high voltage slow waves (Fig.1b). Serum and CSF anti-measles antibodies by complement fixation were increased to 1/16 (normal: 1/4 or lower) and 1/512, respectively. Inosiplex, interferon beta and carbamazepine were given, but mental and motor functions deteriorated, leading to death in the 7th month of follow-up.

Case 2

A seven-year-old boy was admitted with progressive weakness of right-sided extremities of 2.5-months duration, memory disturbances and atonic seizures of 1.5-months duration. He was born after a normal pregnancy and delivery and had normal mental and motor milestones. He had measles infection at

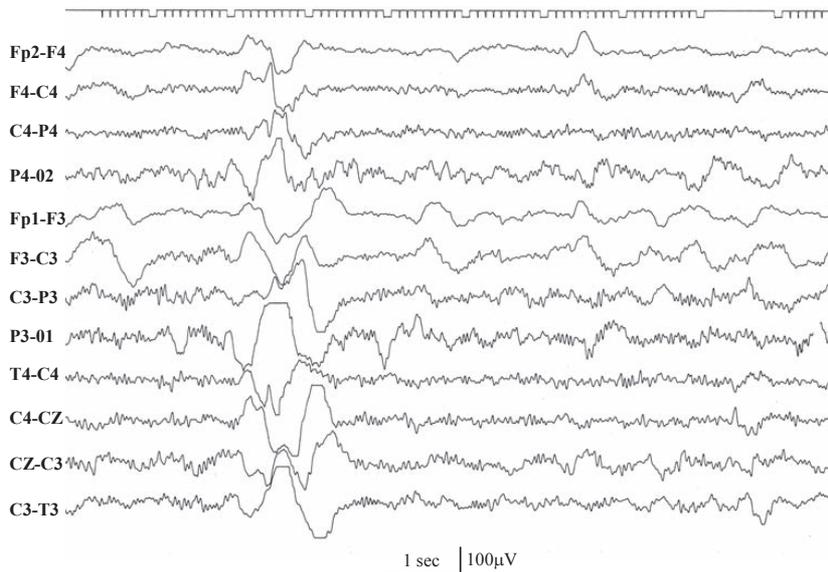


Fig. 1a. Awake EEG of Case 1, showing asymmetric periodic complexes, which are higher in amplitude on the left side, and slower background activity of the left hemisphere.

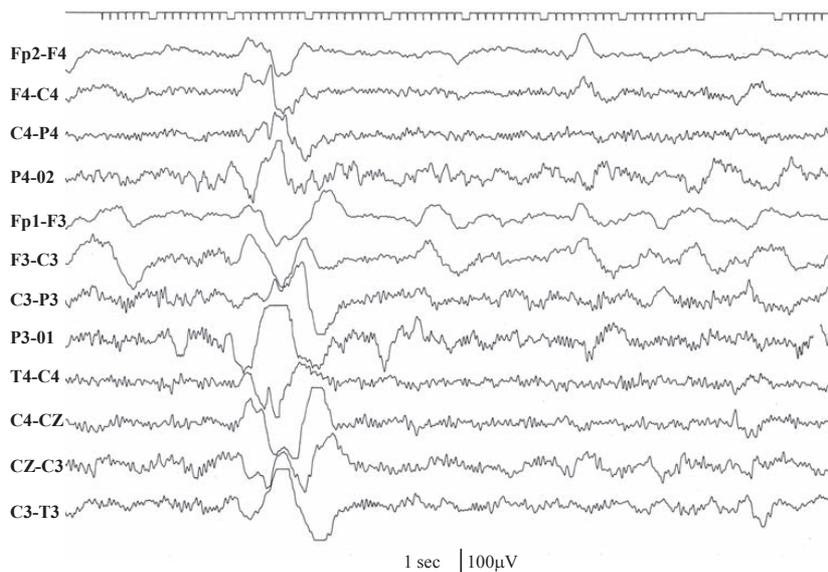


Fig. 1b. Awake EEG of Case 1 after diazepam administration, showing the asymmetry of the periodic complexes.

2.5 years of age. Neurological examination showed confusion and left-sided hemiparesis with increased deep tendon reflexes and muscle tone in the involved side. Laboratory investigations including tandem mass screening, blood lactate and ammonia were normal. CSF analysis revealed no cells, and normal protein (12 mg/dl) and glucose (64 mg/dl). Cranial MRI was normal. A routine awake EEG demonstrated paroxysms of generalized spike and multi-spike-slow wave activity and high voltage slow waves. EEG after diazepam injection revealed periodic generalized high voltage slow waves. Increased anti-measles antibody was detected in serum (1/256) and CSF (1/8) (normal: 1/4 or lower) by complement fixation. A treatment regimen consisting of inosiplex, interferon beta and carbamazepine was administered. His neurological status deteriorated in the following six months with the appearance of quadriparetic syndrome and extrapyramidal rigidity.

Case 3

A four-year-old boy was admitted with gait abnormality of one-week duration. He had normal mental and motor milestones. His past family history and medical history were negative except for measles infection at age two. Neurological examination showed truncal ataxia, wide-based gait, dysmetria, dysdiadochokinesia, nystagmus and intentional tremor in the hands. Laboratory investigations including tandem mass screening, blood lactate, ammonia, vitamin B₁₂ and E, folic acid, alpha fetoprotein, urine organic acid analysis and urine vanillylmandelic acid were within normal ranges. Cranial and spinal MRI and electromyography were normal. CSF examination showed no cells, and normal protein and glucose. Awake EEG showed background abnormality with high theta waves in the bilateral posterior regions. He was discharged with partial improvement of ataxia. Ataxia persisted to the 2.5-month follow-up when he had generalized tonic clonic seizures. At this time, EEG after diazepam injection showed periodic generalized high voltage slow wave complexes. Increased titers of anti-measles antibody in serum (1/512) and CSF (1/8) (normal: 1/4 or lower) were found by complement fixation. Inosiplex, interferon beta, carbamazepine and lamotrigine were administered, but he developed further mental deterioration, visual loss and dysphagia and expired seven months after the onset of the disease.

Case 4

This eight-year-old boy was referred to our hospital because of drowsiness, vomiting and focal motor seizures in the left arm and right hand. His motor and mental development had been normal. He had no history of measles infection. Neurological examination showed stupor, papilledema and increased muscle tone in the right upper and lower extremities. Cranial MRI showed meningeal contrast enhancement, narrowing of the frontal horns of the lateral ventricles and loss of cortical sulci due to cerebral edema in the frontoparietal regions (Fig. 2). Lumbar puncture revealed no cells,



Fig. 2. T1-weighted cranial MRI of Case 4 showing meningeal contrast enhancement, narrowing of the frontal horns of the lateral ventricles and loss of cortical sulci due to cerebral edema.

and normal protein (15 mg/dl) and glucose (68 mg/dl). Acetazolamide and dexamethasone were administered. Laboratory investigations including tandem mass screening, serum lactic acid, and ammonia was normal. Polymerase chain reaction (PCR) analysis for echovirus, Epstein-Barr virus, adenovirus, herpes simplex virus and tuberculosis in serum and CSF gave negative results. In the fourth day of hospitalization, myoclonias involving the right arm appeared. EEG showed bursts of high slow waves and high amplitude generalized rhythmic 3- to 4-Hz spike-wave discharges followed by intervals of electro-decremental activity (Fig. 3a). A repeat EEG after diazepam injection showed the persistence of high slow waves associated with spike-wave activity while generalized rhythmic spike-wave activity significantly decreased (Fig. 3b). Increased

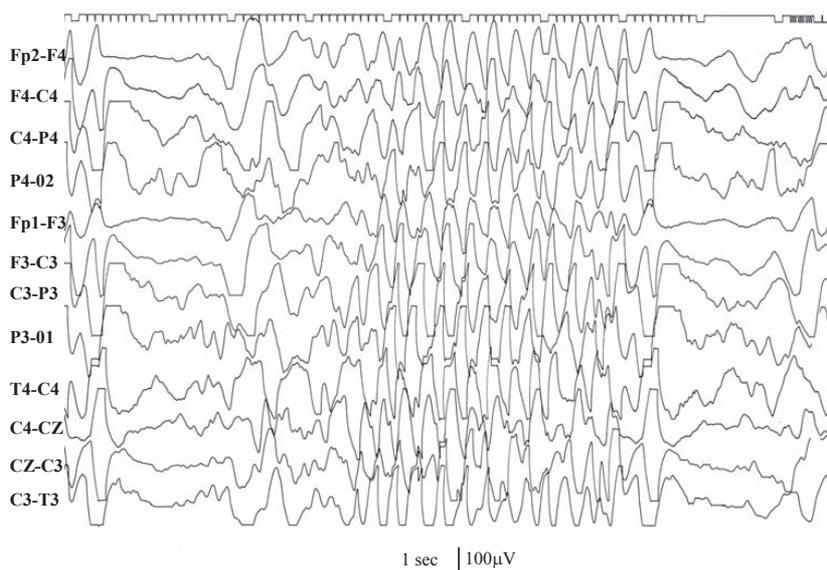


Fig. 3a. Awake EEG of Case 4 showing the bursts of generalized high amplitude slow waves and rhythmic spike-wave activity followed by electro-decremental periods.

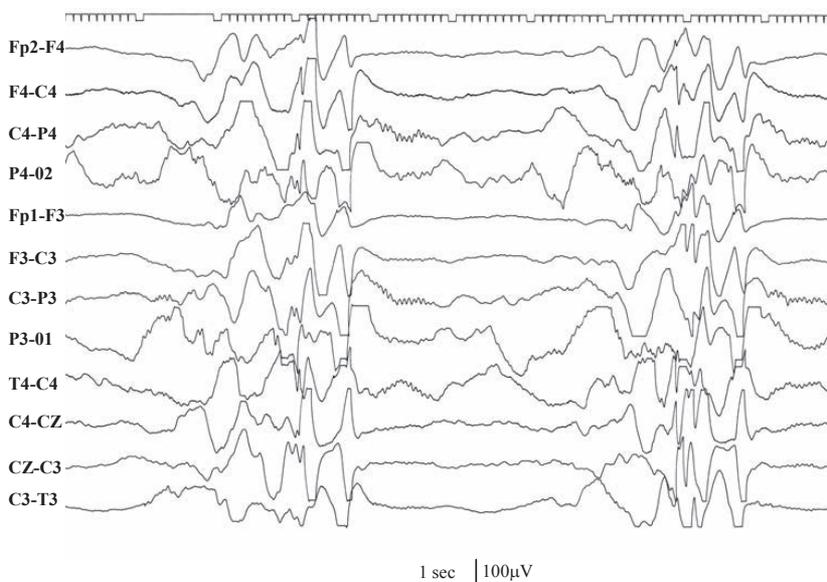


Fig. 3b. EEG of Case 4 after diazepam injection showing delta waves and spike-wave discharges.

titers of measles specific antibody in serum (1/512) and CSF (1/32) (normal: 1/4 or lower) were found by complement fixation. Inosiplex, interferon beta, carbamazepine and clonazepam were administered. He died 2.5 months after the onset of the disease.

Discussion

Our patients displayed unusual clinical features of SSPE including hemiparesis, ataxia or acute encephalopathy at onset of the disease.

Subacute sclerosing panencephalitis rarely presents with unilateral neurological deficits in childhood. Hemiparesis was the leading symptom in two of the patients (Cases 1 and 2). A stroke-like onset of SSPE, characterized by hemiplegia, usually associated with aphasia and epileptic seizures, was previously described in several children⁵⁻⁸. Histopathological study of a hemiplegic SSPE patient showed perivascular cuffing and intimal thickening of the small arteries with resultant occlusion and occasional

recanalization in the brain, considering vascular involvement⁶. Cortical atrophy and subcortical white matter involvement were also shown in cranial imaging studies of some SSPE patients with hemiparesis^{7,8}. Cranial MRI of our two patients were normal, excluding cerebral infarction or hemorrhage.

Another patient (Case 3) manifested with acute cerebellar ataxia. Other causes of cerebellar ataxia like infection, neoplasms, postinfectious ataxia, intoxication, and metabolic and degenerative disorders were excluded by cranial MRI and other appropriate laboratory studies. Acute cerebellar ataxia occurs very rarely as the initial symptom of SSPE⁹. His ataxia was progressive and associated with disturbed background activity on EEG. Interestingly, the symptom of another SSPE case with ataxia improved initially with methylprednisolone, but was followed by rapid deterioration⁹. We also observed partial recovery of the ataxia for a short period in our patient without any treatment. Such spontaneous partial or complete remissions may occur during the course of SSPE³, which may account for false beneficial effects of coincidentally administered drugs.

Subacute sclerosing panencephalitis shows fulminant clinical presentation in approximately 10% of the patients¹⁰. It may cause acute encephalopathic disease¹⁻³. Case 4 presented with decreased consciousness, partial seizures and findings of increased intracranial pressure, mimicking acute encephalitis. MRI abnormalities like contrast enhancement and cerebral edema also strengthened this possibility. However, the patient did not have pleocytosis in the CSF. Periodic EEG complexes and appearance of myoclonias allowed us to differentiate SSPE. This patient exhibited an advanced clinical stage of SSPE at the beginning of the disease course. SSPE with acute fulminant onset leads to death within three months of the diagnosis. The exact mechanism underlying rapidly progressive clinical course of SSPE is not known¹. Steroid administration is observed to accelerate the course of SSPE (Anlar et al. unpublished observation). Steroid treatment for brain edema might also have contributed to the early appearance of myoclonias in our patient.

The diagnosis of SSPE was established by the demonstration of characteristic periodic EEG complexes in all of the patients. Periodic complexes generally appear in early stages.

They are frequently generalized, but can also be focal or unilateral¹¹. The presence of functional cerebral cortex and subcortical white matter has been suggested to be necessary for the expression of periodic complexes; damage to these structures could prevent the appearance of periodic complexes^{11,12}. However, one of our patients (Case 1) demonstrated asymmetrical periodic complexes with higher amplitude of the slow waves in the more severely involved cerebral hemisphere contralateral to the hemiparesis. Awake EEG of Case 4 also showed an unusual abnormality characterized by bursts of periodic complexes consisting of high slow waves and generalized spike-slow wave activity followed by electro-decremental intervals. Burst of generalized spike-slow wave activity might represent severe cortical and subcortical involvement¹¹.

Magnetic resonance imaging abnormalities of SSPE include variable cortical atrophy, ventricular enlargement and white matter changes^{13,14}. However, MRI findings are not correlated with the clinical features at the early stages of SSPE. It could even be normal in the first year of the disease¹⁴. In our patients, cranial MRI investigations were not helpful in the diagnosis of SSPE. Contrast enhancement and cerebral edema in Case 4 were the only MRI abnormalities determined in our patients. Contrast enhancement can rarely be seen in SSPE. It does not correspond to a certain clinical type or stage of SSPE¹³. Cerebral edema with local mass effect was also described in several SSPE patients, which was suggested to indicate an early or active disease¹³.

In conclusion, our cases showed that SSPE should be included in the differential diagnosis of hemiparesis, acute cerebellar ataxia with progressive nature, and acute unidentified encephalopathy. An EEG with diazepam injection could be distinctive for SSPE, revealing the periodic complexes even before the appearance of other typical features.

REFERENCES

1. Garg RK. Subacute sclerosing panencephalitis. *Postgrad Med J* 2002; 78: 63-70.
2. Öztürk A, Gurses C, Baykan B, Gökyiğit A, Eraksoy M. Subacute sclerosing panencephalitis: clinical and magnetic resonance imaging evaluation of 36 patients. *J Child Neurol* 2002; 17: 25-29.
3. Anlar B. Subacute sclerosing panencephalitis. Diagnosis and drug treatment options. *CNS Drugs* 1997; 7: 111-120.

4. Hirano A, Ayata M, Wang AH, Wong TC. Functional analysis of matrix proteins expressed from cloned genes of measles virus variants that cause subacute sclerosing panencephalitis reveals a common defect in nucleocapsid binding. *J Virol* 1993; 67: 1848-1853.
5. Tamari H, Matsukura M, Matsuda I, Ueda K, Ohtsuka H. An acute variant of subacute sclerosing panencephalitis: an autopsy case report. *Brain Dev* 1981; 3: 87-91.
6. Imai M, Hamano S, Noda Y, Nara T, Ogawa Y, Maekawa K. Fulminant subacute sclerosing panencephalitis: clinical and neuropathological observations. *No To Hattatsu* 1997; 29: 494-499.
7. Dimova P, Bojinova V. Subacute sclerosing panencephalitis with atypical onset: clinical, computed tomographic, and magnetic resonance imaging correlations. *J Child Neurol* 2000;15: 258-260.
8. Ozyurek H, Degerliyurt A, Turanli G. Subacute sclerosing panencephalitis presenting with hemiparesis in childhood: case report. *J Child Neurol* 2003; 18: 363-365.
9. Bobele GB. Subacute encephalopathy in a 5-year-old boy. *Semin Pediatr Neurol* 1999; 6: 168-171.
10. Risk WS, Haddad FS. The variable natural history of subacute sclerosing panencephalitis: a study of 118 cases from the Middle East. *Arch Neurol* 1979; 36: 610-614.
11. Markand OM, Pasnzi JG. The electroencephalogram in subacute sclerosing panencephalitis. *Arch Neurol* 1975; 32: 719-726.
12. Santoshkumar B, Radhakrishnan K. Periodic electroencephalographic pattern in subacute sclerosing panencephalitis modified by preexisting damaged cerebral hemisphere. *Electroencephalogr Clin Neurophysiol* 1996; 99: 440-443.
13. Anlar B, Saatçi I, Kose G, Yalaz K. MRI findings in subacute sclerosing panencephalitis. *Neurology* 1996; 47: 1278-1283.
14. Brismar J, Gascon GG, von Steyern KV, Bohlega S. Subacute sclerosing panencephalitis: evaluation with CT and MR. *AJNR Am J Neuroradiol* 1996; 17: 761-772.