ORIGINAL ARTICLE

Subacute Sclerosing Panencephalitis : Clinical and Laboratory Manifestations

by

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Abstract

We reviewed clinical and laboratory findings of 12 cases of Subacute sclerosing panencephalitis (SSPE) hospitalized at our department from 1985 to 1991. All cases were diagnosed and hospitalized at the 2nd stage. The principal clinical manifestations were mental changes, myoclonus, and frequent falls. Other clinical manifestations were ocular changes, involuntary movements, loss of social contact, and spasticity. Diagnosis was based on suppression-burst pattern in EEG and positive antibody titer to measles in serum and cerebrospinal fluid. CT scan was not diagnotic, since it was either normal or showed only non-specific cortical atrophy. Eleven patients (91, 7%) recalled a history of measles in the past. Age of onset of SSPE varied among cases and was difficult to specify precisely due to its subtle nature. None of the cases had been vaccinated against measles.

SSPE is a rare disease, but is almost always fatal with prolonged suffering of the patient. Based on our experience with SSPE patients, we recommend to broaden the immunization programme against measles.

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Introduction

Subacute sclerosing panencephalitis, (SSPE) is a rare degenerative disease of the central nervous system in children and adolescents, which is usually fatal (1,2,3). Measles virus has been the suspected agent which causes SSPE based on electron microscopic examination which showed paramyxovirus particles in the brain (4), positive antibody titer to measles in serum and cerebrospinal fluid, measles antigen in the cerebral cortex (1) and successful isolation of measles virus in the brain of the patients (5,6).

Several complications of measles are well known such as diarrhea, bronchopneumonia, and encephalitis (7). On the contrary, SSPE as one of the worst complications is not well known. In this paper we report clinical and laboratory manifestations of SSPE patients hospitalized in our hospital between January 1985-March 1991.

Materials and methods

This is a retrospective study done by studying the medical records of SSPE patients who were hospitalized at the Department of Child Health, Dr. Cipto Mangunkusumo General Hospital between January 1985-March 1991. We studied history of measles infection, history of immunization against measles, and clinical manifestations. EEG was performed in every patients and was reviewed. CT scan was performed in several patients and we reviewed the results. Because of technical difficulties and financial reasons, antibody titer to measles was only performed in some of the patients, Immunoglobulin G examination was done in only 1 patient.

Results

Number of patients

In seven years period there were 12 cases of SSPE, with 1 to 3 patients admitted annually. No increase or decrease in the number of patients every year was observed (Table 1). Boys were more often affected than girls with a ratio of 5:1.

Table 1. *Annual distribution according to age and sex of 12 patients with SSPE at the Dept. of Child Health, Dr. Cipto Mangunkusumo Hospital, Jakarta*

Year	Boys	Girls	Number of Patients
1985	1	1	2
1986	1	-	1
1987	1	1	2
1988	3	-	3
1989	1	-	1
1990	2	-	2
1991	1		1
Total	10	2	12

Table 2. *Sex, age, and age of onset of SSPE patients*

No	Name	Sex	Age (years)	Age of onset (years)
1.	C	M	12	10
2.	A	M	11	10 6/12
3.	ODS	M	5	3
4.	SE	F	5 10/12	5 7/12
5.	T	M	5 6/12	5 5/12
6.	D	M	7 4/12	6 6/12
7.	HS	M	11	10 8/12
8.	CM	F	6 6/12	5 6/12
9.	DA	M	8	7 5/12
10.	NH	F	9 6/12	9 5/12
11.	AS	M	4 6/12	4 4/12
12.	F	M	10	9 6/12

Age of patients and age of onset

The age of the patients at the time of diagnosis was between 4-12 years. Age of onset varied between 3-10 years (Table 2). If we looked carefully at the age of onset, there were 2 peaks, i.e. between 9-10 years of age in 5 cases (41,7%) and 3-5 years in 5 cases (41,7%).

Table 3. *History of measles, age of measles, and immunization against measles in SSPE patients*

No	Name	History of measles infections	Age at measles infection	Immunization against measles
1.	C	+	Forget	_
2.	A	+	Forget	_
3.	ODS	+	1	_
4.	SE	+	1	_
5.	T	+	1	_
6.	D	+	1	_
7.	HS	+	Forget	_
8.	CM	_	_	_
9.	DA	+	forget	_
10.	NH	+	2	_
11.	AS	+	1	_
12.	F	+	2	_

History of measles, and immunization against measles

Eleven patients (91,7%) suffered from measles in the past, 4 out of them did not remember the age when they suffered from measles. None of the cases had had immunization against measles (Table 3). It was difficult to know the interval between measles and onset of SSPE.

Clinical manifestations

Only one patients was referred with a correct diagnosis by a pediatric neurologist. Other patients were referred because of deterioration, psychiatric illness, epilepsy, paresis, or only with description of manifestations such as confused speech, unable to walk, frequent falling, or frequent jerks.

In the beginning of the illness, all patients sought medical help because of frequent jerks and frequent falling. Onset began with change in behavior, and intellectual deterioration. They showed irritability, aggression, were easily upset, negativistic attitude, refusal to involve in a social events, learning difficulty, and declining of school performance. Loss of social contact was found in 5 patients (41,7%); in 4 patients it was seen in the first examination while one showed deterioration two months after the initial examination.

Extrapyramidal signs such as involuntary movements was found in 11 patients (91,7%) while spasticity as a pyramidal sign was detected in 7 patients (58,3%). Ocular disturbance was seen in 4 patients (33,3%), i.e. papil atrophy accompanied by visual disturbances, conjugate deviation of the eyeballs, nystagmus, and macular lesion each in 1 patients.

Table 4. *Clinical manifestations of SSPE patients*

No	Patient	Mental changes	Social contact	Myo clonus + falling	Involuntary movements	Ocular disturbance	Paresis
1.	C	Yes	Good	Yes	Yes	Papil atrophy visual disturbance	Yes
2.	A	Yes	Poor	Yes	Yes	Papil atrophy Macular lesion	Yes
3.	ODS	Yes	Poor	Yes	Yes	Papil atrophy Nystagmus	Yes
4.	SE	Yes	Good	Yes	Yes	Normal	No
5.	T	Yes	Poor	Yes	Yes	Normal	Yes
6.	D	Yes	Good	Yes	Yes	Normal	Yes
7.	Hs	Yes	Poor	Yes	Yes	Normal	Yes
8.	CM	Yes	Good	Yes	Yes	Papil atrophy Conjugate deviation	No
9.	DA	Yes	Poor	Yes	Yes	Normal	Yes
10.	NH	Yes	Good	Yes	No	Normal	No
11.	AS	Yes	Good	Yes	Yes	Normal	No
12.	F	Yes	Good	Yes	Yes	Normal	No

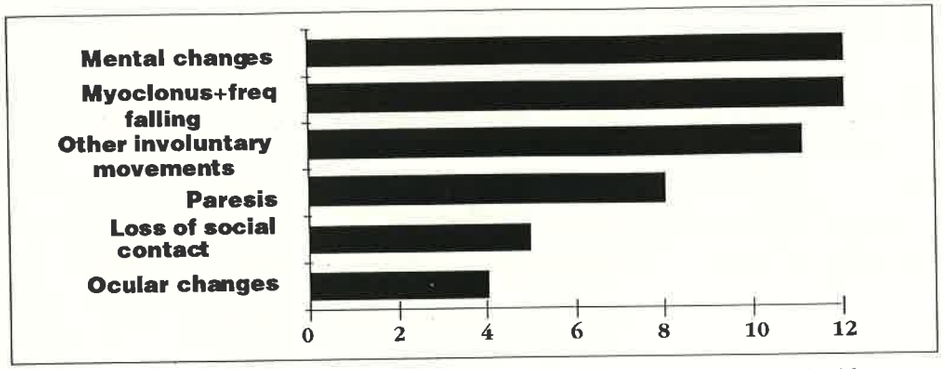

Figure 1. *Clinical manifestations of SSPE patients in the Dept. of Child Health, Dr. Cipto Mangunkusumo Hospital, Jakarta 1985 -1991*

Table 5. *Laboratory findings of SSPE Patients*

No	Name	Measles antibody		Immunoglobulin-G	
		Serum	CSF	Serum	CSF
1	C	1/512	1/64	-	25,8
2	A	1/512	-	-	-
3	ODS	1/32	-	-	-
4	SE	-	-	-	-
5	T	1/8	-	-	-
6	D	1/160	1/40	1680	218,7
7	HS	1/160	1/20	-	-
8	CM	1/640	1/80	-	-
9	DA	1/160	1/20	-	-
10	NH	1/160	1/80	-	-
11	AS	1/160	1/40	-	-
12	F	1/80	1/20	-	-

- Not done

Antibody titer against measles and immunoglobulin G

Antibody titer to measles was examined in the sera of 11 patients and in the cerebrospinal fluid of 8 patients. All showed a positive result. In 2 serum examinations we found a low titer of antibody, 1:32 and 1:8 each. Unfortunately the examination of antibody titer in the cerebrospinal fluid in those 2 patients was not performed (Table 5). Examination of immunoglobulin G (IgG) titer was performed in the serum of 1 patient and in cerebrospinal fluid of two patients and showed a significant increase (Table 5).

Table 6. *Electroencephalographic and CT scan findings of SSPE patients*

No	Name	EEG	CT scan
1	C	S-B pattern	Normal
2	A	S-B pattern	-
3	ODS	S-B pattern	-
4	SE	S-B pattern	-
5	T	S-B pattern	Normal
6	D	S-B pattern	-
7	HS	S-B pattern	Normal
8	CM	S-B pattern	Cortical atrophy
9	DA	S-B pattern	cortical atrophy
10	NH	Slow spike-wave	-
11	AS	1. Diffuse slowing 2. S-B pattern	-
12	F	S-B pattern	-

Electroencephalographic examination was performed in all patients. Eleven patients (91,7%) showed suppression-burst pattern while one patient showed slow spike-wave pattern (Table 6). One patient, AS, showed diffuse slowing in the beginning of illness which then developed suppression-burst pattern.

CT scan was performed in only 5 patients. Two out of them showed cortical atrophy while the other three showed normal CT scans (Table 6).

Diagnosis

In 10 patients (83,3%) diagnosis was made based on clinical manifestations, typical EEG pattern, and positive serum and cerebrospinal fluid antibody titer against measles. In the other 2 patients, diagnosis was based only on clinical manifestations and typical EEG pattern because serum antibody titer was low while cerebrospinal fluid antibody titer not examined.

Discussion

Many hypotheses have been proposed to look for the relationship between measles infection and SSPE (3). Measles virus consists of several proteins, each of which can cause different antibody responses. Those proteins are L (large), H (hemagglutinin), P (phosphoprotein), NP (nucleocapsid), FO (fusion), A (actin), M (matrix) protein. The first four proteins cause transcription, absorption, neutralization, and virion structure. FO cause fusion, a method of replication. The effect of A protein has not been discovered. The function of M protein is to join intracellular viral nucleocapsid with the cytoplasmic membrane, an important process before budding or vesicle formation can occur. Vesicle formation is an effective

way of viral replication and can cause spreading of the virus into its environment and attacks other cells.

Normal measles virus which has all the 7 proteins is called as lytic. Non-lytic virus, which is also known as persistent virus, lose several of the proteins. If M protein is deficient, vesicle formation cannot occur and the only way to replicate is via fusion, a primitive process of replication. Transmission to other cells occur via melting between 2 cells. In SSPE patients, there are increase of antibody to all of the measles proteins except to M protein (3).

If a person is genetically susceptible, an incomplete response occurs when he is attacked by measles virus. Only M protein is destroyed, while other proteins persist. The virus will change its behavior from lytic to non-lytic and persists intracellularly, especially in the central nervous system. This virus has no contact with extracellular space because it can not perform vesicle formation. That virus is still alive and replication occurs slowly via fusion between one cell and another. The cells in the central nervous system are very close one to another, causing easy fusion. When the cell dies, the virus will escape to the extracellular space and causes increase of antibody titer to all measles proteins except protein M.

We have reported 9 out of these 12 patients before (8). It seems that SSPE is a rare disease. Jabbour et al. (2) found an incidence of 1:1.000.000 in children in USA between the year 1969-1970. Another study found 453 cases in USA between 1960-1976, so the estimated incidence is 3,5 for every 10 million of population less than 20 years old every year (9). There is a male preponderance. Jabbour et al. (2) reported 3,3:1 male to female ratio while Modlin et al. (9) reported 2,3:1 male to female ratio. This sex preponderance tends to be less obvious in older age groups (8).

The reported age of onset varied between 1-32 years with a median of 9 years, 85% out of them were between 5-14 years of age (10). The subtle clinical manifestations in the beginning of illness cause difficulties in determining the age of onset. We found that it was difficult for the parents to recall the exact age of measles infection. Eleven patients (91,7%) suffered from measles, as recalled by parents. Modlin et al. (10) estimated that 5,2 to 9,7 cases of SSPE will occur in every 1 million measles patients. History of measles infections can be elicited in 93.3% of SSPE patients. Most of them suffered from measles at the young age, 46% at less than 2 years old and 24% at less than 1 year old. Jabbour et al. (2) and Modlin et al. (10) found an interval of 5-7 years between measles infection and onset of SSPE. None of the patients had been vaccinated against measles. It is still a controversial matter whether immunization against measles can cause SSPE. Modlin et al. (10) predicted the possibility of SSPE in 0.5-1.1 cases every 10.000.000 immunization. The latest hypothesis is immunization against measles will decrease the incidence of SSPE drastically (10).

This illness is characterized by mental changes and motoric dysfunctions which occur slowly, but progressively become worse with seizures, coma, emaciation, followed by death (10). Clinically there are 4 stages of SSPE :

Stage I

Neurological symptoms are caused by inflammation (irritation), necrosis (destructive) and gliosis (repair) in succession (3). In the beginning, the virus resides in cerebral cortex which

contains many neurons and glias, causing mild and non spesific polioencephalitic symptoms such as irritability, negativism, lethargy, malaise, dementia, difficulty in concentrating, decline of school performance, and personality changes. EEG examination will show diffuse slowing which is non specific (11). After several weeks to months, all the intellectual functions will be lost and the patient cannot speak anymore.

cause the origin is in the subcortex area, not in cerebral cortex. In this stage, the specific EEG changes known as suppression-burst pattern consist of slowing down of the normal rhythm with low voltage, interrupted by high voltage slow wave complexes preceded by sharp wave or spikes (Fig. 2). Those complexes occur periodically, paroxysmal, bilateral, synchronous every 3 to 30 second, lasting for 1-3 second. Those

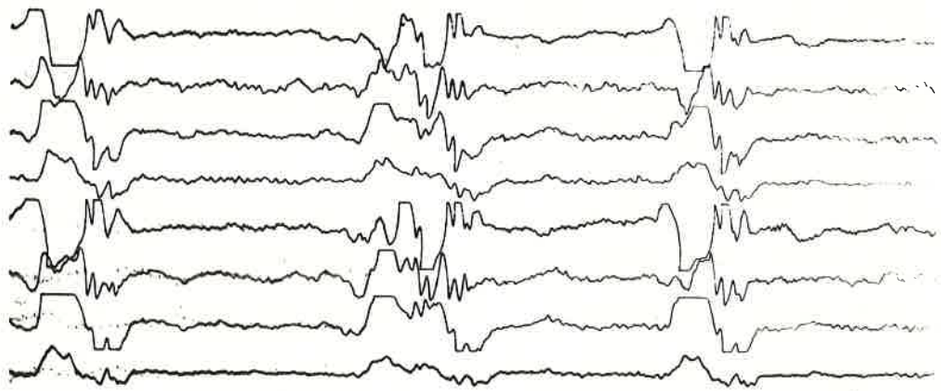

Figure 2. *Suppression burst pattern*

Stage II

The process will propagate rostrocaudally. Involvement of subcortical white matter will cause specific symptoms which are known as the 2nd stage. Extrapyramidal irritation will cause myoclonus and involuntary movements. The myoclonus occur repeatedly with short interval. The patien shows frequent falling and difficulty in walking. Other motoric dysfunctions occur because of the involvement of the long tracts. Myoclonus is not myoclonic epilepsy because complexes occur together with myoclonus attacks (11,12).

Stage III

Subcortical white matter is destroyed in this stage. Dementia, pyramidal and extrapyramidal signs become worse. The patient becomes immobile.

Stage IV

Permanent destruction of the central nervous system. The patient loses all functions of the central nervous sys-

tem. He is in vegetative state with spastic quadriplegic position (11,13). The time between onset of symptoms till death varied; usually the patient dies 6 months to 3 years after the onset (10).

It is interesting to find out the fact that SSPE is not a well-known condition, only one of our patients was referred with a correct diagnosis after seen by a pediatric neurologist. It is hardly possible indeed to make a correct diagnosis at the beginning of the illness because the clinical manifestations are very subtle. We have to think of the possibility of SSPE if a patient showed myoclonic jerks accompanied by frequent falling, especially if there is also deterioration of mental function. Ocular manifestations are common in SSPE patients (13). We found ocular lesions in 6 patients (50%) consisting of papil edema or papil atrophy, focal chorioretinitis in the macula, visual disturbance, nystagmus, and strabismus.

In measles patient without complications the serum antibody titer to measles is 1:260 in the acute phase and then decreases to 1:8 or 1:20 after 2-3 years. In SSPE patients, serum antibody titer to measles is higher, usually between 1:64-1:2048 or more, while the titer in the cerebrospinal fluid is between 1:8-1:64 (14,15). Horta-Barbosa et al. (16) stressed that detection of positive antibody to measles in the cerebrospinal fluid had a high diagnostic value. Negative antibody to measles in SSPE patient is very .. common but has been reported (17). Increase of cerebrospinal fluid gamma globulin has some values for diagnostic purpose, but this examination is not specific (12,15). This is not a standard examination, but can be performed in remote areas where the examination of antibody to measles cannot be performed.

Head CT scan in the beginning shows small ventricles with obliteration of sulci and interhemispheric fissures. Brain atrophy will develop later . Some patients may show normal. CT scan (13). Because of the low positive results in SSPE, CT scan is not a standard examination in our SSPE patient.

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