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CLINICAL AND LABORATORY FINDINGS IN A SERIES OF SUBACUTE SCLEROSING PANENCEPHALITIS*

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Subacute sclerosing panencephalitis (SSPE) is characterized by progressive neurologic symptoms like behavioral changes, intellectual deterioration, myoclonic attacks, vegetative state and death. The probability of spontaneous improvement is about 5 percent[1]. Laboratory methods such as EEG, cerebrospinal fluid (CSF) globulins, brain histopathology, measles antibodies in CSF, and computerized tomography (CT) support and confirm the diagnosis[2].

The relation of this disease to measles infection is well known and the incidence of SSPE has decreased in countries where vaccination against measles is widespread[2]. Since measles was common in Turkey prior to the large vaccination campaign in 1985, SSPE is still seen frequently in this country. The SSPE registry in Turkey has collected the data of 402 patients seen between the years 1975-1987. This paper summarizes the clinical and laboratory findings of this series which is one of the largest reported so far.

Material and Methods

The epidemiologic, clinical and laboratory data of patients diagnosed as SSPE in state hospitals, university hospitals and private offices were collected by the use of forms specially designed for computers. At least three of the following criteria were considered necessary for diagnosis:

- typical clinical presentation
- characteristic EEG pattern
- brain biopsy
- CSF globulin levels
- measles virus antibody titer 1/8 or higher in CSF

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A history of early measles infection (prior to two years of age) was present in most (65%) of the cases. The presenting signs and symptoms were recorded by the patient's physician. Clinical staging was done as previously described[2].

CSF protein and globulin levels were measured according to standard procedures. The other laboratory results reported in this study are only those performed or confirmed at Hacettepe University Faculty of Medicine Children's Hospital. Measles antibodies in CSF were measured by the complement fixation technique, using a microtiter system with 2 units of antigen (Whittaker, M.A. Bioproducts Inc., U.S.A.) and 4 Hemolytic dose 50. Serial dilutions of patient sera and CSF were made. Negative and positive controls for serum and CSF were tested together with patient samples. The results were evaluated as a reciprocal dilution of sample yielding 50 percent lysis of the hemolytic system[3]. EEGs were eight channel recordings using an international 10-20 electrode placement, and mono and bi-polar tracings. A periodic high-voltage slow wave pattern was taken as the "typical" EEG; generalized or focal spike or spike-and-wave activity or asymmetry in background bioelectric activity were classified as "other" EEG findings. The CT studies were performed with a Tomoscan 300 scanner. Children younger than seven years of age were sedated with oral trichlorethyl phosphate. In this age group, slices of six mm and in older children, slices of nine mm thicknesses were obtained. Contrast material was injected when necessary.

The brain biopsies were routinely obtained from the frontal gray and white matter. The material was processed according to standard techniques and stained with hematoxylin-eosin. They were classified as: 1) glial proliferation, inflammatory changes, demyelination and neuronal inclusion bodies; 2) glial and inflammatory changes and demyelination without inclusion bodies; 3) normal biopsy.

Results

There were 402 patients, 285 males and 117 females. The male/female ratio was 2.43. Their ages ranged between 3-24 years. The patients older than 20 years of age (seven patients) will be evaluated separately and their results are not included in this paper.

The duration of the illness varied from two to 72 months (mean 15 ± 11).

Clinical signs : The first symptoms of the illness are shown in Table I in order of frequency. Fifty-seven patients (14.4%) showed unusual signs or symptoms at presentation (Table II). In 23 of them, only the unusual symptom was present at the beginning. In the remaining 34 patients, the atypical manifestations accompanied the classical signs such as mental deterioration or myoclonus. Seven additional patients experienced a significant head trauma prior to neurological symptoms.

TABLE I: Initial Signs and Symptoms

	n*
Myoclonic jerks	108 (26.9%)
Mental deterioration + myoclonic jerks	71 (17.6%)
Mental deterioration	65 (16.2%)
Behavioral changes + mental deterioration + myoclonic jerks	55 (13.7%)
Behavioral changes + mental deterioration	31 (7.8%)
Behavioral changes	27 (6.7%)
Behavioral changes + myoclonic jerks	22 (5.3%)
Other (unusual) signs and symptoms	23 (5.8%)
	402

* case frequency

TABLE II: Initial Atypical Signs and Symptoms

	n*
Generalized seizure	17 (30 %)
Headache	11 (19 %)
Papilledema	9 (16 %)
Cerebellar signs	6 (10.5%)
Visual disturbances	3 (5 %)
Focal seizure	3 (5 %)
Hemiparesis	2 (3.5%)
Hemidystonia	2 (3.5%)
Chorioretinitis (unilateral)	2 (3.5%)
Neck stiffness	1 (2 %)
Vertigo	1 (2 %)
	57

* case frequency

The age range of these patients was between 4-17 years and the male female ratio was 2.66. These values did not differ from the patients presenting with the classical onset.

CSF studies : The CSF protein level was determined in 148 patients; it was normal in 122 (83%) and elevated in 26 (17%). The elevated protein levels varied between 54-96 mg/dl. In only one case it was found to be 402 mg/dl.

Measles antibody levels in CSF and serum are shown in Table III. In many cases of SSPE confirmed by other methods, measles antibodies were found to be at intermediate values such as 1/4 CSF and 1/16 or 1/64 in serum. In 19 patients, measles antibodies were low or intermediate in serum and high in CSF.

The tests were performed twice on seven patients. In two of them, the first titration was normal, but the second, done two or four months later, was elevated. The first and second results were the same in the other five patients.

Electroencephalography : Although all the patients had an EEG, only those whose recordings were satisfactory were evaluated (354 patients). The EEGs were obtained in Stages I, II or III. In 199 patients, diazepam was injected intravenously during the recording; an EEG tracing was obtained before, during, and five minutes after diazepam administration (This is a routine procedure in Hacettepe University Children's Hospital for suspected cases of SSPE). The blackground bioelectric activity was slow in most patients and the typical pattern (high-amplitude bursts and suppression periods) were observed in the majority (Table IV).

In 20 patients in whom the EEG was normal or showed only slowing of background activity, an EEG with diazepam was obtained. In 16 of them the pattern diagnostic of SSPE was observed after diazepam injection. Two of these patients were in Stage I, one was in Stage III and the others in Stage II.

Brain biopsy : The brain biopsies were performed in 17 patients in Stage II or III. The results are shown in Table V. Most of the specimens were found to be consistent with SSPE; inclusion bodies were seen in six.

Computerized tomography : The CT results are shown in Table IV. Normal scans and cortical atrophy were the most common findings.

TABLE III: Measles Antibodies, Complement Fixation

Titer in CSF	$< 1/4$	1/4	$\geqslant 1/8$
n = 70	5	24	41
Titer in serum	$\leqslant 1/8$	1/16 - 1/64	$\geqslant 1/128$
n = 68	2	44	22

TABLE IV: EEG Results

	Normal	Typical	Other	Total
Routine EEG - n (%)	11 (3.3)	312 (88)	31 (8.7)	354 (100)
EEG with diazepam-n (%)	3 (1.5)	188 (94.5)	8 (4)	199 (100)

TABLE V: Brain Biopsy Results

Stage Histopathology group	1	2	3
Stage II	3	6	–
Stage III	3	4	1

TABLE VI. Computerized Tomography (CT) Findings

	CT		
Stage	Normal	Cortical atrophy	Other*
Stage I	3	–	–
Stage II	26	6	8
Stage III	25	7	1
Total	54	13	9

* Hypodense areas in the occipital white matter (five cases), brain edema (two cases), and hypodense area in a parietal lobe (two cases).

Discussion

In general, the clinical course of SSPE starts with intellectual deterioration followed by myoclonic jerks, progresses with dementia, vegetative dysfunction, spasticity, coma and death. Besides this well-known presentation, unusual manifestations can occur either alone or associated with classical signs and symptoms[1] and may lead to erroneous diagnosis. In our series, the proportion of atypical signs and symptoms was 14 percent. In seven other patients, a recent trauma was present in the history and seemed to be related to the symptoms. Headache and papilledema occurred together or separately. In our series they were observed together in five patients in whom intracranial tumors were suspected on admission. Although seizures can occur at any stage in SSPE[2,4],

major seizures as initial symptoms usually lead to a diagnosis of epilepsy, as was the case in our patients presenting with a generalized seizure as the initial symptom. Asymmetric findings on neurological examination can also suggest diagnoses other than SSPE. Eye findings, when present in SSPE, are described as chorioretinitis, and, less frequently, nystagmus, papilledema, and optic atrophy[5]. We observed that papilledema was not unusual. Begeer et al[6] have described visual impairment as an early sign and reported associated parietooccipital abnormalities in EEGs[6].The EEGs of our three patients with visual complaints showed no posterior abnormalities; they were typical for SSPE. Although SSPE usually starts with psycho-intellectual symptoms[1], in our series, however, this was not the most frequent. The reason may be that at least in some patients, this stage may be overlooked by parents or attributed to other causes. In three patients, previous neurologic illnesses were present; tuberous sclerosis, cerebral palsy and sequelae of tuberculous meningitis, respectively. In these patients, the first symptoms of SSPE were thought to be related to the previous neurologic situation.

In a recent review of the criteria in the diagnosis of SSPE, Dyken[2] has stressed the necessity of measuring measles antibodies and has proposed CT as an important diagnostic tool. During the 12-year period in which our patients were seen, the diagnostic criteria showed some changes. In the early years, clinical and EEG findings, a history of early measles infection, and brain biopsy, when possible, were required. Measles antibody titration became available in the last few years and gained importance in the diagnosis. EEG is a readily available method and has great practical value[7]. It was helpful in the diagnosis of most of our patients, especially when diazepam was administered intravenously during the recording. Lombroso[8] has emphasized the effect of diazepam on EEG abnormalities in SSPE. In 42 of our patients, most of whom were in Stage I of the disease, the EEG was normal or not typical for SSPE. In 20 of these cases, an EEG with diazepam was obtained and the characteristic pattern became obvious in 16 of them after the injection. In 15 others, a second EEG taken one or two months later was diagnostic. Sisk and Griffith[9] have reported normal EEGs in some SSPE patients even with moderately advanced (Stage I or II) disease. Among our cases with normal tracings, there were both Stage I and Stage II patients (7 and 4, respectively). Ibrahim and Jeavons[10] have reported unusual EEG findings in a significant proportion of proven SSPE cases.

The CT scans were normal in Stage I; an equal incidence of normal findings or atrophy were seen in Stages II and III. Uncommon CT findings like brain swelling, neovascularization or tissue breakdown have been described in SSPE[2]. We had nine such patients, all of whom were in Stage II. The clinical course of the cases with unusual CT findings were not different from the others.

Brain histopathology, although not advised routinely[2,11] is one of the important elements in diagnosis. Ohya et al[12] have reported that histopathologic features depend on the stage of the disease as well as on the area examined. In our series, repeated examinations of brain tissue were not possible. The biopsies were routinely taken from the frontal areas and in most cases were reported as compatible with subacute encephalitis. Inclusion bodies were seen in six patients. If more caudal (parietooccipital or brain stem) examinations had been performed, a higher yield could have been expected, since the disease affects the occipital areas and later involves the brain stem[12].

In our study, the complement fixation technique was the only method used for measles antibody titration. A titer of 1/8 or higher is considered necessary for the diagnosis. Of our 70 patients in whom this test was done, not all had high antibody levels. In all of these patients, the diagnosis was confirmed later by clinical course, biopsy, or a second antibody titration. The proportion of the patients with high antibody levels in CSF varies according to different methods. Gnehm et al[13] have advised the use of different techniques when necessary. Mandelbaum et al[14] have proposed a more sensitive radioimmunoassay for detecting decreased antibody response to M protein.

We can draw conclusions from our data that a considerable proportion of SSPE patients (14%) present with unusual signs and symptoms, either alone or associated with classical ones. In 12% a routine EEG may fail to suggest SSPE and in some of these an EEG with diazepam will show the typical pattern. Complement-fixation antibodies against measles in CSF are elevated in 58.5% of the patients. CT is found to be normal in most of Stage II and III patients while 15 to 20 percent show cortical atrophy.

Summary

Subacute sclerosing panencephalitis is a chronic neurologic disorder usually presenting with mental deterioration and myoclonus and progressing to coma and death. Measles antibodies in cerebrospinal fluid (CSF) and serum, EEG, histopathologic findings in brain and computerized tomography (CT) are important elements in diagnosis. In this paper, the clinical manifestations and laboratory findings of our series comprising 395 patients are reported. Myoclonus and mental deterioration were the most frequently observed symptoms. EEG, especially if diazepam is administered intravenously during the recording, is helpful in the diagnosis. Measles antibodies in CSF can be found at low levels even with advanced disease. Cortical atrophy or normal scan are the most frequent findings on CT.

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