Epidemiological Findings and Clinical and Magnetic Resonance Presentations in Subacute Sclerosing Panencephalitis

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Subacute sclerosing panencephalitis (SSPE) is a rare, progressive, inflammatory neurodegenerative disease. This study investigated the relationships of clinical stage with epidemiological and magnetic resonance imaging (MRI) findings in SSPE by retrospective review of 76 cases (57 male) diagnosed by typical periodic electroencephalographic features, clinical symptoms and elevated measles antibody titre in cerebrospinal fluid. Clinical stage at diagnosis was I or II in 48 patients, III in 25 and IV in three. Prominent findings at presentation were atonic/myoclonic seizures (57.9%) and mental deterioration with behaviour alteration (30.3%). Frequent MRI findings (13 – 32 patients) were subcortical, periventricular and cortical involvement and brain atrophy; the corpus callosum, basal ganglia, cerebellum and brainstem were less frequently involved. Five patients had pseudotumour cerebri. Cranial MRI at initial diagnosis was normal in 21 patients (19 stage I/II, two stage III/IV). Abnormal MRI findings were significantly more frequent in the later stages, thus a normal initial cranial MRI does not exclude SSPE, which should, therefore, be kept in mind in childhood demyelinating diseases even when the presentation is unusual.

KEY WORDS: SUBACUTE SCLEROSING PANENCEPHALITIS; MAGNETIC RESONANCE IMAGING; ELECTROENCEPHALOGRAM; EPIDEMIOLOGY

Introduction

Subacute sclerosing panencephalitis (SSPE) is a neurodegenerative disease of the central nervous system caused by defective measles virus. Its pathogenesis has not yet been established. The disease develops several years after measles infection and frequently presents with altered behaviour, myoclonus, mental deterioration, seizures, extrapyramidal dysfunction and abnormal vision. The occasional patient may show atypical signs, which can make the diagnosis of SSPE difficult. No curative treatment is available. Although complete or partial remission occurs occasionally, SSPE frequently results in death after several years.1 – 5

Cranial imaging studies have a limited role in the early diagnosis of the disease. During the early stages of SSPE, cranial computed tomographs are usually normal. Magnetic resonance imaging (MRI) is very
sensitive in diagnosing white matter abnormalities and early changes appear as high-intensity areas in the occipital or frontal subcortical white matter. The grey matter may remain intact even in later clinical stages.5–11

The aim of this study was to review MRIs and the clinical and epidemiological findings of SSPE cases diagnosed at Harran University Paediatric Neurology Clinic.

**Patients and methods**

**PATIENTS**
The records of patients diagnosed with SSPE at Harran University Paediatric Neurology Clinic between 2005 and 2009 were reviewed retrospectively.

**DIAGNOSIS AND CLINICAL FEATURES OF SSPE**
Diagnosis of SSPE was on the basis of typical clinical, electroencephalographic (EEG) and MRI findings of the disease and the presence of elevated measles antibody titres. Measles antibody titres in cerebrospinal fluid (CSF) and serum were measured by enzyme-linked immunosorbent assay. The measles antibody index was defined as CSF measles antibody level/serum measles antibody level; a value > 1.5 was considered positive for SSPE, indicating intrathecal synthesis of antibodies against measles. The following were retrospectively reviewed: presenting symptoms; age at measles infection; duration of measles infection; age at diagnosis of SSPE; length of the latent period (period between the patient’s age at measles infection and their age at diagnosis of SSPE); clinical stage at the initial diagnosis of SSPE; and neurological, EEG and imaging findings. For clinical staging of SSPE, the criteria of Jabbour et al.12 were used (stage I, personality changes and/or behaviour disturbance; stage II, convulsive motor signs, myoclonus, poor coordination, choreoathetosis and tremors; stage III, coma, opisthotonus, decerebrate rigidity and no response to any stimulus; stage IV, loss of cerebral cortex function, less frequent myoclonus and diminished hypertonia).

**MRI EXAMINATION**
A 1.5 T system (Signa; GE Medical Systems, Milwaukee, WI, USA) was used for MRI examination of the central nervous system. For all patients, T2 images were obtained in the axial plane (repetition time [TR] 4300 ms, echo time [TE] 100 ms, number of excitations [NEX] 1), T1 images in the axial and sagittal planes (TR 500 ms, TE 15 ms, NEX 1) and FLAIR (fluid-attenuated inversion recovery) sequences in the coronal plane (TR 9000 ms, TE 100 – 150 ms, NEX 1). Slice thickness was 5 mm, slice interval was 0.5 mm, field of view was 200 – 220 mm and matrix size 256 × 256 mm.

**STATISTICAL ANALYSES**
Data were analysed with Student’s t-test, Pearson’s correlation test and the $\chi^2$ test using SPSS® version 11.5 software (SPSS®, Chicago, IL, USA) and $P < 0.05$ was considered statistically significant.

**Results**
The records of 76 patients (male : female ratio 3 : 1 [57 males, 19 females]) diagnosed with SSPE at Harran University Paediatric Neurology Clinic between 2005 and 2009 were available for analysis. All patients were from rural areas of Turkey.

A history of measles infection was reported in 57 patients (75.0%), whereas the remaining 19 patients (25.0%) did not report a clear history of measles. A total of 66 (86.8%) of the patients had never been immunized against measles, five patients (6.6%) had received measles vaccination and...
the measles vaccination history of the remaining five patients (6.6%) was unclear.

Age at diagnosis of SSPE, age at measles infection and the length of the latent period for these patients are shown in Table 1. Measles infection in the first year of life had occurred in 27 of the 57 patients (47.4%) with a history of measles and four more patients had become infected before they reached 1.5 years old (31/57 patients; 54.4%). The mean ± SD latent period was 5.56 ± 2.22 years (range 2.0 – 11.8 years) and was similar in males and females. There was no significant correlation between age at measles infection and age at presentation with SSPE. At the time of presentation of SSPE, 48 patients (63.2%) were in stage I or II of SSPE, 25 (32.9%) were in stage III and three (3.9%) were in stage IV.

Figure 1 shows the frequencies of symptoms and signs at the time of diagnosis of SSPE in the 76 patients: 44 (57.9%) presented with atonic/myoclonic seizures; 23 (30.3%) with mental deterioration and behaviour alterations; three (3.9%) with vision loss (two had mildly abnormal electrophysiological test results although ophthalmological examination and EEG

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis of SSPE (years)</td>
<td>7.47 ± 2.31</td>
<td>7.43 ± 2.15</td>
</tr>
<tr>
<td>Age at measles infection (months)</td>
<td>21.38 ± 17.7</td>
<td>22.29 ± 15.2</td>
</tr>
<tr>
<td>Latent period (years)</td>
<td>5.56 ± 2.22</td>
<td>5.78 ± 2.05</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD. No statistically significant differences between the gender (P > 0.05).

**TABLE 1:** Comparison between males and females of age at diagnosis of subacute sclerosing panencephalitis (SSPE) and at the time of measles infection, and the length of the latent period between these diagnoses in the patients studied

**FIGURE 1:** Symptoms and signs at the time of diagnosis of subacute sclerosing panencephalitis (76 patients [57 males, 19 females]; A, atonic/myoclonic seizures; B, mental deterioration and behaviour alterations; C, vision loss; D, generalized tonic-clonic seizures; E, pseudotumour cerebri)
were normal); five (6.6%) with vomiting, headache and ataxia associated with increased intracranial pressure and papilloedema (pseudotumour cerebri); and one (1.3%) with generalized tonic–clonic seizures.

The MRI findings for the patients at the time of diagnosis of SSPE, according to clinical stage, are shown in Table 2 and Figs 2 – 6. Periventricular and subcortical involvement was prominent in stage II; cortical, subcortical, periventricular and corpus callosum involvement and brain atrophy predominated in stage III; and cortical, subcortical, brainstem and cerebellar involvement and brain atrophy predominated in stage IV. Across all 76 cases, the most frequent involvement was subcortical (31 cases; 40.8%), followed by periventricular involvement (23; 30.3%) and brain atrophy (21; 27.6%). The three most frequent sites of involvement were the frontal lobe of the brain (19 cases; 25.0%), the parietal lobe (14; 18.4%) and the occipital lobe (12; 15.8%). A total of 19 out of 48 cases (39.6%) diagnosed in stage I/II and two out of 28 cases (7.1%) diagnosed in stage III/IV had a normal cranial MRI. The frequency of abnormal MRI findings was significantly higher in stages III/IV than in stages I/II (P < 0.01).

### Discussion

Subacute sclerosing panencephalitis is a rare, progressive neurological disorder of childhood and early adolescence that develops more frequently in childhood.12 – 14 Its diagnosis is based on clinical and EEG findings and on levels of measles antibodies in the CSF and serum.15 Although measles infection has no gender predilection, it is interesting that SSPE was more frequent in males than females in the present study (male : female ratio 3 : 1) and this has also been found in some previous studies.8,15 – 17 SSPE usually develops after a latent period of 6 – 8 years from the primary infection.8 Anlar et al.18 reported that the age at presentation of SSPE declined from 13 to 7.6 years between 1975 and 1999. The overall mean age at presentation with SSPE was 7.44 years in the present study and, therefore,

<table>
<thead>
<tr>
<th>MRI findings</th>
<th>I (n = 9)</th>
<th>II (n = 39)</th>
<th>III (n = 25)</th>
<th>IV (n = 3)</th>
<th>Total (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No abnormality</td>
<td>8</td>
<td>11</td>
<td>2</td>
<td>–</td>
<td>21</td>
</tr>
<tr>
<td>Cortical involvement</td>
<td>–</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Subcortical involvement</td>
<td>1</td>
<td>14</td>
<td>14</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>Basal ganglion involvement</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Periventricular involvement</td>
<td>–</td>
<td>13</td>
<td>9</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Involvement of corpus callosum</td>
<td>–</td>
<td>–</td>
<td>5</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>Involvement of brainstem</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Brain atrophy</td>
<td>–</td>
<td>1</td>
<td>17</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Cerebellar involvement</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pseudotumour cerebri</td>
<td>–</td>
<td>4</td>
<td>1</td>
<td>–</td>
<td>5</td>
</tr>
</tbody>
</table>

In some patients more than one structure was involved.

*According to Jabbour et al.12
accord with the findings of Anlar et al.\textsuperscript{18} and indicate a possible shortening of the latent period of SSPE over time.

Measles infection at an early age has been accepted as a risk factor for SSPE.\textsuperscript{8,19}
According to a report published by the American Academy of Pediatrics in 1988, 75% of SSPE patients had measles before the age of 4 years. In the present study, the mean age at measles infection was 21.84 months. There was no significant correlation between age at measles infection and age at presentation of SSPE.

The first symptoms of SSPE are usually myoclonic/ataxic seizures, mental deterioration, behaviour alteration or vision impairment. Bojinova et al. reported that 35% of 40 SSPE patients presented with mental deterioration, 29% had extrapyramidal hyperkinesia, 15% had epileptic seizure, 10% had hemiparesis and 10% had vision impairment. Nunes et al. reported that the first symptom was myoclonus or tonic-clonic seizures in 22 of 48 SSPE patients and behaviour alterations in seven patients. Öztürk et al. reported that 50% of their patients presented with behaviour alteration, 30% with atonic/myoclonic seizures and a few with vision impairments and generalized tonic-clonic seizure. In the present study, 57.9% of patients presented with atonic/myoclonic seizures, 30.3% with mental deterioration and behaviour alteration, 3.9% with vision impairment, 1.3% with generalized tonic-clonic seizures and 6.6% with increased intracranial pressure and papilloedema (pseudotumour cerebri). Most patients, therefore, presented with atonic/myoclonic seizures and no behaviour alteration, which may be attributable to the low educational status of the families who might not have identified the mood changes.

Atonic/myoclonic seizures is a common presentation in SSPE, however several studies have reported that other types of seizure, including partial or generalized seizures mimicking epilepsy, might be the initial manifestation of SSPE. In the present study, only one patient presented with generalized tonic-clonic seizure; follow-up examinations indicated SSPE in this case. Another SSPE patient (male aged 12 years) presented versive seizure attacks resistant to epilepsy treatment. We suggest, therefore, that SSPE should be kept in mind when assessing epileptic children with any type of seizure in conjunction with a history of measles.

Generally, visual abnormalities are seen in 10 – 50% of SSPE patients and usually arise from cortical blindness, chorioretinitis or optic atrophy. Khadilkar et al. reported the mean age of patients who had vision impairment as 14.8 years. In the present study three patients (3.9%) had vision loss at the time of presentation of SSPE; two of these had mildly abnormal electrophysiological test results. Ophthalmic examinations were normal in all three patients. Cortical blindness was considered in these patients.
SSPE presenting with acute vision loss has been reported previously and the current relatively large series of SSPE cases shows that early ocular features are not an uncommon clinical finding in SSPE.

Five patients presented with increased intracranial pressure and papilloedema (pseudotumour cerebri) in the present study and there are several reports in the published literature of SSPE patients presenting with these symptoms. A recent study from Turkey reported that diagnostic lumbar puncture in patients with SSPE was associated with significantly increased intracranial pressure. We suggest, therefore, ophthalmological examination of the retina and fundus and measurement of intracranial pressure during the initial diagnostic lumbar puncture in SSPE patients.

Computed tomography findings are generally normal in the early stages of SSPE. As the disease progresses, atrophic changes and hypodensities of white matter are indicative of demyelinating areas. Compared with computed tomography, MRI is a superior method for detecting white matter abnormalities. In the early stages, hyperintense areas are observed on T2-weighted images.

Brismar et al. graded radiological findings of SSPE according to white matter changes as well as the degree of atrophy. They demonstrated that approximately 75% of 44 patients had white matter changes and there was a statistically weak correlation between clinical stage and MRI changes. Interestingly, they also noted that some patients in stage III and even some in stage IV had normal MRI findings, whereas some patients in the early clinical stages had severely abnormal MRI findings. The grey matter was intact in their stage I/II patients, but was affected in eight of 23 patients in stage IIIB/IV. They also found that grey matter lesions were not related to white matter changes and the degree of atrophy. The grey matter lesions were usually located in the cortical grey matter as well as in the thalamus, pons, brainstem, cerebellar peduncles and basal ganglia.

Anlar et al. reported that the most frequent changes in the MRIs of 26 SSPE patients were periventricular involvement, subcortical white matter involvement and brain atrophy, in order of decreasing frequency. They stated that involvement of the basal ganglia, thalamus, brainstem and corpus callosum and isolated cortical (hippocampal) involvement were unusual. Öztürk et al. showed cortical involvement in 13 patients, subcortical involvement in 13, atrophy in three and basal ganglion involvement in two out of 26 SSPE patients; 20 of these 26 patients were in stage II of the disease.

Alkan et al. found subcortical and periventricular white matter involvement in 63.3% of 11 stage II SSPE patients. In addition, seven patients in stage III had both periventricular and subcortical white matter involvement.

Tuncay et al. demonstrated normal cranial MRIs in five patents and abnormal MRIs in 10 out of 15 patients. They stated that early imaging findings included asymmetrical cortico-subcortical involvement, cortical atrophy and multifocal deep white matter involvement. There was no significant relationship between clinical stage and MRI findings in their study. Evaluation of the relationship between clinical stage and MRI findings in the present study showed abnormal MRI of the brain in 29 out of 48 stage I/II SSPE patients and in 26 out of 28 stage III/IV patients. As described above, similar findings have been reported in previous studies, reflecting the natural course of the disease, although MRI may also
be normal in the later stages and severe cerebral atrophy may be seen in early-stage SSPE patients.\textsuperscript{16}

The localization of MRI alterations in SSPE has been studied and the most commonly involved lobes have been found to be the parietal and parieto-occipital lobes.\textsuperscript{14,17} Some studies have found that MRI alterations begin in the subcortical occipital white matter.\textsuperscript{13–16} Like the imaging studies, a neuropathological study also indicated that the disease started in the posterior areas of the cerebral hemispheres (mainly in the parieto-occipital and posterotemporal cortex) and later progressed to involve the subcortical and deep white matter.\textsuperscript{32} In accord with these previous studies, the parieto-occipital lobe was commonly involved in the present study, although frontal lobe involvement was also frequently seen.

Öztürk et al.\textsuperscript{17} reported that periventricular white matter and cortical involvement were the most frequent sites of involvement in SSPE patients. The most commonly involved sites in the brain were periventricular white matter according to Anlar et al.,\textsuperscript{15} subcortical white matter according to Brismar et al.,\textsuperscript{16} and asymmetrical cortical and subcortical involvement was most frequent according to Tuncay et al.\textsuperscript{13} Subcortical involvement was found to be the most frequent in the present study, followed by periventricular involvement and some rare involvements previously reported in the literature, such as involvement of the corpus callosum, brainstem, cerebellum and basal ganglia.\textsuperscript{15,16}

In summary, the present study included the largest number of patients to date among published comparisons of clinical and MRI findings in SSPE. The MRI findings became more apparent at more advanced clinical stages. Involvement of rare sites was also found, such as the brainstem, cerebellum, basal ganglia and corpus callosum. In conclusion, SSPE may present with diverse clinical manifestations and unusual MRI findings and should, therefore, be kept in mind in childhood demyelinating diseases, even when the presentation is unusual.

**Conflicts of interest**

The authors had no conflicts of interest to declare in relation to this article.
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