Electroencephalographic and imaging profile in a subacute sclerosing panencephalitis (SSPE) cohort: A correlative study

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Abstract

Objective: There are only a few studies correlating diverse radiological and EEG features of subacute sclerosing panencephalitis (SSPE). The objective of the study was to (a) describe EEG profile and (b) correlate it with the clinical and imaging data of patients with confirmed SSPE.

Methods: This study was conducted at a University teaching hospital in south India and involved 58 patients (M:F = 37:21, age: 12.3, SD 4.8 years) of SSPE. Diagnosis of SSPE was based on the characteristic clinical manifestations, and raised IgG (≥1:625) anti-measles antibody in cerebrospinal fluid (CSF) by ELISA in all the patients. Scalp EEGs were recorded on 16 channel machines using standard parameters and procedures. The EEG, clinical and imaging data were reviewed.

Results:EEGs were frequently abnormal: typical (37) and atypical (21). Diffuse slowing of background activity (BGA) was noted in 46 records being asymmetrical in six. Periodic complexes were periodic (32), quasi-periodic (21) or a-periodic (4). Periodic complexes (PC) (amplitude: 370.7, SD 171.2 μV; duration – 1.7, SD 2.0 s; inter-complex interval: 8.4, SD 9.2 s) were symmetrical in 39 and asymmetrical in 19. CT (32) and MRI (23) scans were normal in 16 patients while others had white matter (15), cerebral edema (8), cerebral atrophy (8), basal ganglia (2), and thalamic (2) changes. There was an independent association of frontally dominant slowing of BGA (p = 0.04) and typical PCs (p = 0.03) with the diffuse cerebral edema on imaging. White matter changes correlated with slowing of BGA (p = 0.04), but not with typical PC (p = 0.16).

Conclusions: This study provides valuable insight into the structural and clinical correlates of EEG changes in SSPE. Significance: Irrespective of the incidence of occurrence of SSPE in a community, a clinician should be aware of the wide spectra of EEG findings. This study also discusses the possible underlying structural and clinical correlates.

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Keywords: CT; EEG; MRI; Periodic complexes; SSPE

1. Introduction

Subacute sclerosing panencephalitis (SSPE) is a rare, but serious, disease of the central nervous system caused by persistent infection of a mutant measles virus (Greenfield, 1950). It has a progressive course and results in premature death, within 2–4 years of onset (Cobb et al., 1984). Due to its varied manifestations at presentations, early diagnosis and clinical staging are not always easy (PeBenito et al., 1997; Yaqup, 1996). The electroencephalographic (EEG) pattern in SSPE is one of the characteristic and disease-specific of all EEG patterns (Cobb, 1966; Miller and Westmoreland, 1983; Markand and Panszi, 1975). Periodic complexes, the hallmark of the disease, do occur in a wide variety of neurological conditions like CJD, anoxic encephalopathy, metabolic encephalopathy, hepatic failure, drug
toxicity, thyrotoxicosis, progressive myoclonic epilepsy among others, in most of instances either periodicity is lacking or, sharp waves/trihaphasic waves form the complexes (Storm van Leeuwen, 1964; Lesse et al., 1958). Imaging findings in SSPE are usually not correlated with the clinical stage of illness (Ozturk et al., 2002). Studies correlating imaging and EEG changes in SSPE are sparse in the literature.

The objective of the study was to (a) describe the various EEG profiles and (b) correlate it with the clinical and imaging data of patients with confirmed SSPE.

2. Materials and methods

This study was conducted at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, a tertiary care University teaching hospital in south India and involved 58 patients (M:F = 37:21) of SSPE evaluated from October 2004 to April 2006. Diagnosis of SSPE was based on the characteristic clinical manifestations of progressive cognitive and/or behavioral changes, myoclonus and raised IgG (> 1:625) anti-measles antibody in cerebrospinal fluid (CSF) by ELISA in all the patients. This cut-off CSF titer has been established in our Neurovirology laboratory after evaluation of over 300 CSF samples in 1986–87 obtained from patients with neurological illnesses other than SSPE and individuals undergoing spinal anesthesia for minor surgical ailments (Poornima et al., 1989). We have not carried out any specific test to determine disruption of blood–brain barrier. However, we had carried out oligoclonal antibody banding in the 1980s and 1990s in some patients, which showed that the anti-measles antibodies in the CSF were indeed due to intrathecal production and not due to passive transfer of antibodies as a result of breach in blood–brain barrier (Shetty et al., 1989). Analysis of oligoclonal bands in the CSF was not carried out in the present study.

Sculp EEGs were recorded on 16-channel “Galileo NT (EBN)” machine, employing International 10–20 system of electrode placement using standard parameters and procedures e.g. High filter: 70 Hz; Low filter: 0.1 Hz; Recording time: 30 min; Sensitivity: 7 μV/mm; Sweep speed: 10 s/page; Sampling rate: 256 Hz. Thirty-nine patients had an awake resting record, with additional sleep recording data of patients with confirmed SSPE.

Recording time: 30 min; Sensitivity: 7 μV/mm; Sweep speed: 10 s/page; Sampling rate: 256 Hz. Thirty-nine patients had an awake resting record, with additional sleep recording in 19 patients (spontaneous: 11, drug induced: 8). Activation procedures included hyperventilation in 38, photic stimulation (5–50 Hz for 5 s at a stretch with eyes open and closed) done in all records. Sound (n = 31) and noisecessive stimuli (n = 14) were also given in a few. Surface EMG electrodes (filter band pass: 20 Hz–2 KHz; Sweep speed: 10 s/page) were placed on biceps or tibialis anterior muscles to ascertain the relationship of myoclonic jerk with the periodic complexes (PCs). All the data were documented by SP. The EEG data were reviewed and analyzed by SS, who was unaware of the clinical details about the patients. About 20–30 consecutive PCs were analyzed to determine the inter-complex interval and both mon- and bi-polar montages were chosen to determine its morphology. The reference electrode of the monopolar montage was linked to earlobes. EEG changes were considered typical if there were high voltage (300–1500 μV) bursts of repetitive polyphasic slow wave complexes ranging from 0.5 to 2 s in duration occurring periodically at 4 to 15 s with or without electrodecremental pattern (Cobb, 1966). Other patterns were classified as atypical. The periodic complexes (PCs) were defined as periodic, quasi-periodic and a-periodic. Periodic PCs were high voltage repetitive polyphasic and sharp and slow wave complexes ranging from 0.5 to 2 s in duration usually recurring every 4–15 s. A-periodic PCs were diffuse 1–3/s activity of fairly rhythmmic character but without periodicity. Quasi-periodic were those complexes with variable inter-complex intervals (Niedermeyer, 1993a,b).

The clinical data and Jabbour staging were recorded and the course of the disease was classified according to previously established criteria (Jabbour et al., 1975). Images of the brain could be carried out in 44 patients (CT scan: 32, MRI: 23). It was not possible in the rest due to non-affordability of imaging costs or the data were not available for review. The images were reviewed by SS and SR for the ventricular size, cortical, brainstem and cerebellar atrophy and focal abnormalities in the brainstem, thalamus, basal ganglia, corpus callosum, periventricular white matter, subcortical white matter and cortex. Signal changes, mass effect, evidence of edema, and, when available enhancement characteristics were also noted.

SPSS vs10 software was used for statistical analysis. The mean values and the standard deviation were calculated. Fischer’s exact test was used to compare clinical features and EEG parameters. Pearson $\chi^2$ test was applied to compare imaging findings with EEG parameters, and clinical features. The data were considered to be associated if ‘p’ value was lesser than 0.05 ($p < 0.05$).

3. Results

The mean age at presentation was 12.3, SD 4.8 years and the mean interval from onset of neurological symptom to the diagnosis of SSPE was 123.6, SD 158.5 days. History of measles infection was available in 21 patients (36%) and preceded the symptoms of SSPE by 2.7, SD 6.8 years (range: 1–20 years). Information regarding vaccination against measles was available in 39 patients (67.2%) and 9 patients (15.5%) were immunized. At the time of presentation their clinical staging was: stage I: 6 (10.2%), stage II: 37 (64%), and stage III: 15 (25.8%). Follow-up information was available in 42 patients. The course was rapid in seven, chronic progressive in 31, and relapsing–remitting in four. The clinical details of the patients are described in Table 1. Thirty-two patients underwent evaluation with cranial CT while 23 had undergone MRI (Table 2; Fig. 1A–F).
3.1. EEG observations

The EEGs were abnormal in all the patients. The abnormalities persisted both in awake and sleep records. Typical EEGs pattern was observed in 37 patients and it was often (64%) noted in stage II compared to other stages.

(a) Periodic complexes (PCs) (Figs. 2A–D and 3A–D):

The most striking and frequent EEG abnormality was the presence of PCs ($n = 57; 98$%). These were periodic in 32 (55%), quasi-periodic in 21 (36%), and a-periodic in four (6%) records. The PCs consisted of bursts of 2–4 high amplitude slow (delta) waves with mean amplitude of 370.7, SD 171.2 μV and mean duration of 1.7, SD 1.0 s. The complexes occurred quasi-periodically and the mean interval between the complexes in each EEG was 8.4 s (range: 3–20 s). The periodic complexes were symmetric in 39 (66%) and asymmetric in 19 (33%) patients (Figs. 2B and 3B). The amplitude was moderate (100–300 μV; $n = 24$) to high (300–800 μV; $n = 32$) in the majority (96.5%) and in 2 patients it was lesser than 100 μV. Varied morphology and variable and/or prolonged inter-complex intervals between PCs were often observed in stage III (Fig. 3A). There was no change of morphology, inter-complex intervals or periodicity with any stimuli: photic stimulation, hyperventilation or sensory stimuli.

Table 1
Clinical manifestations in patients with SSPE ($n = 58$)

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>$N$ (%)</th>
</tr>
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<tbody>
<tr>
<td>Myoclonus</td>
<td>54 (93)</td>
</tr>
<tr>
<td>Generalized</td>
<td>41 (71)</td>
</tr>
<tr>
<td>Focal</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Seizures</td>
<td>38 (65)</td>
</tr>
<tr>
<td>Generalized</td>
<td>28 (48)</td>
</tr>
<tr>
<td>Focal</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>17 (29.3)</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>21 (37)</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Monoplegia</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>14 (24)</td>
</tr>
<tr>
<td>Extrapyramidal</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Behavioral problems</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

Table 2
Imaging findings in SSPE

<table>
<thead>
<tr>
<th>Radiological features</th>
<th>CT ($n = 32$) $N$ (%)</th>
<th>MR1 ($n = 23$) $N$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>11 (34.3%)</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>5 (15.6%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Diffuse cerebral atrophy</td>
<td>4 (12.5%)</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Density/signal changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter</td>
<td>10 (31.2%)</td>
<td>15 (65.2%)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>2 (6.2%)</td>
<td>2 (8.6%)</td>
</tr>
<tr>
<td>Thalamic</td>
<td>2 (6.2%)</td>
<td>2 (8.6%)</td>
</tr>
<tr>
<td>Brainstem (pons)</td>
<td>0</td>
<td>1 (4.3%)</td>
</tr>
</tbody>
</table>

Fig. 1. Imaging findings in SSPE CT scan observations (A–C) in patients with SSPE. (A) diffuse edema, (B) extensive white matter hypodensity, (C) mild cerebral atrophy; MRI findings (D–F), (D) symmetrical thalamic and striatal signal changes with temporal region hyperintensity (Right > Left), (E) bilateral parieto-occipital white matter hyperintensities, and (F) diffuse atrophy.
(b) **Background activity** (BGA): It was normal in 6 patients (10.3%), all in stage I. In the rest (89.6%), slowing of BGA was noted. The slowing was of high amplitude, bilaterally symmetrical and synchronous in 46 (79.3%) and asymmetrical, predominantly in frontal leads in 6 (10.3%). The asymmetry of BGA and PCs always co-occurred. Frontal rhythmic delta activity was seen in six records.

(c) **Epileptiform discharges**: These were noted in 42 EEGs (72.4%) and comprised of spike and sharp waves,
with or without slow waves (Fig. 3C). They were generalized ($n = 28$), lateralized to one hemisphere ($n = 4$), focal ($n = 7$) and multifocal ($n = 3$). Focal discharges were noted mostly from frontal and parietal regions.

(d) Unusual features:

(i) **Two types of PCs in one EEG**: In 21 patients, the records showed 2 types of PCs in the same record; high amplitude bisynchronous, symmetrical single or double delta waves with two inter-complex intervals, respectively (Fig. 3A). In majority of these patients, there were 1:1 synchronous myoclonic jerks with both types of PCs.

(ii) **Abortive PCs**: In 3 patients, PCs after occurring at constant interval, were at times noted to atenuate in amplitude.

(iii) **Difficult to detect low voltage PCs**: In 2 cases with low voltage PCs (Fig. 2D) or when the BGA between the PCs had relatively high voltage, it was difficult to detect the complexes.

(iv) **Isolated non-periodic transients**: In 3 cases, the initial records showed non-periodic generalized high voltage transients but during the later part of the record showed PCs.

(v) **Short interval PCs similar to the EEG of Creutzfeldt-Jacob Disease (CJD)**: In 2 patients, there were periodic triphasic waves occurring at extremely short intervals of 1 s (Fig. 3D).

(vi) **Periodic lateralized epileptiform discharges (PLEDs)**: Ten EEG records (17.2%) showed PLEDS (Fig. 3C).

### 3.2. Relationship of clinical features and EEG

Focal seizures and myoclonus did not have correlation with asymmetry in EEG (Fischer’s exact test; $p = 0.18$). There was significant correlation between asymmetry of BGA and that of PCs with lateralizing neurological deficit (Fischer’s exact test; $p = 0.03$). Four patients had hemiplegia on the ipsilateral side of higher amplitude discharges in EEG, while 5 others (2: hemiplegia; 3: monoplegia) had on the opposite side and 1 had symmetrical and synchronous EEG abnormalities.

### 3.3. Association of imaging and clinical features

The imaging findings of 44 patients (CT = 32; MRI = 23) are described in Table 2. Eleven patients underwent both CT and MR imaging. CT scan was abnormal in 7 of them: diffuse edema (3), diffuse atrophy (3), and thalamic hypodensity (1). MRI in these patients revealed: diffuse atrophy (3), white matter signal changes (6), and thalamic signal abnormalities (1). There was no signal change in the corpus callosum while 1 patient had brainstem signal changes on MRI. There was no enhancement noted in the post contrast CT (Iodine) and MRI (Gadolinium) scans.

Brain edema and atrophy were seen in all stages. The signal intensity changes were noted commonly in stages II and III of the illness. The parieto-occipital WM signal changes were mostly observed in stage II; and the frontoparietal or diffuse signal changes were found in stage II or III. No association was found between focal seizures
or lateralizing neurological deficits and imaging findings, since most of the images revealed bilateral or diffuse abnormalities. However, association was significant between visual deficits and bilateral occipital/parieto-occipital signal changes ($\chi^2 = 5.1; p = 0.03$). One patient did not have periodic complexes in EEG. However, the MRI could not be carried out and the CT scan had revealed diffuse cerebral edema.

### 3.4. Association of imaging and EEG (Fig. 4A–D)

Two of the EEG parameters namely – frontally dominant slowing of BGA ($\chi^2 = 4.1; p = 0.04$) and typical PCs ($\chi^2 = 4.1; p = 0.03$) were associated independently with the diffuse cerebral edema on imaging. There was no significant association between cerebral atrophy and background slowing ($\chi^2 = 3.1; p = 0.63$). Focal EEG changes were striking in frontal and parietal regions, which showed association with the focal white matter (WM) signal abnormalities in the same regions in the MRI ($\chi^2 = 4.9; p = 0.04$). Bilateral symmetrical parieto-occipital white matter signal intensity changes were noted in 6 patients, and 3 of these patients had predominant slowing in the parietal and parieto-occipito-temporal leads, two showed bi-frontal slowing and one had slowing in fronto-parietal leads. One patient had bilateral occipital WM signal intensity changes (R > L) with the EEG showing symmetrical bi-frontal slowing with typical PC. Eight patients had fronto-parietal signal intensity changes and among them 5 patients had additional temporal region involvement. All 8 patients had intermittent slowing of BGA to delta range in the frontal leads. There was good association between BGA slowing to delta range and MRI signal abnormalities ($\chi^2 = 4.9; p = 0.04$). There was no association between asymmetric EEG abnormalities like PLEDs, asymmetrical PCs, and asymmetrical BGA with the imaging findings, since most of the images revealed bilateral or diffuse abnormalities. In 7 patients with focal epileptiform discharges and in four with lateralized discharges, no focal lesions were evident but were diffuse. None of the patients showing PLEDS in EEG had asymmetric imaging findings.

### 4. Discussion

EEG study is integral to the diagnosis of SSPE. The stereotyped EEG complexes occurring at a regular interval and having a constant relationship to myoclonus make this as, one of the most characteristic and specific of all EEG patterns (Cobb, 1966). Imaging procedures are not required for the diagnosis, but help in the differential diagnosis. There is a wealth of reports probing into correlation of imaging and clinical staging in SSPE. However, there is a scarcity of literature correlating EEG and imaging observations. We have analyzed this innovative dimension in the present study.

Though pioneering studies had revealed that stage II of SSPE is characterized by bilaterally symmetrical and synchronous generalized, stereotyped high amplitude delta waves (“Radermacker” or “R” complexes) recurring at fairly regular intervals of 5–15 s (Cobb, 1966; Markand and Panszi, 1975; Radermacker and Poser, 1960), complexes of unusual morphology do occur in SSPE (Cobb, 1966; Bostem et al., 1973; Passouant et al., 1970). In the present study, atypical changes were observed in as many as one-third of patients with SSPE. We however did not analyze the EEG data according to different age groups, since the mean age of the cohort was 12 years and maturation to the adult posterior alpha rhythm (10/s) in the EEG is attained by this age (Niedermeyer, 1993a,b).

There is no consensus regarding anatomical site of origin of these PCs. Their close association with myoclonus suggests that they might be of cortical origin and supports an experimental study showing the myoclonus to be due to degeneration of the cortical neurons rather than to an inflammatory reaction (Storm van Leeuwen, 1964; Lesse et al., 1958). However, others hypothesize their origin from deep thalamic or mesencephalic-recticular origin with relative cortical integrity (Cobb, 1966; Sayeed et al., 1975) or due to involvement of both grey and white matter resulting in a disturbance of the normal cortico-subcortical electrical interaction (Gloor et al., 1968) or secondary to white matter lesions taking off the insulating effect (Storm van Leeuwen, 1964). Oga et al. (2000) proposed sensorimotor integration as the mechanism of these periodic phenomena in SSPE. Two of our patients had pre-existing infantile hemiplegia and mild mental retardation with their CT scans revealing gliosis. Their EEGs showed typical bilaterally symmetrical Periodic complexes. Proper electrophysiological studies into the genesis of the PCs might unravel the dynamic changes in the cerebral electrical activity when a progressive encephalopathy supervenes pre-existing brain damage (Narayan et al., 1997).

The CT scan observations of WM changes with cerebral atrophy in our patients are consistent with previous reports (Jayakumar et al., 1988). Two patients showed lesions in the basal ganglia and thalami (stage II). Clinical and pathological evidence of involvement of basal ganglia and cerebellar nuclei in SSPE is known (Dyken, 1985). There was no correlation between CT findings and duration, and course of the illness in our study and similar was the observation by Krawieki et al. (1984). However, Pederson and Wulff (1982) reported cerebral edema in early stages and atrophy in later stages contrary to our observation. This is attributable to highly variable natural course of the disease (Dyken, 1985).

Unlike CT, MRI is more sensitive in detecting abnormalities and allows a more accurate study of the lesions (Tuncay et al., 1996; Murata et al., 1987). Normal MRI was found only in 5 patients in the first 4 months of the disease in our study. There was poor correlation between the clinical stage of SSPE and the severity of MR findings as reported earlier (Miller et al., 1990; Dietrich et al., 1990). This could be because MRI detects changes in tissue water and its physical state, whereas the clinical features depend
on interference and damage to axonal and neuronal function; these two phenomena need not be directly related (Winer et al., 1991). MR Spectroscopy (MRS) studies have shown features suggestive of inflammation in stage II and of demyelination, gliosis, cellular necrosis, and anaerobic metabolism in stage III (Alkan et al., 2003). However, MRS analysis was not carried out in our patients.

MRI demonstrated symmetrical parenchymal lesions in the grey matter, the subcortical and periventricular white matter, thalami and basal ganglia in our patients examined at different times after onset. Though EEGs in 6 of our patients showed frontal rhythmic delta activity, which has been postulated to be diencephalic in origin (Markand and Panszi, 1975), imaging did not reveal corresponding abnormality. None of our patients showed any signal intensity change in the cerebellum. One patient showed signal change in brainstem (pons). Two of our patients had CJD like picture in EEG but characteristic radiological picture of CJD was lacking (Schwaninger et al., 1997). Severe cerebral atrophy was seen in 5 patients. Apparently, atrophy is a result of post-inflammatory tissue damage and may occur earlier in some patients with a faster course (Anlar et al., 1996). Studies have reported cerebral edema on MRI during early stages of SSPE. However, we observed edema in all stages. In our study, MR findings were consistent with those reported in the literature (Tuncay et al., 1996; Murata et al., 1987; Winer et al., 1991; Alkan et al., 2003). Although cortical and subcortical lesions correlated with the clinical findings, the extent and location of the periventricular WM lesions and cerebral atrophy did not reflect the neurological status in many patients (Anlar et al., 1996). Our study revealed normal MR findings in 4 patients with stage I, and one of stage II disease. Widespread periventricular hyperintensities and cerebral atrophy were noted in many patients with stage II and III disease. It may be noted that the MR signal changes were seen predominantly involving the parieto-occipital and postero-temporal areas (stage II) followed by fronto-parietal/diffuse signal changes (stage III). Correlation of MRI observations by Anlar et al. suggested that cerebral edema correlated with slowing of BGA, active metabolism in stage III (Alkan et al., 2003). However, we did not appreciate similar observation with the PCs, which may support their deep nuclear origin. Further studies are needed in this context.

This is one of the largest studies of its kind. Wide spectra and atypical findings in EEGs of patients with SSPE were often observed. The exact reason though unknown could be due to the dynamic nature of the illness, and variable and protein underlying structural changes. The WM signal intensity changes had a significant relation with atypical EEG findings. Electrophysiological and imaging changes correlated to a certain extent.

References


