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Subacute Sclerosing Panencephalitis - A Clinical and Pathological Study

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Abstract

Fiftyfive cases of subacute sclerosing panencephalitis (SSPE) seen over a period of 22 years were studied. All patients were below 22 years (range 3-22 years) with a male preponderance. The initial symptoms consisted of myoclonic jerks, generalised tonic clonic seizures and behavioural changes. The clinical course consisted of progressive intellectual deterioration with involuntary movements (myoclonic jerks in 96.36 per cent, choreo - athetosis in 26.63 percent) and pyramidal sings (50.9 percent). The characteristic electroencephalographic finding was slowing of the background with periodic complexes consisting of high voltage, slow waves (occasionally sharp waves and spikes). On histology a spectrum of changes characterised by Dawson's inclusion encephalitis, Pette and Dorings nodular panencephalitis and Van Bogaerts sclerosing encephalitis were observed. It is stressed that there three probably represent different stages of the same illness in evolution. Nearly 28 percent were dead in ten months and none showed any improvement or remission.

It is estimated that in India about 21 million pre-school children acquire measles infection annually and nearly 75 percent of them develop clinical symptoms [1]. Nearly 2,00,000 children die every year due to measles and its complications. SSPE, the persistent form of measles infection of the central nervous system (CNS) is not uncommon in India [2]. However published reports are only few and pathological reports are also rare [2], [3], [4], [5], [6] and [7]. Though Dawson's inclusion body encephalitis [8], Pette and Doring's nodular panencephalitis [9], and Van Bogaert's sclerosing leucoencephalitis are distinct pathological entities, they represent various phases of pathological stages of the same illness [10]. Active immunisation against measles probably reduces this complication as evident from the reports from United States [11]. Till the same is freely available in India awareness of the various clinical and pathological features are essential in the proper and early diagnosis and will go a long way in reducing the misery of the parents. Here we are reporting one of the largest series of (55 cases) SSPE from South India with an emphasis on pathology during the evolution of this illness.

Material

Fiftyfive cases of SSPE seen as inpatients at National Institute of Mental Health & Neuro Sciences over a period of 22 years from 1962 to 1983 formed the basis of this study. The diagnostic criteria followed were

(1) classical clinical history of progressive intellectual deterioration with involuntary movements, mainly myoclonic jerks
(2) Electroencephalogram (EEG) characterised by typical period complexes
(3) Histological evidence in 22 cases.

EEG was done in all the 55 cases, 6 of them having two or more records. Routine cerebrospinal fluid examination was done in all the patients while the colloidal gold curve examination was carried out in 25 patients. Brain biopsy of the non-dominant frontal lobe was done in 22 cases and were diagnosed as SSPE. However histological material was available in only 14 cases for a review by one of us. (SKS,) who reviewed all the material for the sake of uniformity in assessing the grade and type of lesion. In two cases complete autopsy was performed and brain was available for study. The materials were fixed in 10 percent neutral formalin. Routinely haemotoxilin and eosin, thionine stain for neuronal density and morphology, PTAH for gliosis were done and when indicated luxol fast blue stain for myelin and Cajal stain to study the astrocytic cell morphology were done. The various histological features were graded depending upon the severity and the extent of involvement and the degree of neuronal loss, microglial and astroglial responses.

Results

Age distribution of the patients are given in Fig. 1 Only one patient belonged to higher socio-economic group as compared to 16 in middle socio-economic group and 38 in lower socio-economic group. Urban versus rural ratio was 1:1.8. No familial clustering of cases was seen. Past history of measles was elicited in 22 cases with the duration varying from 1 to 7 ½ years. Precipitating factors were noticed in 24 patients (fever and respiratory infection in 15, focal sepsis in 5, head injury in 4). The initial symptoms were myoclonic jerks in 43 (78.18 percent) generalised tonic clonic convulsions in 11 (20 percent) and behavioural changes in 21 (38.18 percent). The generalised tonic clonic seizures were rarely recurrent. The various clinical symptoms and signs are given in table 1. CSF examination revealed protein of more than 55 mg percent in 6 and a shift to the left in Lane's colloidal gold curve in 13 our of 25 patients. Background was alpha in 1, theta in 26, delta in 22 and indeterminate in 6. Periodic complexes were seen in 53 patients (other two were confirmed by biopsy). The complexes consisted of high voltage slow wave in 44, slow waves with sharp elements in 5, slow waves with spikes in 4. The duration of the periodic complexes varied from half to eleven seconds and the intervals between the complexes varied from 4 to 20 seconds. Myoclonic jerks whenever present were time locked with these complexes. Repeat EEG's done in 6 patients at interval of 2-8 weeks did not reveal any additional information.

Age distribution in SSPE.

Table I - Symptoms and signs in SSPE

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Pathology

Grossly the brain in case I, revealed meningeal cloudiness with normal gyral pattern. Serial coronal slicing showed granularity and softening of the grey matter in the parietal and occipital lobes and relatively firm white matter. The deep nuclear masses and the long fibre tracts were unremarkable. The ventricles were of normal size. The brain of case 2 was grossly unremarkable. No significant pathology was observed in other organs but for bronchopneumonia.

The histological study of the brain revealed a spectrum of changes (table 2). The three histological types, Dawson's inclusion encephalitis, Pette and Doring's nodular diffuse encephalitis and Von Bogaert's subacute encephalitis representing a continuum in the evolution of the same disease and differential response of the body to the viral invasion were observed. In 4 cases, the histological features were not clear cut enough for exact classification, but the findings were sufficiently distinct in association with clinical features for a diagnosis of SSPE.

Table II - Pathological features

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GN - Gliomesenchymal Nodules
N - Neuronal intra nuclear inclusions
OL - Oligodendroglial intranuclear inclusions
D - Dawson's Type
PD - Pette Dorings Type
VB - Van Bogaerts Type

The meningeal inflammation was minimal in spite of cloudiness observed on gross examination. Meninges revealed minimal infiltration by lymphocytes, plasma cells and activated histiocytes, even adjacent to severely affected cerebral cortex of Dawson's inclusion encephalitis. The inflammatory component around the vessels, extending down from the surface was variable, at places forming a dense cuff (Fig.2).

Dense perivascular lymphocytic cuffing, a feature of viral encephalitic process. H.E. 64

Dawson's inclusion encephalitis was found in one of the autopsied cases (Case 1). Necrotising cortical lesions were seen involving the occipital and parietal cortex and to a lesser degree, the frontal lobe. There was no associated haemorrhagic component. The cortex was disorganised with patchy neuronal degeneration and loss, rod cell proliferation and gitter cell formation. There was associated astroglial proliferation but sparse fibrillary gliosis. In grossly softened areas, this process has involved the entire thickness of cortex with profound neuronal loss (Fig. 3A). Numerous intranuclear inclusions were observed, the ones in oligodendroglia outnumbering the inclusions in the neurons in the softened zones (Fig. 3B). The white matter involvement was minimal, confined to the areas adjacent to affected cortex. It revealed myelin pallor and astrogliosis. Similar microglial and astrocytic response was observed in the pontine nuclei, the diencephalic structures, the cerebellum being well preserved.

Necrosis of the cerebral cortex, with relative sparing of superficial layers - Dawson's inclusion encephalitis (Case 1). H.E. 36.

Higher magnification of the necrotic zone showing intranuclear inclusions in the neuron (arrow) and

oligodendroglia. Note inclusions filling up both the nuclei in a binucleated oligodendroglia on the left (Case 1). H.E. 200.

Pette and Doring's nodular encephalitis with diffuse microglial (rod cell) proliferation with focal, large gliomesenchymal nodule formation (Fig. 4) in different parts of the cerebral cortex and brain stem was observed in case 5. Three other biopsied cases also showed similar histological features. Intranuclear inclusions were sparse and were observed in only 2 case (Case 6,7) suggesting a probable transition from Dawson's type to Pette - Doring type of reaction. Perivascular lymphocytic and plasma cell cuffing was prominent, mainly in the grey matter. A differential diagnosis of Japanese encephalitis and other endemic arbovirus encephalitis were considered but excluded because of the absence of necrolytic lesions, occasional presence of intranuclear inclusions, an antecedent history of measles, and the clinical evolution of the disease with EEG findings.

- ***A microglial nodule and diffuse rod cell proliferation in the cortex. Pette-Doring's diffuse encephalitis (Case 6).***

Van-Bogaert's encephalitis was commonest and was found in 7 cases. The characteristic feature was astrocytic proliferation throughout the white matter and lower strata of cortex. The neuronal loss in the lower cortex was evident, their place being occupied by the hypertrophic fibrillary astrocytes and gamistocytes (Fig. 5A - 5B). The proliferation of astrocytes and gliosis was more than indicated by the degrees of myelin loss. In one instance (Case 10) intranuclear inclusions were observed. In case 11, along with significant gliosis, a few gliomesenchymal nodules were also observed, representing a probable transition from the inflammatory phase to healing stage of SSPE.

- ***Van Bogaert's sclerosing leuco-encephalitis showing dense gliosis and astrocytic proliferation in the subcortical zone (Case 13). H.E. 160.***
- ***Cajal stain demonstrating hypertrophic astrocytes with course and large processes (Case 13). 200.***

One noteworthy feature was the patchy nature of distribution of the pathological lesions in both the autopsied cases which could not be appreciated in the biopsy material.

Discussion

Van-Bogaett [10] in 1957 described the similarities in the hitherto described independent entities i.e., Dawson's inclusion body encephalitis, Pette and Doring nodular panencephalitis and Von-Bogaert's subacute encephalitis. It was only after the identification of the common etiological agent i.e., the measles virus the concept of SSPE got well established [12]. SSPE is one of the common cause of progressive intellectual deterioration in children in India. However there are only a few clinical and pathological reports from India [2], [3], [4], [5], [6] and [7]. It is a disease of childhood, cases beyond 20 years of age are rare. Male preponderance is a common feature seen in almost all the series including the present one [2], [13]. Though this hospital (NIMHANS, Bangalore) caters to all socio-economic groups the relative high occurrence of SSPE in the low and middle socio-economic group is striking. Similar data is not available from other centers of the country for a better evaluation. Absence of familial clustering confirms to the non genetic nature of the illness. Jabour [14] described 4 clinical stages of SSPE. The cases in the present series mostly belong to the 2nd stage. Only one patient at the time of presentation could be categorised to stage 1 without any involuntary movements but he drifted to the 2nd stage in about four months. This clustering of cases around second stage can be explained by the diagnostic criteria used in the present series. The typical EEG changes of periodic complexes

are mainly seen in the 2nd stage and the biopsy was invariably not done in 1st stage. Van Bogaert described 4 modes of presentation [10]
(1) temporal lobe onset-generalised seizures with behavioural changes
(2) occipital lobe onset-hemianopia and/or cortical blindness
(3) Parietal lobe onset-apraxia, agnosia
(4) frontal lobe onset-behavioural changes.

None of our cases presented with occipital or parietal lobe features to begin with even though these areas were involved pathologically when studied. This is similar to the findings of Lensy [13] and Singhal [2]. The incidence of generalised seizure (20 percent) was similar to the earlier reports [2]. Nearly 28 percent were dead in ten months as compared to 30 percent within two years in Bombay series [2]. None of the patients showed improvement or remission, a finding common to all Indian reports [2], [3], [4], [5] and [6]. Thirty six percent of our patients were still alive on follow up varying from six months to three years and were clinically either status quo or in decorticate state.

Lensy et al [13] have noticed 5 different stages of EEG, abnormality on serial recordings in SSPE.

Stage

1. Disorganisation of background with random slow or sharp waves.
2. 1.5-3 Hz slow sharp waves bioccipital or bifrontal predominance.
3. Spike and waves, 2-3 Hz usually synchronous.
4. Slow, spike & wave complex with periods of low amplitude background in between.
5. Flat record with low voltage indeterminate or fast activity.

However they found no definite correlation of EEG staging with clinical staging. They noticed the EEG changes predate the corresponding clinical stages. In the present study most of the cases belong to the clinical stages II and III which usually showed the EEG changes of stage IV i.e., periodic slow, sharp or spike complexes with intermittent electrical silence. Only one patient showed similar EEG changes but was in clinical stage I. Two cases showed no periodic complexes but still were in the clinical stage II. This clustering of cases to a particular group is probably because of selection criteria i.e., typical EEG changes and or biopsy proof. Serial EEG examination would have been more useful in correlating EEG changes with clinical stages.

We did not find a definite correlation between the duration of illness, the clinical stage of illness and the type of histological lesion. This may be due to the differential immune status of the patient and the degree of penetration of virus, thus leading to different morphological forms of sclerosis and leuco encephalitis. The intranuclear inclusion bodies were seen in some but none had intracytoplasmic ones. The variability in the occurrence of inclusion bodies indicates the cyclic proliferation of the viral antigen as is demonstrated in vitro. Whether the appearance of inclusion bodies corresponds to the periods of the exacerbation or reactivation of latent infection is not clear. The Dawson's inclusion form probably represent the acute stage of the intense mesenchymal and glial nodule formation indicates the defence reactability of the host, while in sclerosing leucoencephalitis gliosis predominates probably representing the healing phase. The myelin loss observed is rather secondary. The perivascular round cell infiltration is common to all stages and is non specific in nature. In areas endemic to arbovirus infection problems in pathological diagnosis are expected. Similarly in Dawson's inclusion stage, herpetic encephalitis needs to be excluded [8]. Demonstration of measles viral antigen in the brain tissue forms the unequivocal evidence for the casual relation of this virus in the evolution of SSPE

[11]. In view of the patchy nature of involvement, characteristic pathological features may not be observed in some of the biopsy samples. SSPE especially involving the frontal lobe in the later stages leads to dementia. Occurrence of Alzheimer's fibrillary changes in the neurons is some of the cases lends support to this contention.

In India, measles vaccination of the children is not a routine practice. In view of the high incidence of fatality due to complications of measles and the morbid nature of SSPE this assumes greater importance. Observations in USA showed a decline in the incidence of SSPE following intensive immunisation against measles [10]. The high occurrence of SSPE in low and middle socio-economic groups who are maximally exposed to measles suggest that similar protective programme is essential for our population. A detailed epidemiological study to evaluate the incidence of measles and its neurological complications is needed in this direction to evolve a national policy.

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