

REVIEW ARTICLES

The syndrome of seizures in association with single small enhancing CT lesions (SSELs)

Satish JAIN *MD DM*

Indian Epilepsy Centre, New Delhi, India

Abstract

Neurocysticercosis is an important cause of seizures in developing countries. Most patients with neurocysticercosis have multiple intra-cranial cystic or calcified lesions. The syndrome of seizures in association with single, small enhancing CT/MRI lesions (SSELs) accounts for about 10% of epilepsy patients seen at major neurological centres in India. The clinical features of this syndrome and possible factors responsible for its etio-pathogenesis have been reviewed. In a large study on such patients, seizures were partial with or without secondarily generalized in 86% and majority (97%) of patients was treated with a single AED. Significant resolution of the CT/MRI scan lesion was noted within 6 months in 53% cases while only on anti-epileptic drugs. Two-thirds of patients had no seizures while on single AED and additional 18% had no seizures even after AEDs were withdrawn. A family history of seizures was noted in 21% probands and 60% of affected sibs had syndromic concordance with probands. HLA class II genomic typing was done to identify the role of hereditary factors in the etio-pathogenesis of this syndrome. There was a positive association of HLA - DRB1*13 ($P_c= 0.036$) with this syndrome.

Seizures in association with single, small enhancing CT/MRI lesions (SSELs) seems to be a “benign localization related epileptic syndrome” expressed in a subset of Indians genetically predisposed to seizures. This syndrome may be an example of “multi-factorial inheritance” with one gene predisposing to seizures while the other gene may be responsible for susceptibility to an environmental agent like cysticercosis.

Epilepsy has always been recognized as a disease and a large number of controversies in regards to every aspect of the disease have been prevailing since the days of ancient civilizations. Detailed accounts of the disease are available throughout the human history. Many concepts about the disease have changed over the centuries with advancements in the understanding of different aspect of epilepsy. The basic clinical fundamental remains true even today that the disease is characterized by ‘recurrent unprovoked seizures’.

While India has continued to share with the rest of the world most of the important aspects of common neurological diseases, it has always been believed that certain factors may be peculiar to or influencing the incidence of epilepsy in

India. Peri-natal insult, infections and infestations of the central nervous system being common in any developing country including India could be responsible for the belief that epilepsy may be more common among populations living in developing countries.

The Indian Council of Medical Research (ICMR) in early seventies decided to undertake a multicentric prospective study on ‘epidemiology of epilepsy’, keeping all these factors in mind and recognizing the diverse socio-cultural and environmental milieu of Indian population. The final report of the ICMR study was published in 1989 and contains voluminous data on 3,439 epilepsy patients seen in 5 different centres across the country. The ICMR study report contains some very interesting data that has been meticulously collected, most of the important features of the disease were in accordance to those reported from other countries.¹

Long before the ICMR report was ultimately published, a very interesting epileptic syndrome first came to the attention of neurologists in India in the late seventies and early eighties. This was mainly as a result of the addition of CT scanning to the diagnostic kit for patients with epilepsy.

Address correspondence to: Prof. Satish Jain, MD; DM, Epileptologist, Sir Ganga Ram Hospital & Director – Indian Epilepsy Centre. A-258, Defence Colony, New Delhi - 110 024 (India). Phone: 91-11-2433 3331, 91-11-2433 5214, Fax: 91-11- 2433 3330, Email: satjain55@hotmail.com.

The CT scan revealed some very unusual and interesting abnormalities in some epileptic patients from India who are otherwise absolutely normal. It can be assumed with a fair degree of certainty that these abnormalities must have existed in such patients even before the introduction of CT scanning in India. The so called 'Disappearing CT Lesions or Single, Small, Enhancing Lesions' are now accepted to be a common finding in a large number of epileptic patients from India.

The entire Indian literature on this subject including the series presented by many authors in the Annual Conferences of the Neurological Society of India (NSI) till the end of 1988 was reviewed and published.² Most of the patients with this epileptic syndrome are young and have a few partial with or without secondarily generalized seizures. Occasionally they may even have evanescent post-ictal focal neurological deficits. The CT scans usually shows a small subcortical contrast enhancing hyperdense disc or ring lesion surrounded by a large zone of low

attenuation. The CT scan appearance returns to normal or almost normal (complete or nearly complete resolution) within a few weeks without any specific therapy except anti-epileptic drugs (AEDs) to control seizures (figure 1).

ETIOLOGY OF SSELs

For many years since its initial observation, the possible etiology of SSELs was thought to be tubercular. This assumption was based mainly on two reports from the All India Institute of Medical Sciences (AIIMS), New Delhi on patients that included a sub-group consisting mostly of children and young adults who had presented with seizures. The CT scans showed small disc or ring lesions. These patients were treated with anti-tubercular drugs in addition to AEDs and the lesions had disappeared completely or reduced significantly on CT scan examinations performed subsequently. This was perhaps the main reason for these lesions being labeled as tubercular.^{3,4} Most of the patients

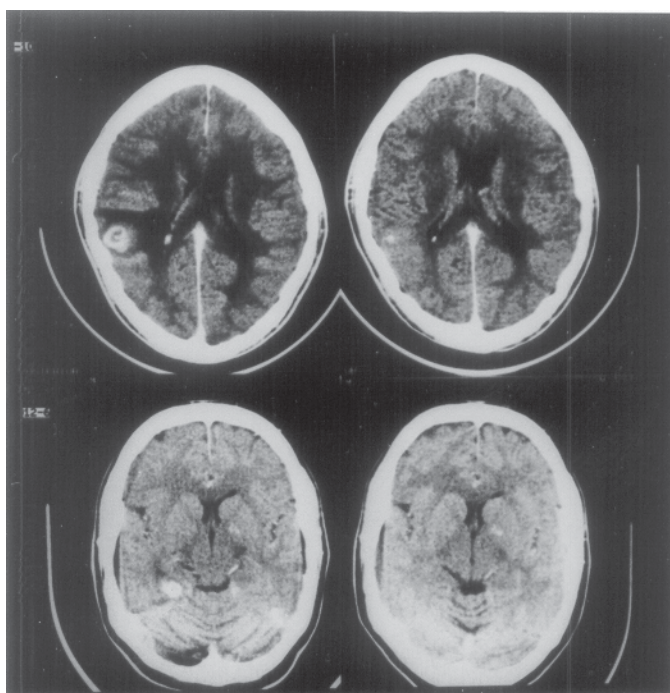


Figure 1: Contrast enhanced CT scans of two patients who presented with a few left partial with secondarily generalized seizures. The CT scan picture on the first patient (top left) shows a ring enhancing lesion with surrounding edema in the right fronto-parietal region that shows a near complete resolution in the CT scan done about 5 months later (top right). The CT scan picture of the second patient (bottom left) shows a small disc lesion with minimal surrounding edema in the right posterior parietal region that shows complete resolution in the CT scan done about 3 months later (bottom right).

with this syndrome during the early eighties were treated with anti-tubercular drugs. As a resident in Neurology from 1982-84, I have been a witness to anti-tubercular drugs being prescribed to hundreds of such patients being treated in different neurological centres of Delhi and New Delhi. At one stage there was a shortage of anti-tubercular drugs in these twin cities - not because of a large number of cases of tuberculosis but because these drugs were being prescribed to all patients with the syndrome of SSELs!

The credit for the hypothesis that SSELs may not be of tubercular origin also goes to the team from the AIIMS, New Delhi. It was during discussion in the morning Neuroradiology conferences at the AIIMS, an observation was made that most of these patients were otherwise healthy young individuals who had no problems except for a few seizures and they had no evidence of tuberculosis elsewhere in the body. At that time all such patients were investigated with an X-ray of the chest and blood test for erythrocyte sedimentation rate. Mantoux test was also conducted on many patients. Based on this experience at the AIIMS, New Delhi it was decided to observe such patients without anti-tubercular drugs. All such cases were regularly followed-up and discussed in the neuroradiological conferences held in the AIIMS and many visiting neurologists and neurosurgeons who saw the CT scans of these patients could provide us no clues about the possible etiology of the SSELs. A series of the first few cases of seizures with SSELs were presented at the American Epilepsy Society Annual Meeting at Washington D.C. in 1983.⁵

The earliest cases with this syndrome were seen at the centres in northern parts of India. Neurologists in southern India initially thought that this syndrome was peculiar to Indians living in the North. The probable reason for this observation being the availability of CT scans was restricted to only in northern India during that period. In the next few years, CT scans became available in most of the centres all over the country. Patients having seizures in association with SSELs were then documented from almost all the centres. Since then there have been many series reporting on a variable and large number of cases.⁶⁻²⁴

There have been many attempts to clarify the situation with regards to this syndrome. These have included the formation of a Consensus Group by the Neurological Society of India that had several meetings. There is still a lot of confusion

about the policy to be followed in managing these cases. The major issue of the debates is the possible etiology of these lesions. Initially the main reason for this was that patients in whom the lesions disappeared or would have disappeared were confused with those in whom the lesions had persisted or increased in size and/or number. The latter group consists of patients who have been shown to have tuberculomas, cysticercus granulomas, micro-abscesses, focal encephalitis and even cryptic vascular malformations. Unfortunately the reversible SSELs seen in many of the patients have a CT and MRI image morphology very similar to that reported in biopsy proved cases of different etiologies.

The main emphasis concerning the possible etiology of the SSELs has shifted from tubercular granuloma in the early eighties to cysticercal granuloma in the nineties. In the last 10-15 years we have on one hand been able to save these patients from loads of anti-tubercular drugs, but on the other hand nearly all such patients are now subjected to a course of anti-cysticercal drugs. This is because of the current belief of most of the neurologists of our country that almost all the SSELs have a cysticercal etiology. This belief is based upon the biopsy findings of cysticercal granuloma in some cases with similar looking CT lesions.^{16,18,20,25,26} Additionally, many cases with similar looking CT lesions have been reported among series reporting on clinical manifestations of cerebral cysticercosis. It has even been suggested that SSELs constitute the commonest form of neurocysticercosis in India.²⁷

Reports on biopsy of these lesions do suggest that in some cases the pathology be indeed of cysticercal origin. Here it must be remembered that other pathologies like tubercular granuloma, micro-abscesses, focal encephalitis, chronic inflammation and even cryptic vascular malformations have been reported in a significant number of cases.^{16,18,20,25,26} Additionally, some features of this syndrome suggest that the pathology of these lesions may not always be cysticercal. First, these lesions being always single and resolve spontaneously. Second, none of our cases have gone on to develop multiple lesions with the image morphology suggestive of cysticercosis. This feature has not been reported in the literature till now from other centres also. Third, the resolution of a large number of these lesions as early as one week after the first CT scan, and the reported no effect of albendazole in the resolution of these lesions.¹⁹ Finally, cases with these lesions have only occasionally been

reported among populations outside India, including people living in countries where cysticercosis is fairly common.

We had earlier reviewed the published reports in which similar looking CT scan lesions have been reported among epilepsy patients from outside India.²⁸ Most reports are of transient or reversible CT scan abnormalities seen after focal seizures²⁹⁻³³ or among series of cases diagnosed as cerebral cysticercosis.³⁴⁻³⁷ In cases reported as transient CT scan abnormalities after focal seizures, the resolution of these lesions was confirmed on a repeat CT scan examination after a variable interval.²⁹⁻³³ In a study from Thailand, 43% of patients diagnosed as cerebral cysticercosis had CT scan lesions similar to SSELs.³⁵ In the group of cases with cerebral cysticercosis with CT scan lesions similar to SSELs, seizures have been documented among many of the cases for which the clinical details are available.³⁴⁻³⁷

INVESTIGATIONS FOR THE ETIOLOGICAL DIAGNOSIS OF SSELs

The most important issue that emerges from this review is that in all these reported series of cases, how was the diagnosis of cysticercosis arrived at? To call all the SSELs as cysticercal cysts without any proof would be not only be unfair but unscientific also. Various immunological tests for anti-cysticercal antibodies in serum and cerebrospinal fluid have not been much helpful. Whether the test conducted was enzyme linked immunosorbent assay (ELISA) or immunoblot assay, only about one-third of the patients with SSELs has been shown to be positive for anti-cysticercal antibodies.^{12,17,38} A recently published report compared the results of ELISA and electro-immunoblot transfer (EITB) on the sera of 37 patients with SSELs and 5 with typical multilesional cerebral cysticercosis. EITB was positive in 18 of 37 (49%) SSELs patients and all 5 (100%) patients with multiple cysticercosis. On the other hand, ELISA was positive in 21 (57%) SSELs patients and only 4 (80%) patients with multiple lesions.²⁴

After getting no definitive diagnostic help from immunological tests, one had to rely on the biopsied material. It is an accepted fact the many of the biopsied SSELs have been shown to be of cysticercal origin but not 'all' of them. In a study only 7 of 15 (48%) cases who had excision biopsy showed definitive evidence of cysticercosis and indirect evidence of a parasitic etiology was

present in another 5 (33%), while remaining 2 specimens showed only inflammation. Biopsy samples of all 10 patients who had a CT guided stereotactic biopsy showed inflammation and gliosis only.^{39,40} In another report on excision biopsy on 18 patients, only 7 (39%) had evidence of cysticercosis.²⁰ In all the reports that have included biopsied material, histopathological evidence of tubercular granuloma, micro-abscess, focal meningoencephalitis and even cryptic vascular malformations has been documented in a significant number of cases.^{16,18,20,25,26,39,40}

ROLE OF HEREDITARY FACTORS

In the Neurosciences Centre, AIIMS, New Delhi we had aimed to establish a genetic database to form a hypothesis on the possible genetic contributions in different epileptic syndromes. We first reported the occurrence and pattern of different epilepsies and epileptic syndromes in 1,219 Indian probands and their relatives. The concordance of epilepsies between probands and relatives was also analyzed. Nineteen percent (231 of 1,219) probands had first or second degree relatives affected with seizures. Incidence of positive family history in probands with generalized epilepsies and the syndrome of SSELs were comparable and significantly higher than probands with localization related epilepsies. This study concluded that a significant percentage of first and second-degree relatives of probands with all types of epileptic syndromes have seizures. The risk of relatives being affected varied as a function of the relation with the proband. Concordance of epileptic syndrome between probands and relatives was related to the epileptic syndromes in probands. Based on the clinical features of probands with seizures in association with SSELs and a high incidence of positive family history of seizures, it was proposed that the syndrome of SSEL is probably a benign epileptic syndrome seen among Indians genetically predisposed to seizures.⁴¹

Distribution of human leukocyte antigen (HLA) class I and II alleles among patients with many different epileptic syndromes have been studied by several investigators.⁴²⁻⁵¹ These studies suggest a variable role of the HLA system in different epileptic syndromes. In view of the much higher occurrence of seizures in association with SSELs in the Indian population and our earlier experience of 25% of these probands having a positive family history of seizures, we had proposed the role of hereditary factors in the

etio-pathogenesis of this syndrome. We had investigated and reported the preliminary results of HLA studies in 63 Indian probands with the peculiar syndrome of seizures in association with SSELS. The frequency of HLA-A11 was decreased ($p < 0.05$) while that of HLA-B 63 ($p < .05$) and HLA-B 58 ($p < 0.025$) were increased in probands as compared to healthy controls. These values were not significant after application of correction factor for p-value.²⁸

In continuation of our previous report, we subsequently defined the clinical features of the syndrome of seizures associated with SSELS in 235 Indian probands and seizure types among their family members. Additionally, we investigated the role of hereditary factors in this syndrome by HLA class II genomic typing in randomly selected 41 probands. Similarly, family data was collected on relatives of 212 additional probands with neurological diseases other than epilepsy. HLA class II antigens were studied using PCR amplified DNA and sequence specific oligonucleotide probe (PCR-SSOP) hybridization. The seizures in 86% SSELS probands were partial with or without generalization, 77% had less than 5 seizures before first CT scan. Evanescent focal neurological deficits after seizures were noted in 40%. Most patients (97%) were treated with a single antiepileptic drug. Significant resolution of the CT scan lesion was noted within 6 months in 125 of 235 (53%) cases. Two-thirds of patients had no seizures while on single antiepileptic drug, and additional 18% had no seizures even after their antiepileptic drugs were withdrawn. We concluded that the syndrome of seizures in association with SSELS seems to be a 'benign localization related epileptic syndrome'.⁵²

Epilepsy among relatives of Indian probands having seizures in association with SSELS was more than 3 times as common as compared to relatives of probands with other neurological diseases. A family history of seizures was noted in 21% probands, the ratio of affected first: second-degree relatives was 4.3:1. Interestingly, the affected first-degree relatives of probands with this syndrome very often have a localization-related epileptic syndrome (localization related epilepsy syndrome in 19/35 including those with SSELS) while second-degree relatives frequently express a generalized epileptic syndrome (6/11). The affected sibs have the maximum concordance for a localization related epilepsy syndrome (12/20). Curiously, we had 8 relatives (7 first- and only 1 second-degree) who had seizures in association with SSELS ('affected pairs'). Among

these, 5 were sibs who were concordant for this syndrome. Among all affected sibs, 60% had syndromic concordance with probands. There was a positive association of HLA - DRB1*13 ($P_c = 0.036$) with this syndrome.⁵²

Our findings of a substantial number of probands having a positive family history of seizures and of 'affected pairs with SSELS' within these families are the first of their kind. These lend support to our hypothesis of genetic contributions in the etiopathogenesis of this syndrome and can be taken as evidence in favour of a hereditary susceptibility to some environmental agent. The high incidence of affected family members of probands could point to an inherited susceptibility for seizures among Indians. On the other hand, it is possible that relatives of the patients were also exposed to the same causative agent for SSELS (through food and water for cysticercosis) as the patients. The high prevalence of seizures among relatives could thus be a reflection of an exposure to a common environmental agent in susceptible family members. Our results of HLA studies among SSELS probands point to the inherited susceptibility to an infective agent, which in most cases could be of cysticercal etiology.⁵²

Based on our data, we hypothesize that more than one 'gene' could be involved in the pathogenesis of this syndrome. The ratio of affected first and second-degree relatives was 4.3: 1, suggesting involvement of multiple genes. In a monogenic disorder, the ratio of affected first and second-degree relatives is expected to be closer to 1: 2. Among relatives of SSELS probands, the affected sibs exhibited a high degree of syndromic concordance as compared to affected second-degree relatives. The high incidence of affected family members could also be taken to support our hypothesis that these Indian families are genetically predisposed to seizures. The 'first' gene provides susceptibility to seizures in these families. Those individuals who have an additional 'second mutated gene' exhibit an inherited susceptibility to an environmental agent. The peculiar interaction between this inherited susceptibility to seizures (first gene) and an environmental agent (second gene) may be responsible for this syndrome. Those individuals who carry both the genes, are susceptible to a monophasic, possibly immune mediated, neuronal insult resulting in the syndrome. In view of the fact that some degree of inflammation has been documented in almost all the biopsy reports of SSELS, our hypothesis of an immune-mediated,

antigen antibody interaction as a likely cause for this syndrome is a possibility. The agent responsible in many cases could be cysticercal antigen but even then this syndrome must be an example of a very benign type of neurocysticercosis as most cases have only a few seizures and the SSELs resolve on a repeat CT scan.

SSELs PRESENTING WITHOUT SEIZURES

Further, a few cases with SSELs and no seizures have also been reported. The first case with SSEL in a patient of headache was reported from our centre in 1986.⁵³ Two more cases of SSELs with acute severe headaches have subsequently been reported.^{54,55} Seven cases of SSELs in non-epileptic patients were presented at the Annual Conference of the Neurological Society of India in 1997. Six of the seven patients had presented with headache.⁵⁶ Many other similar cases have been seen by different individuals across different centres in India. One such patient (seen personally) developed partial simple seizures on follow-up. Such cases could provide a link to investigate the possible etiology of SSELs.

IS IT A SEPARATE EPILEPSY SYNDROME?

Unfortunately, no other major study investigating the role of hereditary factors has been conducted till date from other centres in India. The results reported by us need to be confirmed in a much larger number of patients and their family members. We have recently reported the occurrence of seizures among first and second degree relatives of 5,628 Indian probands with epilepsy and 3,357 probands with non-epilepsy neurological disorders (that acted as control population). Probands with seizures in association with SSELs accounted for 11.8% of the total (666 of 5,628). A family history of seizures was positive among 22% of SSELs probands.⁵⁷ The only other similar report documented a family history of seizures among 6 of 20 (30%) Indian children presenting with seizures in association with SSELs.⁵⁸

This syndrome that accounts for about 10% of all epilepsy cases seen in major hospitals in India and has a fairly well defined benign clinical course. It appears to be a good candidate for being classified as a separate entity in the proposal for revised classification of epilepsies and epileptic syndromes of the Commission Classification and Terminology of the International League Against Epilepsy.

CONCLUSIONS

The syndrome of seizures in association with SSELs accounts for about 10% of all epilepsy cases seen in major neurological centres in India. In most cases this syndrome is a benign, monophasic, self limiting, localization related epilepsy. The etiology of SSELs in many cases is cysticercal in origin but many other pathologies have been documented in these patients. Hereditary factors do play a role in its pathogenesis. These individuals may be genetically susceptible to an interaction with an environmental agent like cysticercosis. Cases with SSELs without any seizures and other similar aspects of the syndrome may provide further clues to its etio-pathogenesis.

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