SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

STUDY OF REFERRAL PATTERNS FOR TEMPORAL LOBE EPILEPSY IN A TERTIARY EPILEPSY SURGERY CENTRE IN INDIA

Thesis submitted in partial fulfillment of the rules and regulations for

DM Degree Examination of

Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

DR. AJAY ASRANNA I.P.

DM Neurology Resident

Month and Year of Submission: October 2016

Department of Neurology

Sree Chitra Tirunal Institute for Medical Sciences and Technology

Thiruvananthapuram

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DECLARATION

I, **Dr Ajay Asranna I. P.,** hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology**.**

Thiruvananthapuram

Date:

Dr Ajay Asranna I.P.

DM Neurology Resident

SCTIMST

Forwarded

The candidate, **Dr Ajay Asranna I.P.** has completed the project under my guidance.

Thiruvananthapuram

Date:

Dr. Ashalatha Radhakrishnan

Additional Professor

Department of Neurology

SCTIMST

Forwarded

The candidate, **Dr Ajay Asranna I.P.,** has carried out the minimum required project.

Thiruvananthapuram

Date:

Dr.Muralidharan Nair

Professor and Head

Department of Neurology

SCTIMST

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Dr Ajay Asranna I.P.

Senior Resident

Department of Neurology

SCTIMST

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INTRODUCTION

There are estimated to be about 50 million people with epilepsy worldwide, a majority of whom live in low-income and lower middle income countries.[1] Approximately 20 to 30% of persons with epilepsy have drug-resistant seizures that are not adequately controlled by pharmacotherapy [2]. Mesial temporal lobe epilepsy (MTLE) is the prototype of a surgically remediable epilepsy syndrome with mesial temporal sclerosis (MTS) being the commonest etiology [3]. The last decade has seen growing evidence for the benefits of epilepsy surgery. In 2001, a randomised control trial affirmed the superiority of surgical treatment over medical treatment in refractory TLE (Temporal lobe epilepsy). [4] In 2003, the American Academy of Neurology in association with the American Epilepsy Society and the American Association of Neurological Surgeons recommended that patients with disabling complex partial seizures should be considered for referral to an epilepsy surgery centre on failing adequate trials of first line antiepileptic drugs (AED). [4] Further, to better define pharmaco-resistance and resolve the controversy over the timing of referral, the International League Against Epilepsy (ILAE) proposed a consensus definition for drug resistant epilepsy in 2009[5].

Despite these developments, surgical treatment for TLE remains underutilized even in developed countries.[6, 7] Furthermore, studies have not shown a trend towards earlier referral despite guidelines for referral once the patient becomes pharmaco-resistant. The number of epilepsy surgeries in developing countries show an increasing trend, but the reasons related to this increase are still unclear.[8] The temporal trends of referral and the impact of increasing

evidence for epilepsy surgery on referral in low and middle income nations has not been investigated. A study of the patterns of referral to an epilepsy surgery centre could give valuable insights into the extent to which existing facilities are being utilised as well as loopholes in the organisational structure. This could influence policy decisions regarding future projects related to epilepsy care. In this study, we analysed the patterns of referral to a tertiary epilepsy surgery centre in India catering to all epilepsy sub-types and the trends in referral patterns over time.

REVIEW OF LITERATURE

Epilepsy is on the commonest neurological disorders and leads to significant morbidity and mortality.

Epidemiology of epilepsy: Estimates suggest that there are about 50 million people with epilepsy worldwide, a majority of whom live in low-income and lower middle income countries. [1] The Global Burden of diseases 2010 study reported that epilepsy contributed to 253 disability adjusted life years (DALYs) per 100,000 people globally and to 0.75% of the total Global Burden of Disease. [9] This is equivalent to breast cancer in women and lung cancer in men. [3] The prevalence of epilepsy in India in various studies is around 2.5 to 11.9 per 1,000 population.[10] It is estimated that India has around 6- 10 million patients with epilepsy which accounts for one fifth of the global burden. [11] A recent population based study from Kolkota in an urban setting reported an age-adjusted annual incidence rate of epilepsy of 38.3 per 100,000. In the same study the all-cause standardized mortality rate (SMR) of epilepsy was 2.4 and the burden of epilepsy in the year 2007–8 revealed the overall Years of Life Lost (YLL) was 755 per 100,000, and the overall Years of Life lived with Disability (YLD) ranged from 14.45 to 31.0 per 100,000 persons thus underscoring the significant mortality and morbidity associated with epilepsy.[12] In a study done in 2000, the prevalence of epilepsy in Kerala was 4.7 per 1000 patients.[13]

Rationale for epilepsy surgery: Approximately 20 to 30% of persons with epilepsy have drug-resistant seizures that are not adequately controlled by pharmacotherapy and may benefit from surgery.[2] Intractable epilepsy also accounts for a majority of the indirect and direct costs of epilepsy.[14] Surgery offers the best chance of seizure remission in what have been designated as surgically remediable syndromes. Mesial temporal lobe epilepsy (MTLE) is the prototype of a surgically remediable epilepsy syndrome and is the commonest surgically remediable syndrome in adults, is classically pharmaco-resistant and amenable to surgery.[3] Other surgically remediable epilepsy syndromes include discrete resectable structural lesions lead to focal epilepsies, hemimegencephaly, hypothalamic hamartomas, Rasmussen's encephalitis, Sturge-Weber syndrome which are more common in children.[15]

There is robust evidence demonstrating the efficacy of surgery in temporal lobe epilepsy. A randomised control trial in 2001 demonstrated that the surgical group had fewer seizures impairing awareness and a significantly better quality of life than the patients in the medical group.[16] Based on this grade I evidence, in 2003, the American Academy of Neurology (AAN) in association with the American Epilepsy Society and the American Association of Neurological Surgeons recommended that patients with disabling complex partial seizures should be considered for referral to an epilepsy surgery centre on failing adequate trials of first line antiepileptic drugs.[17]A more recent study, the ERSET trial also points to lower probability of seizures following early resective surgery.[18] The last decade has seen rapid advancements in neuroimaging and surgical techniques leading to better safety and outcomes

in epilepsy surgery. A recent meta-analysis demonstrated the safety of epilepsy surgery with low levels of peri-operative mortality- 0.4% of temporal lobe patients and 1.2% for extra-temporal.[19]

Trends in epilepsy surgery & under-utilisation of epilepsy surgery: Despite the robust evidence for epilepsy surgery, there is a distinct lack of momentum for epilepsy surgery despite an increase in the number of epilepsy surgery centres. In a study by Englot et al, studying the trend of epilepsy surgery between1990-2008, an increase in the number of hospitalizations over time was noted. However, this was not accompanied by an increase in surgeries, producing an overall trend of decreasing surgery rates.[6] A similar trend was seen in a study by Schlitz et al from US between1998-2009. [20] Similarly, a stable trend of epilepsy surgeries were reported form a study by Bien et al from Germany. [21] A recent survey from UK reported a decrease in the number of all surgical procedures in both adult and pediatric population, with the exception of Vagal Nerve Stimulation (VNS) implantation.[7] Likely factors associated with this trend included a decrease in epilepsy hospitalizations at the highest-volume epilepsy centres, and increased hospitalizations to lower-volume hospitals that were found to be less likely to perform surgery.[6]

Epilepsy surgery in developing countries and India: In contrast to various studies on epilepsy surgery in developed countries, studies on epilepsy surgery are scanty. A study by Meyer et al showed a treatment gap of over 75% in low-income countries and over 50% in lower middle- and upper middle-income compared to less than 10% in high-income

countries.[22] Epilepsy surgery is available in only 13% of low-income countries compared with 66% of high-income countries.[1] Growing economies like China have benefitted from advanced non-invasive diagnostic tools, increased medical and social acceptance of epilepsy surgery and collaborations with the International League Against Epilepsy and international epilepsy centres. However, the national demand for epilepsy surgery still far exceeds supply. Epilepsy surgery is also underutilized in many economically underdeveloped provinces.[23]

In China, the number of adult and pediatric epilepsy surgeries in major centres increased form 600 cases before the year 2000 to 1100 cases in 2005 and a total of 2500 cases

performed in the country. However, the treatment gap is still substantial with an estimated 6 million people with active epilepsy who are potential surgical candidates. [23]

India belongs to the World Bank 'Lower middle income' category. India is estimated to have at-least 5 million people with active epilepsy, over 1 million of whom have intractable epilepsy and might benefit from surgery. Earlier studies have demonstrated the cost effectiveness of surgery over continued medical treatment in India.[24] A survey by Menon et al in 2012 reported 12 centres 18 centres offering epilepsy surgery in India, half of which were situated in Southern India and at least two-thirds of the centres were under non-governmental management. Furthermore, in contrast to Western trends of decreasing epilepsy surgery, an increasing number of epilepsy surgeries are being performed in India. The study also compared the number epilepsy surgeries including both adult and pediatric epilepsy

surgeries done in major centres across India between 1995–2000 period, and 2007–2012. The total number of surgeries was seen to increase by 3.2-fold, temporal resective surgeries increased by 2.7-fold and extra-temporal resective surgeries increased by 7.1-fold.[8] The reasons for this dichotomy between developed and developing countries could be due to the clearing of backlog patients waiting for epilepsy surgery in developed countries. However, studying the patterns of referral of epilepsy and temporal trends would help in understanding the factors affecting the rate of epilepsy surgeries.

Referral patterns in epilepsy: A study of the patterns of referral to an epilepsy surgery centre could give insights into the extent to which existing facilities are being utilised as well as loopholes in the organisational structure. This could influence policy decisions regarding future projects related to epilepsy care.

Studies on referral patterns in epilepsy in India have been scanty. A study by Thomas et al showed showed that 61.4% of the patients were living in villages; 65% had a monthly income less than Rs. 1000. The mean delay in diagnosis was more for those from villages (13.5 months) as compared to those from urban areas (6.4 months) and for women (11.7 months) as compared to men (7.8 months). Previous consultation before referral included general practitioners (61%), specialists (50%) and neurologist or neurosurgeon (27%). [25] However, temporal trends were not analysed in this study. Another study on epilepsy care in 6 Indian cities revealed that services for epilepsy are urban-based and there is underutilization of services, general practitioners and specialists. The facilities for epilepsy surgery, therapeutic

drug monitoring and clinical psychologist or medical social workers were also found to be limited. [26] However, factors affecting referral for epilepsy surgery in developing countries have not been studied adequately.

Factors affecting referral and surgical treatment: Burneo et al studied the use of surgical treatment for epilepsy among different ethnic and racial groups with surgically remediable temporal lobe epilepsy and reported that African Americans had a 60% less chance to receive surgery than non-Hispanic whites.[27] McClelland et al examined the role of race, age, sex, and insurance status on surgery in pediatric intractable TLE and found that while older age and private insurance status was significantly associated with increased probability of resective surgery, sex and race did not significantly affect the odds of undergoing surgery.[28] The timing of referral i.e. the duration of seizures before the patient was referred to a specialized epilepsy centre is a good index of utilization of services. Studies on factors affecting duration of seizures before referral help in a better understanding of the barriers to epilepsy surgery and temporal trends.

Most studies till date have reported an average delay of two decades before patients are considered for surgery.

In a study conducted at Florida from 2000-02 on 36 patients undergoing temporal lobe surgery, Benbadis et al reported an average duration of 18 years before being evaluated at the centre. 61% of the patients in the study were referred by neurologists while 21% were self

referred. [29] The absence of guidelines on timing of referral was thought be an important cause for this delay in referral. In 2003, practice guidelines by the American Academy of Neurology in association with the American Epilepsy Society and the American Association of Neurological Surgeons recommended that patients with disabling complex partial seizures should be considered for referral to an epilepsy surgery centre on failing adequate trials of first line antiepileptic drugs.

In a study by Choi et al from New York, duration of epilepsy prior to temporal lobe resection was evaluated in 213 patients, who had their first temporal lobe resection at the center between 1996 and 2007. The mean duration of epilepsy was between 21.1 ±14.2 to 22.6 ±12.7 years and showed no decrease in mean duration of seizures over the years.[30] However, this study did not specifically look into the effects of practice guidelines on referral. Haneef et al examined the referral data for patients with TLE from 1995 to 1998

and compared them with data from 2005 to 2008 to determine whether the recommendations resulted in a change in referral patterns for surgical evaluation. The study did not identify a significantly earlier referral for epilepsy surgery. [31] One limitation of the study was that examining changes within 5 years of the AAN practice parameter may have precluded detection of longer term trends in evolution.

In another multi-centric study by Helmstaedter et al from Germany, who studied patients undergoing temporal lobe surgery between 1988 and 2008, patients with MTS were found to

have the longest duration of epilepsy 23 ± 13 years. The duration of seizures were measured from the age at onset to the age at surgery. The limitation of this study was the fact that only surgical patients were included and misses out on referral trends in presurgical patients. Another reason leading to delay in referral was the ambiguity in the definition of pharmaco resistance. A consensus definition was proposed by ILAE in 2009 which defined drug resistant epilepsy as a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[5]

An analysis of the reasons for this delay in referral reveals attitude of the referring physician and neurologists plays an important role. Jehi et al summed up this treatment gap in terms of 'knowledge gap' and 'treatment gap'.[32] 'Knowledge gap' refers to the of referring doctors' knowledge about the timing of referral and the definition of treatment resistant epilepsy.

In a survey of neurologists done by Hakimi et al from USA, nineteen percent responded that all approved AEDs had to fail before a patient could be defined as medically refractory.[33] A survey of neurologists in Italy by Erba et al showed that two thirds of responders are nonaligned with the opinion leaders. [34] In another study from Canada by Roberts et al, more than half of neurologists required patients to be drug-resistant and to have at least one seizure per year before considering surgery, and nearly half (48.6%) failed to correctly define drug-resistant epilepsy. [35] A survey of primary care physicians from India showed very few of

them ever had diagnosed focal seizures, and the majority of them overutilize EEGs, prescribe continuous antiepileptic drug (AED) prophylaxis for febrile convulsions, use relatively expensive AEDs often in combination and in suboptimal doses, and were unaware of alternate treatment options for AED resistant epilepsies.[36] Increasing importance is recently being placed on dissemination of information related to early referrals. Experts have been called upon to take the lead in efforts that go beyond education to include true collaborative initiatives at all levels of our social and health care structure.[32]

'Feasibility gap' refers to inadequate resources as a barrier to epilepsy surgery. More than 75% of neurologists surveyed by Roberts et al identified inadequate health care resources as the greatest barrier to epilepsy surgery. [35] This is particularly true in case of developing countries like India as discussed above. Identifying medical refractoriness among patients with chronic epilepsy in resource-poor countries is challenging given that although many AEDs may be used, they are not administered for sufficiently long periods and in adequate doses, either alone or in combinations. In many geographical regions, local superstitions and customs play a major role in preventing patients from seeking medical and surgical treatment.[37] However, studies have the cost effectiveness of epilepsy surgery even in developing countries. In a study by Rao et al in 2000, it was estimated that the out-of-pocket one-time payment for temporal lobectomy was Rs 47,000 while the total direct medical cost of caring for TLE patients aged 26 to 60 years would be Rs 200,000.[24] Hence the cost factor alone should not preclude referral for epilepsy surgery in drug resistant epilepsy.

Given the burden of epilepsy in India, and the poor utilization of services particularly with reference to epilepsy surgery, there is an urgent need to analyze the reasons and take remedial measures.

Examining the referral trends in epilepsy surgery would help to understand the impact of increasing evidence for epilepsy surgery, the increasing number of epilepsy surgery centres and the socio-demographic changes that effect epilepsy surgery.

However there are no studies on referral patterns for surgically remediable epilepsies like temporal lobe epilepsy from India or other developing countries. Further no previous studies have analysed the trends in referral patterns over time. Such a study would in turn help in pointing out lacunae in existing services and help devise strategies aimed at better epilepsy care and utilization of services.

AIMS AND OBJECTIVES

1. To study the patterns of referral for TLE surgery centre in a tertiary care centre with all facilities after establishment of definite guidelines on the success of epilepsy surgery in TLE over medical treatment.

2. To investigate any changes in the patterns of referral over time spanning last two decades and compare it with a developed country.

Inclusion criteria

1. Age> 16 years

2. Diagnosed to have intractable TLE as per the latest ILAE guidelines[7] after evaluation by clinical, radiological, video-EEG,SPECT/PET/sphenoidal recording/invasive re cording if necessary.

Exclusion criteria

1. Acute or chronic psychosis on treatment

2. Associated generalized epilepsy or Paroxysmal non epileptic events (PNES) or any other type of epilepsy syndrome.

3. Any associated progressive/degenerative neurological condition

4. Any progressive medical condition precluding surgical candidacy.

MATERIALS AND METHODS

Data of 10,348 patients who underwent long-term VEEG monitoring in our Institute, as a part of pre-surgical evaluation were analysed from the prospectively maintained records. Patients who fulfilled the above mentioned inclusion and exclusion criteria and were divided into three groups as five year periods during which they underwent pre surgical evaluation, Group 1: Year 2000-2004; Group 2: Year 2005-2009; Group 3: Year 2010-2014.

1364 patients who fulfilled inclusion criteria were included in the study; 389 in Group 1, 487 in Group 2 and 488 in Group 3**.** Patients attending the epilepsy clinic in our Institute are grouped into various categories based on their socio-economic status and per capita income as low (A,B) and high income(C,D) groups. Referral data with particular reference to state of domicile, income category, duration of epilepsy before referral, age at onset of seizures and number of AEDs tried before referral were analysed. Age at onset of seizures was defined as age of first non-febrile seizure, age at evaluation as the age at the time of first admission for VEEG and duration of epilepsy was the age at evaluation subtracted by the age at onset.

STATISTICAL ANALYSIS

All data were analyzed using SPSS 8, Inc,Chicago, IL,U.S.A. Categorical variables were analyzed in proportions and compared using Chi square test, numerical variables were analyzed using means and SD and compared using ANOVA. As the income group was found

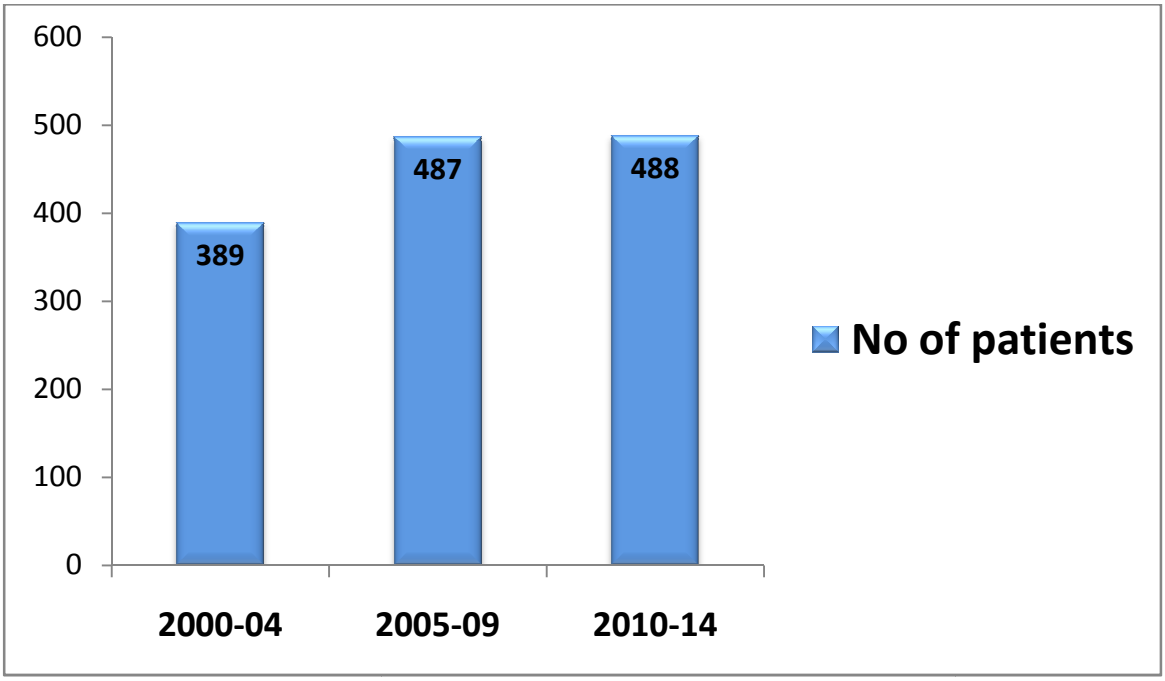
to be a potential confounder, the analysis was repeated after weighting for income group.

Bonferroni post hoc tests analyzed change in duration of epilepsy over time.

RESULTS

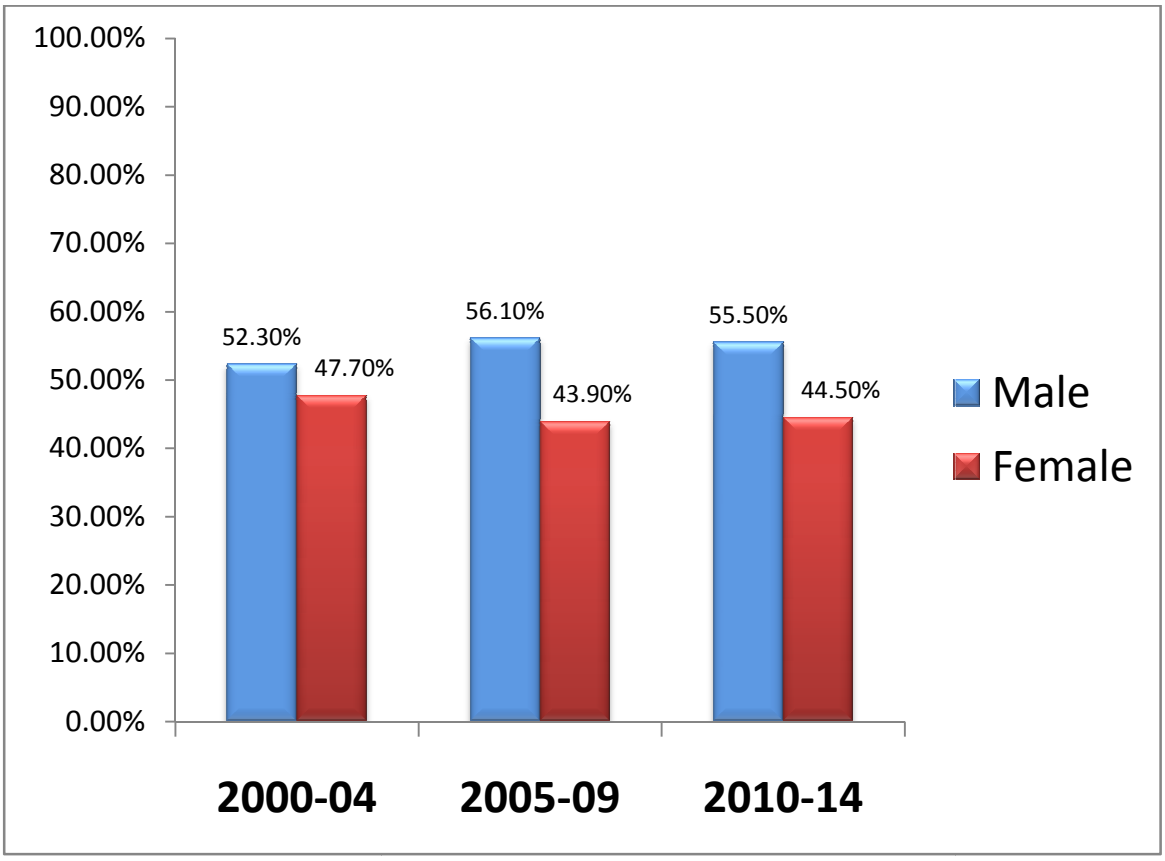
The number of patients referred for presurgical evaluation increased over time from 389 in the Group 1 to 487 and 488 patients in group 2 and group 3 respectively (Figure 1)

Figure 1: Number of patients



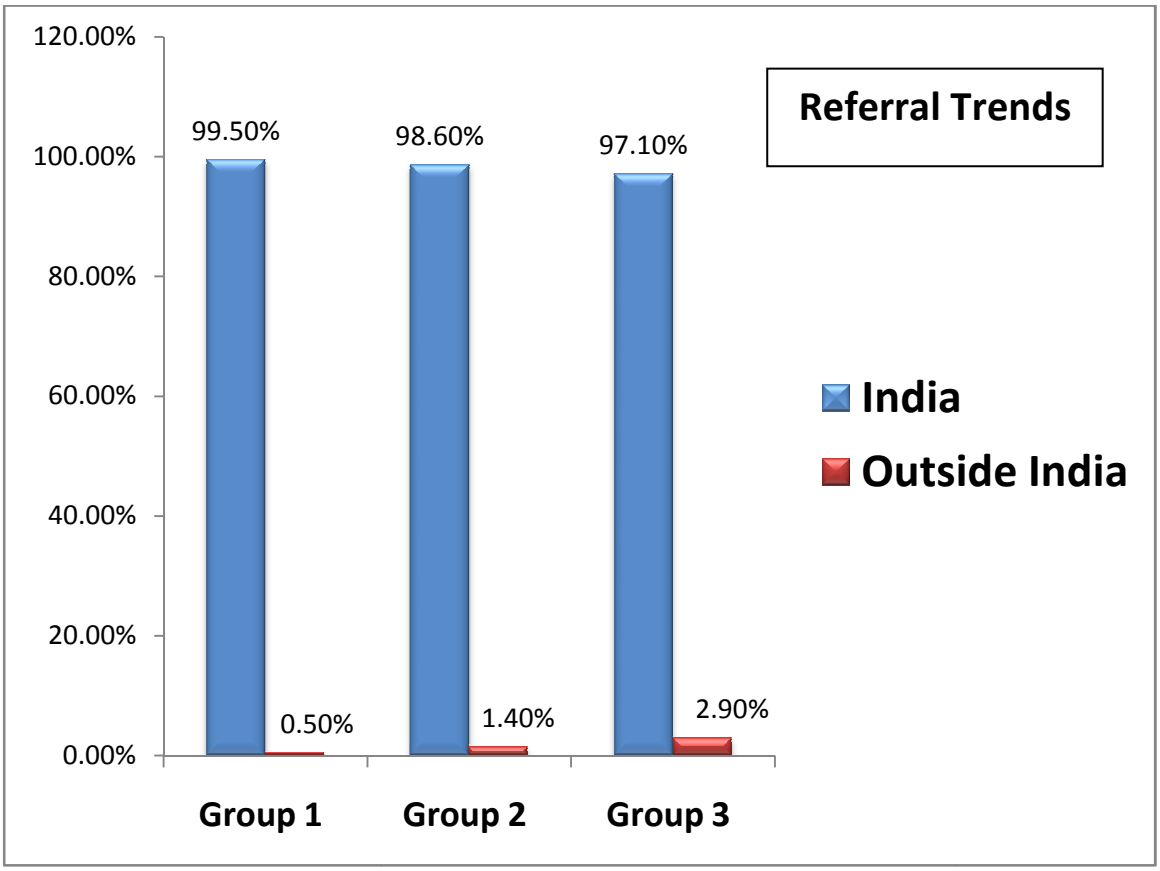
Of the 1364 patients, 747 (54.8 %) were males and 617(45.2 %) were females. There was no significant difference in gender distribution among the groups (p= 0.501). (Figure 2)

Figure 2: Gender Distribution of patients



1341 patients (98.35%) were residents of India while 23 patients (1.75%) had their domicile abroad. There was a trend for increase in the number of patients referred from other countries over time: 0.5% in group 1, 1.4 % in group 2 and 2.9 % in group 3 (p= 0.023). (Figure 3)

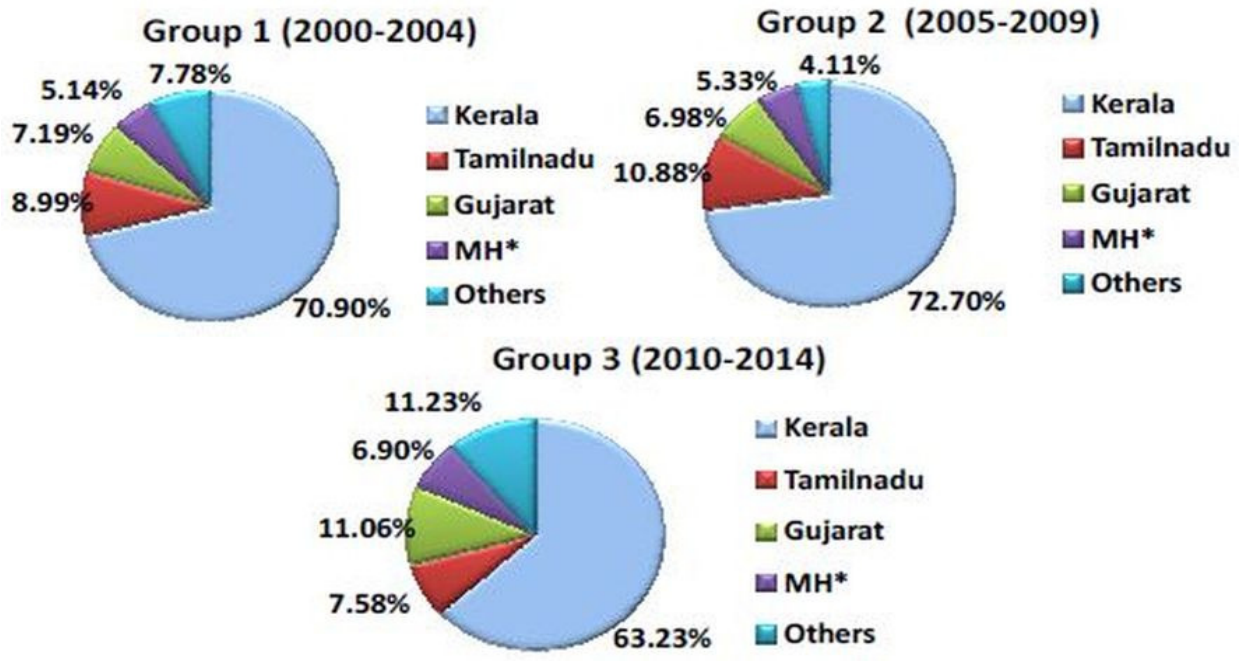
Figure 3: Referral trends - domicile



Of 1364 patients, 805 (59.01%) referrals were from within Kerala, 125 (9.16%) referrals were from Tamil Nadu, 116 (8.50%) were form Gujarat and 80 (5.86%) from Maharashtra, 33(2.41%) patients from West Bengal and Madhya Pradesh, 29(2.1%) from Andhra Pradesh, 27(1.97%) patients from Uttar Pradesh, 25 (1.83%) from Rajasthan, 19 from Karnataka

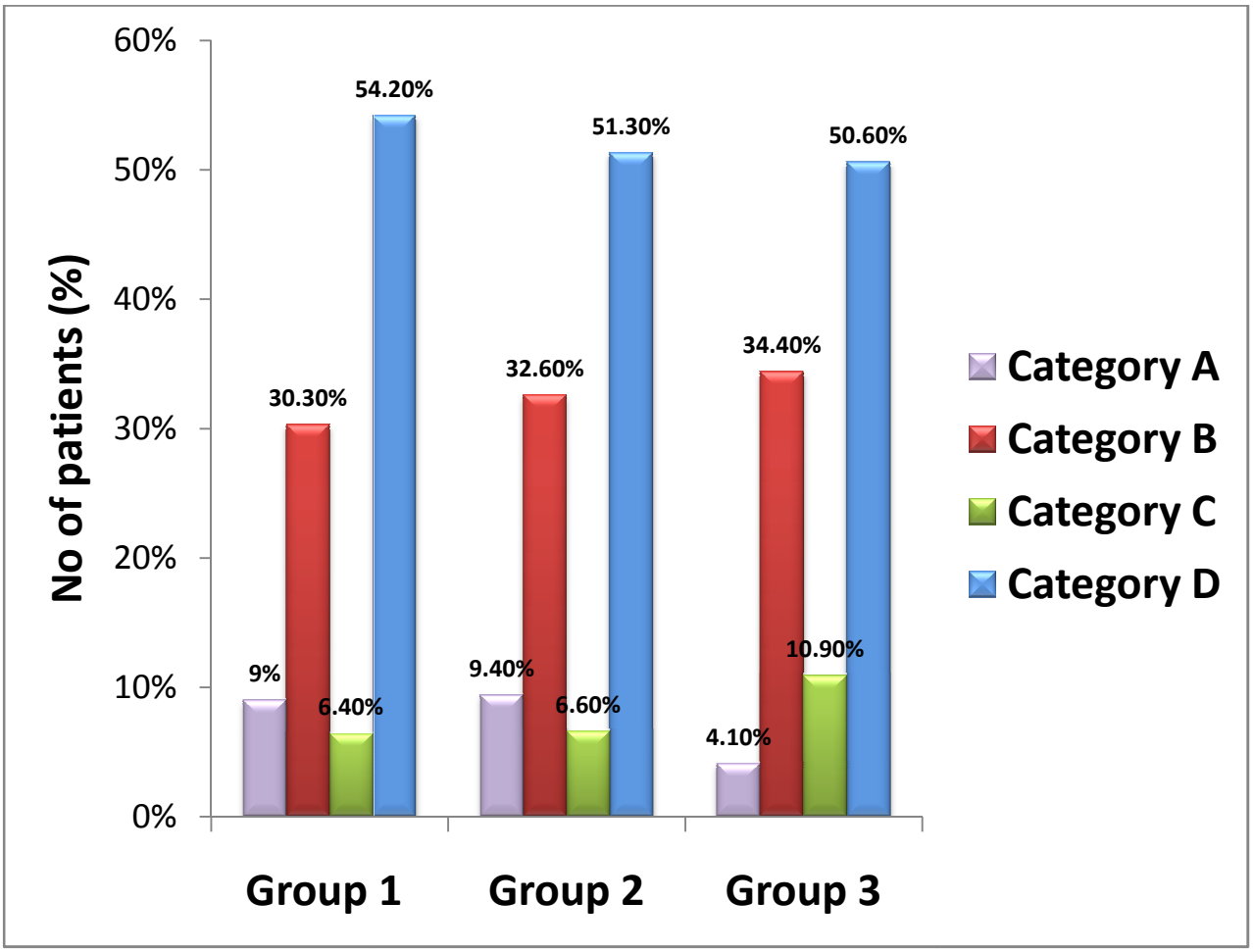
(1.39%). Referrals from within Kerala were 276 in group1, 283 in group 2 and 246 in group 3. The break-up of percentage of patients referred from other states are shown in **Figure 4.**

Figure 4: Referral trends- statewise domicile



Majority of the patients belonged to the highest income category-D (51.9%), followed by B (32.6%), C (8.1%) and A (7.4%). (Figure 5)

Figure 5: Income category



Data related to educational status were unavailable in 703 (51.3%) patients. A majority of the patients had completed high school- 329 (24.1%), 139(10.2%) patients had completed

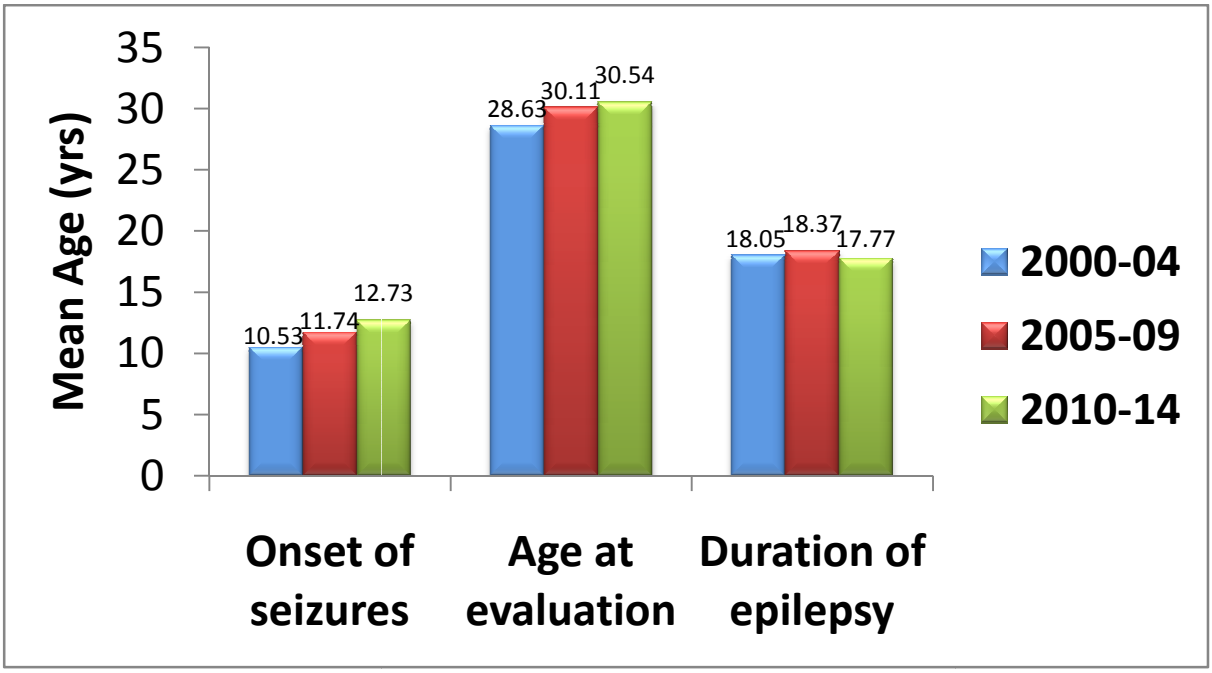
primary school, 102 (7.5%) patients had completed graduation, 73(5.4%) patients had attended higher secondary school and 2 (0.1%) patients were illiterate. The detailed break-up across the three groups are shown in Table 1.

Table 1: Educational Status of patients

Education	Group1	Group 2	Group3	Total
Postgraduate	4	7	5	16
Graduate	21	34	47	102
Higher secondary school	16	28	29	73
High school	84	114	131	329
Primary	61	41	37	139
Illiterate	0	0	2	2

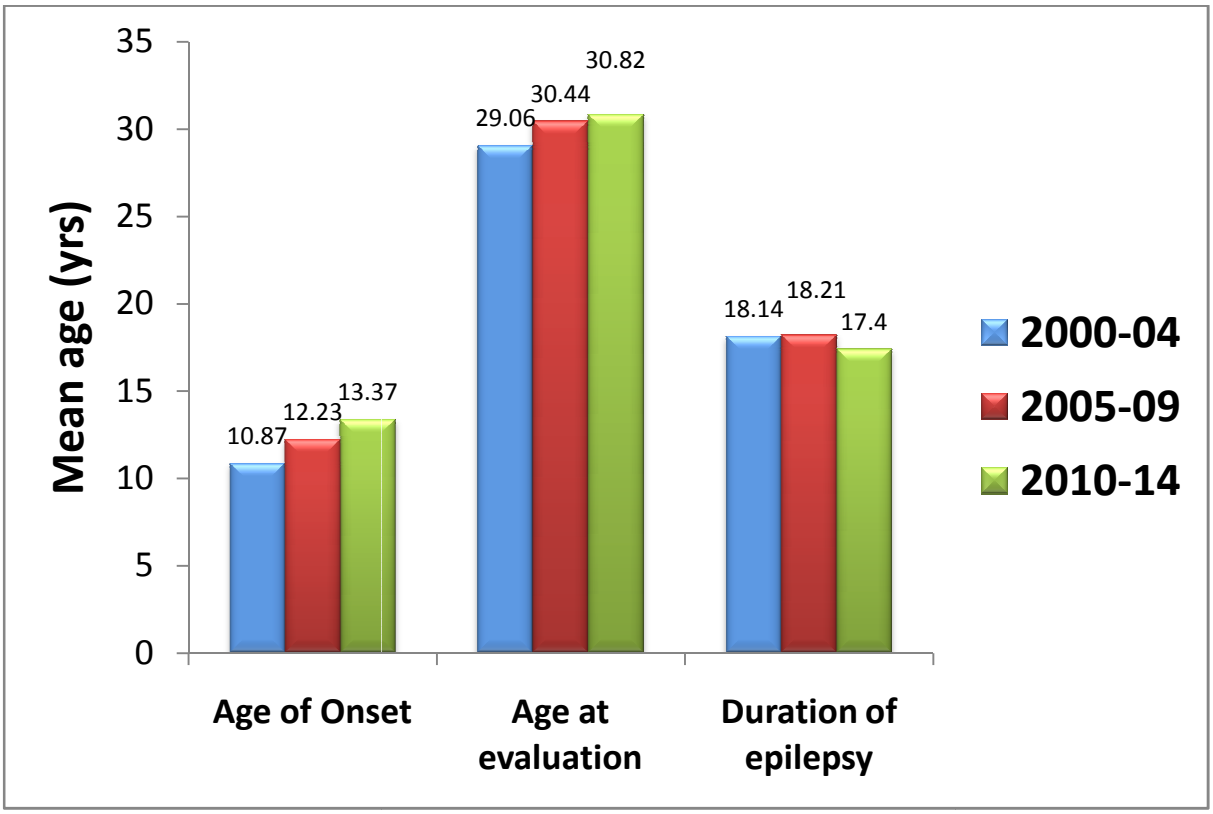
The mean age of onset of seizures was 11.75 ±8.58 years, mean age at evaluation was 29.84 ±9.47 and the mean duration of epilepsy before referral was 18.07 ±9.48 years. There was a significant increase in age at onset of seizures (p=0.001) and age at evaluation (0.009) over time but the mean duration of epilepsy before referral showed no significant change over time (p= 0.612) (Figure 6).

Figure 6: Temporal trends of referral



The age of onset, age at evaluation and duration of epilepsy were analysed after weighting for Gender, income and domicile. While other parameters did not show any change in the pattern, on weighting for income, the age at diagnosis ($p<0.001$) and age at evaluation ($p<0.001$) continued to show an increase significantly, but a significant decrease in duration of epilepsy ($p=0.045$) was also noted (Figure 7).

Figure 7: Temporal trends in referral- weighted for income



The age of onset of seizures, age at evaluation and duration of seizures of the entire study population and after weighting for income are shown in Table 2.

Table 2: Temporal trends in referral

		Crude			Weighted for income group		
		Mean	SD	ANOVA p value	Mean	SD	ANOVA p value
Age of onset	2000-2004	10.53	6.723	.001	10.87	6.804	<0.001
	2005-2009	11.74	8.853		12.23	9.338	
	2010-2014	12.73	9.461		13.37	9.562	
Age at diagnosis	2000-2004	28.63	9.021	.009	29.06	9.232	<0.001
	2005-2009	30.11	9.331		30.44	9.650	
	2010-2014	30.54	9.890		30.82	10.090	
Duration	2000-2004	18.05	8.995	.612	18.14	9.097	0.045
	2005-2009	18.37	9.420		18.21	9.494	
	2010-2014	17.77	9.907		17.40	10.144	

However, post hoc Bonferroni tests revealed significant increase in age at evaluation and age at diagnosis but did not reveal a significant change in duration of epilepsy. (Table 3)

Table 3: Temporal trends in referral- post hoc tests

	Groups compared	**P value**
Age of onset of seizures	Group1 & 2	<0.001
	Group 2 & 3	0.001
	Group 1 & 3	<0.001
Age at evaluation	Group 1 & 2	0.001
	Group 2 & 3	0.859
	Group 1 & 3	0.001
Duration of seizures	Group1 & 2	0.99
	Group 2 & 3	0.069
	Group 1 & 3	0.15

Subgroup analysis: A subgroup analysis of patients with MTS showed a significant increase in age of onset and age at diagnosis but showed no significant change in the duration of epilepsy. A similar trend was seen even after weighting for income (Table 3).

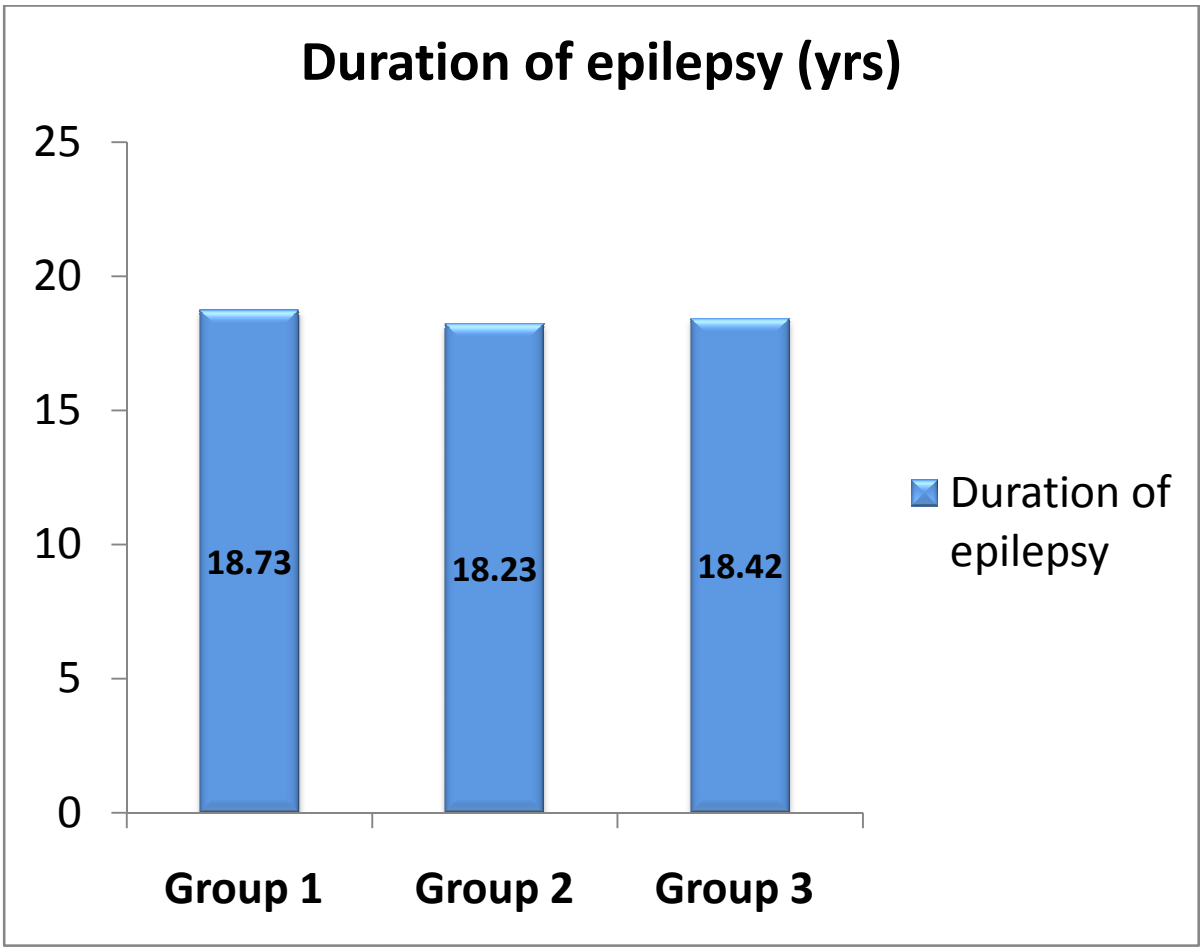
Table 4: Referral trends in subgroup of patients with MTS

					Weighted for income group		
		Mean(years)	SD	p value	Mean(years)	SD	p value
Age of onset	2000-2004	10.45	6.768	0.006	10.85	6.98	<0.001
	2005-2009	11.57	8.66		12.17	9.14	
	2010-2014	12.38	8.96		12.89	8.90	
Age at diagnosis	2000-2004	28.78	9.06	0.018	29.19	9.25	<0.001
	2005-2009	30.31	9.41		30.67	9.78	
	2010-2014	30.62	9.87		30.97	10.04	
Duration	2000-2004	18.27	9.09	0.694	18.28	9.21	.552
	2005-2009	18.73	9.42		18.50	9.53	
	2010-2014	18.23	9.79		18.09	10.07	

The mean duration of epilepsy in patients with MTS did not change significantly over time.

(p=0.694)

Figure 8: Duration of epilepsy in patients with MTS



There was no change in mean number of AEDs tried before referral over time (Table 5).

Table 5: Mean number of AEDs tried before referral

	N	Mean	Std. Error	p value*
2000-2004	389	3.557± 1.204	0.061	
2005-2009	487	3.575± 1.168	0.053	0.680
2010-2014	488	3.626± 1.282	0.0580	

A subgroup analysis of patients on >2 AEDs was made across the groups. 12.9% of patients in Group1, 10.3% in group 2 and 14.4% in group 3 were on 2 or 1 AEDs. When groups 2000-2004 and 2005-2009 are combined, there is a significant difference – the proportion of MTS patients who were treated with >2 AEDs prior to referral have come down from 89.3% to 85.2%. (p=0.043) (Figure 9) (Table 6)

Figure 9: Number of AEDs tried before referral

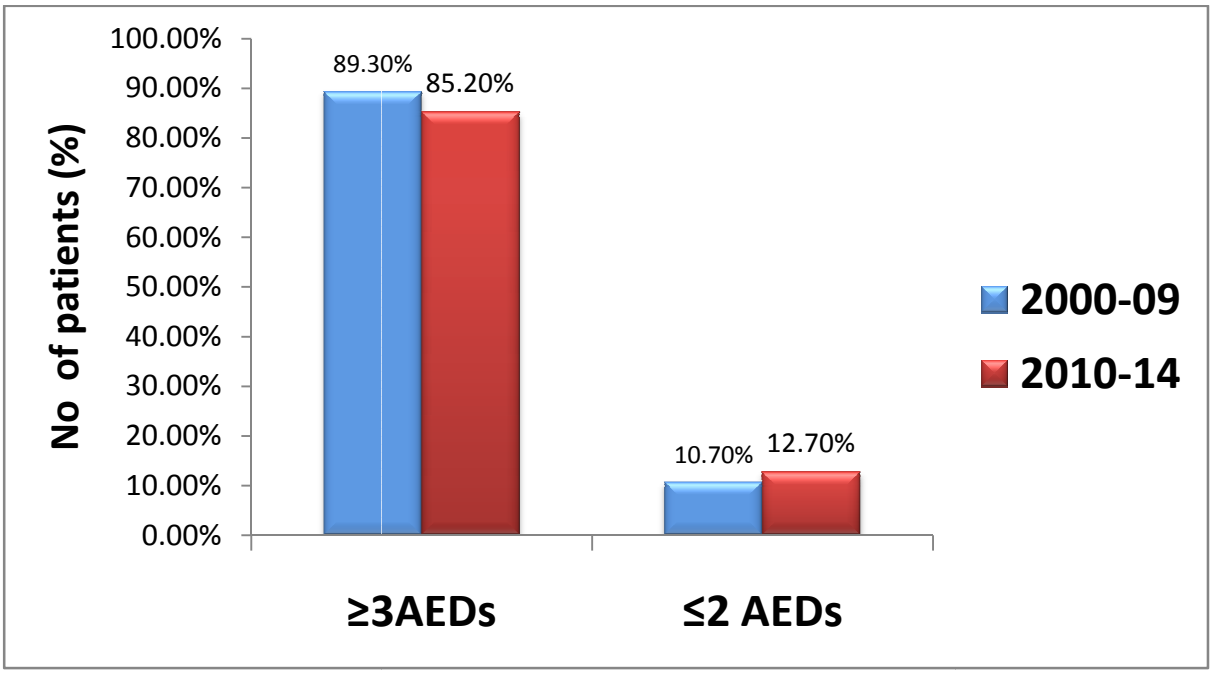


Table 6: Number AEDs tried before referral

More than 2 AEDs			
	No	**Yes**	**p value**
2000-04 & 2005-09	81 (10.7%)	677 (89.3%)	0.043
2010-2014	57 (14.8 %)	328 (85.2%)	

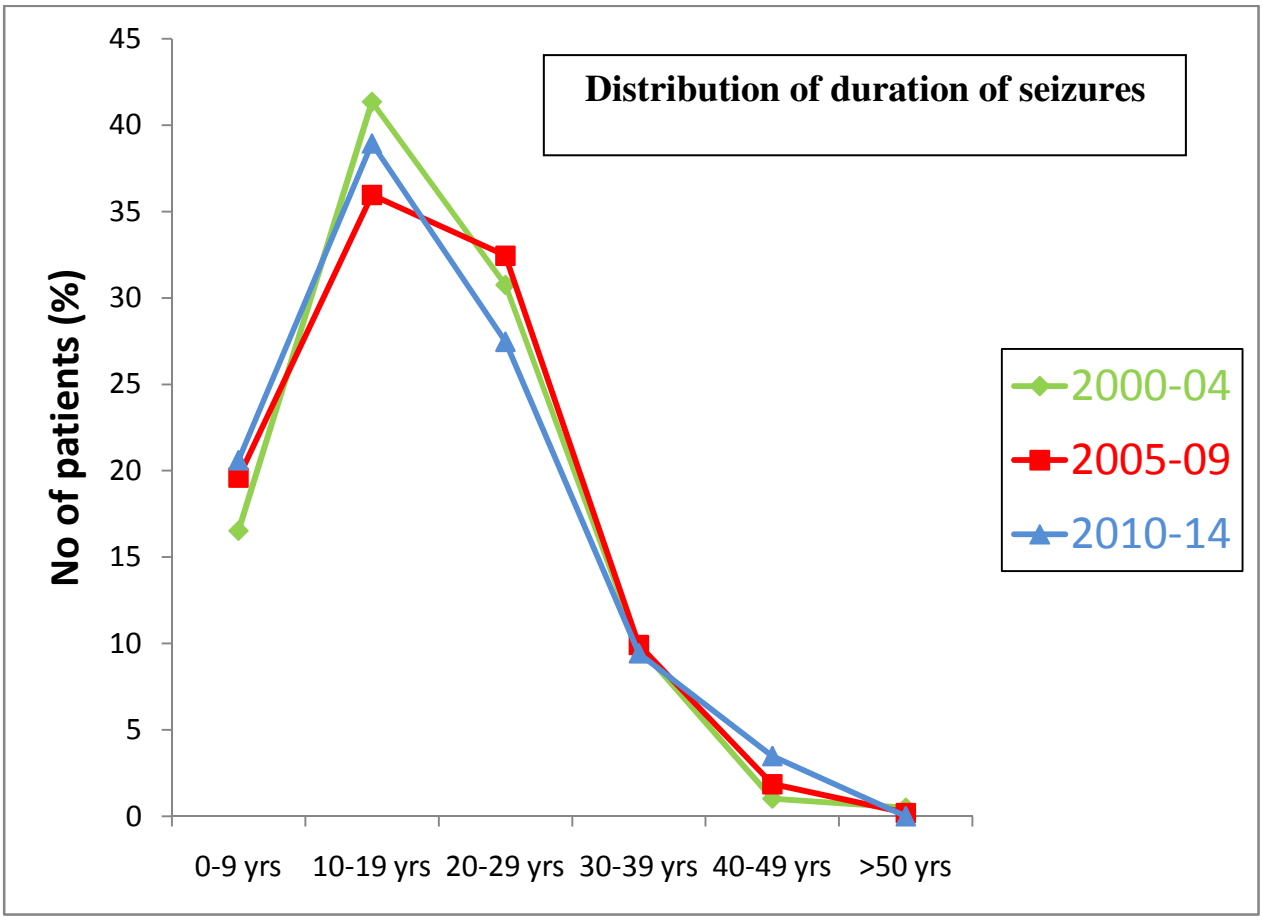
The distribution of duration of seizures shows a higher percentage of patients with duration of epilepsy between 40- 49 in group 3 (3.48%) as compared to group 1(1.03%) and 2 (1.86%)

and could more patients with a longer duration of seizures undergoing pre-surgical evaluation could be a reason. (Table 7, Figure 10)

Table 7: Distribution of duration of seizures

	Group 1	**Group 2**	**Group 3**
0-9 years	16.53 %	19.60 %	20.6 %
10-19 years	41.34 %	35.95 %	38.93 %
20-29 years	30.75 %	32.44 %	27.66 %
30- 39 years	9.82 %	9.92 %	9.43 %
40-49 years	1.03 %	1.86 %	3.48 %
>50 years	0.51 %	0.2 %	0

Figure 10: Distribution of duration of seizures



The most common aetiology was found to be MTS which accounted for 86.7% of the cases.

A similar trend was seen across the groups – 85.6 % in Group 1, 88.04% in Group 2 and 86.1% in Group 3 were diagnosed to have MTS.

Tumours were found to be the second most common cause and accounted for 4.6% of the cases. 3.59% of the cases in Group 1, 5.56 % in group 2 and and 4.68% in group 3 were due to tumours – DNET, ganglioglioma, Fibrillary astrocytomas and low grade gliomas.

Vascular malformations accounted for 1.17% of the cases - 1.29% in group 1, 0.8% in group2 and 1.42% in group 3. The commonest vascular malformation diagnosed was Cavernoma.

1.3 % of the patients had an encephalitic illness as a provoking factor, 2.82% in group 1, 0.4% in Group 2 and 1.01 % in Group 3.

DISCUSSION

Despite accounting for 80% of patients worldwide with epilepsy, epilepsy surgery is available in only 13 % of the lower income countries.[1] Recent years have seen a rapid growth in epilepsy surgery services in developing countries most prominently in India and China. A recent survey recognized 18 centres offering epilepsy surgery in India, half of which were located in South India .[8] The South Indian state of Kerala, where our centre is situated, has a population of 3.33 crores, is ranked 11th in the country in terms of per capita income but has the highest Human development index, which is a composite statistic of life expectancy, education, and income per capita indicators. Kerala's unique feature is how it has leveraged its limited Gross Domestic Product to achieve remarkable outcomes in health, education and quality of life and thus serves as a model state for developing countries.

The epilepsy surgery program in our Institute was started in 1995 and till date 1795 surgeries have been performed. A previous study from our institute in 1996 on referral patterns in epilepsy reported a delay in diagnosis of epilepsy which was significantly more for women and patients from a rural background and revealed that the organization and delivery of neurological services for epilepsy was inadequate.[25] A multi-centric study on epilepsy care in 6 Indian cities in 2001 revealed that services for epilepsy are urban-based and that epilepsy services were underutilized.[26] However, the temporal trends of referral were not examined in these studies.

In our study, the number of patients admitted for pre-surgical evaluation for TLE steadily increased in the first epoch (387 in group 1, 487 in group 2) but remained stable therafter (488, group 3). The number of patients being referred from states other than Kerala increased in the third epoch (29.1% in group 1 to 36.8% in group 3) as did the number of patients being referred from other countries (0.5% in group 1 to 2.9% in group 3).

In contrast to an increasing awareness and therefore establishment of more centres for epilepsy surgery in India,[8] a decreasing trend in epilepsy surgery is seen in developed countries including U.S., U.K, Germany etc.[21] This was previously attributed to a lack of definite guidelines for epilepsy surgery. However, a recent study from U.S. by Haneef et al showed that despite adequate recommendations, no significant earlier referrals for pre-surgical evaluation could be identified.[31] All evidence points to increased risk of recurrence after focal surgery when the duration of preoperative epilepsy is >20 years.[38] Recent evidence also points to lower probability of seizures following early resective surgery especially in childhood, thus highlighting the importance of early referral for pre-surgical evaluation.[18]

Although the number of surgeries for drug-resistant epilepsy in India has risen modestly in the last 1-2 decades with 18 centres doing at least 20 surgeries per year, there is still dearth of adequate number of centres leading to a huge surgical treatment gap.[9] All the more, the average duration of epilepsy before referral we found was 18.42 ± 9.46 years. This is similar to the average duration of epilepsy before evaluation or intervention reported

worldwide **(Table 8)**. Thus no significant trend for an earlier referral to an epilepsy surgery centre was seen in our study over the last 2 decades despite class I evidence and guidelines for early referral.

Table 8: Comparison of studies on duration of epilepsy before referral/ surgery

Author	Year of study	Place of study	No of patients	Duration of epilepsy(yrs)
Benbadis et al	2000-2001	Tampa	36	18
Choi et al	1996-2007	New York	213	21.1-22.6
Haneef et al	1995-98, 2005-08	California	185	17.1- 18.6
Helmstaedter et al	1998-2008	Multicentric, Germany	2812	23±13
Present study	2000-2014	India	1384	18.07 ±9.48

We noticed that age at onset and age at evaluation of TLE was seen to increase i.e. more number of patients had their habitual seizures starting at a later age, but still they reach a surgical care centre very late. This also warrants attention. Helmstaedter et al [39] reported an increasing age at surgery and duration of seizures in patients with histologically proven hippocampal sclerosis which was absent in other etiologies like FCD, gliosis and vascular malformations. Possible explanations suggested include changing incidence of MTS due to better treatment of infections and febrile convulsions, vaccination and better seizure control with newer AEDs which may be applicable in our setting too. Helmstaedter et al also called

for studies from developing countries to identify any change in trends. Our study, being the only study from a developing country thus assumes importance in understanding any changes in epidemiology of MTS over time.[39] Findings of our study, which mirror global studies on age of onset of habitual seizures, point to a change in incidence of MTS. However, this needs to be corroborated with population based studies.

Similarly, the increasing age at evaluation over the years appears to be counter-intuitive. Increasing number of epilepsy surgery centres may lead to more number of patients being evaluated in smaller centres before being referred to a large volume center. However, in our study, patients with prior pre-surgical evaluation were excluded and cannot be the reason for increasing age at evaluation. The distribution of duration of seizures shows a higher percentage of patients with duration of epilepsy between 40- 49 in group 3 (3.48%) as compared to group 1(1.03%) and 2 (1.86%) and could more patients with a longer duration of seizures undergoing pre-surgical evaluation could be a reason. (Figure 10) Haneef et al in their study of referral data between 1995-98 and 2005-08, reported a higher percentage of patients with a longer duration of epilepsy among the latter group. They proposed a tendency to operate on older patients, better awareness among older patients of surgical options which could have counterbalanced the effect of some earlier referrals resulting in no significant difference in the overall results between the groups in the study.[31]

Importantly, early referrals are still low with the proportion of patients referred before 10 years being 16.53 % in group 1, 19.60 % in group 2 and 20.60% in group 3.

While the availability of increasing number of AEDs and ambiguity in definition of drug resistance could partly explain the delay in referral, our study did not reveal any change in the number of AEDs tried before referral over time. Further, the ILAE proposed a consensus definition for drug-resistant epilepsy in 2009 as inefficacy of 2 AEDs to control seizures (5). We also analysed the number of patients referred after a trial of more than 2 AEDs across the three groups, but found no significant difference although a trend towards usage of fewer AEDs before referral was noted in Group 3.

Jehi et al summed up the reasons for delayed referral as "knowledge gap" and "feasibility gap" [32.] Knowledge gap refers to the attitude of treating physicians and neurologists towards epilepsy surgery. Studies from U.S, Italy and a recent one from Canada have recognized that a substantial proportion of neurologists and treating physicians are unaware of the recommendations for epilepsy surgery.[18, 19, 20] Though there are no studies on the attitude of Indian neurologists/ physicians towards epilepsy surgery, the situation is unlikely to be any different. "Feasibility gap" refers to the physical and temporal barriers to epilepsy surgery and could play a particularly important role in developing countries.

This study is the first of its kind from the continent and provides insights into patterns of referral over the last two decades from a developing country. Despite recommendations for early surgery in drug resistant TLE, no significant trend for an earlier referral for pre-surgical evaluation was seen in this study. This calls for intensification of efforts to increase awareness about benefits of early surgery in drug resistant TLE amongst neurologists,

medical practitioners as well as patients and caregivers to ensure timely referral and pre-surgical evaluation.

Limitations of the study:

Our study has a few limitations-the duration of pharmacotherapy before referral would have been a better measure of pharmaco-resistance but could not be assessed given the retrospective nature of the study. Further, details about the designation of the referring doctor, the nature of treatment received before referral and the dose of AEDs were not available in all patients. Finally, these findings are from a single centre and caution has to be exercised before extrapolating the results.

CONCLUSIONS

- There is an increase in number of referrals for temporal lobe epilepsy between 2000-05 and 2006-15.
- There was a trend for increase in number of referrals from outside India over time.
- A majority of references were from within Kerala but over time an increasing proportion of referrals from other states w noted.
- A majority of patients belonged to high income category (51.9%) and only a minority of them (7.4%) belonged to lowest income category.
- Of the available data on education, a majority of patients had completed high school and only a minuscule number were illiterate.
- The mean age of onset of seizures was 11.75 ±8.58 years, mean age at evaluation was 29.84 ±9.47 and the mean duration of epilepsy before referral was 18.07 ±9.48 years.
- There was a significant increase in age at onset of seizures and age at evaluation over time but the mean duration of epilepsy before referral showed no significant change over time.
- On weighting for income, there was a significant increase in age at onset of seizures and age at evaluation over time and a significant decrease in mean duration of epilepsy before referral. However, the post hoc Bonferroni tests showed no significant decrease in mean duration of epilepsy before referral.

- A subgroup analysis of patients with MTS alone showed a mean age of onset of seizures of 11.54 ± 8.30 years, age at evaluation of 29.98 ± 9.50 years and mean duration of seizures before referral of 18.43 ± 9.46 years.
- In patients with MTS, the age of onset of seizures in patients significantly increased over time, the age at evaluation increased significantly over time and the duration of seizures did not change significantly over time. A similar trend was seen even on weighting for income.
- Mean number of AEDs tried before referral was 3.60 ± 1.2
- There was no significant change in the number of AEDs tried over time.
- There was a trend for a decrease in proportion of patients tried on > 2 AEDs before referral over time.

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ANNEXURE

LIST OF ABBREVIATIONS

AED	Anti Epileptic Drug
EEG	Electro Encephalo Graphy
DNET	Dysembryoplastic Neuro Epithelial Tumour
FCD	Focal Cortical Dysplasia
ILAE	International League Against Epilepsy
MTS	Mesial Temporal Sclerosis/ Medial Temporal Sclerosis
MTLE	Medial Temporal Lobe Epilepsy
TLE	Temporal Lobe epilepsy
VNS	Vagal Nerve Stimulation
VEEG	Video Electro Encephalo Graphy

PROFORMA

Name:

Age:

Gender:

Hospital no:

Telephone:

Address:

State of domicile:

Income category:

Educational status:

Initial precipitating injury:

Date of first evaluation in epilepsy clinic:

Age at onset of clinical seizures:

Duration of epilepsy:

Number of medicines tried and over how many years:

Number of doctors who had seen them before undergoing pre-surgical evaluation:

Age at diagnosis:

Type of intervention in this centre: Surgical/ Medical/ Lost to follow-up

If medical, medicines at discharge:

Monthly expenses for medicines:

Reasons for non-surgical management: Infrequent seizures/ Financial constraints/

Unwillingness/ Social issues/ Active psychosis/ Others:

Date of epilepsy surgery, if done:

Engel Epilepsy Surgery Outcome Scale: Class I/II/III/IV

Whether AEDs stopped or not:

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Study of referral patterns for temporal lobe epilepsy in a tertiary epilepsy surgery centre in India

Dr Ajay Asranna I P

Introduction

There are estimated to be about 50 million people with epilepsy worldwide, a majority of whom live in low-income and lower middle income countries.(1) Approximately 20 to 30% of persons with epilepsy have drug-resistant seizures that are not adequately controlled by pharmacotherapy(2). Mesial temporal lobe epilepsy (MTLE) is the prototype of a surgically remediable epilepsy syndrome with mesial temporal sclerosis (MTS) being the commonest etiology (3). The last decade has seen growing evidence for the benefits of epilepsy surgery. In 2001, a randomised control trial affirmed the superiority of surgical treatment over medical treatment in refractory TLE (4). In 2003, the American Academy of Neurology in association with the American Epilepsy Society and the American Association of Neurological Surgeons recommended that patients with disabling complex partial seizures should be considered for referral to an epilepsy surgery centre on failing adequate trials of first line antiepileptic drugs (4). Further, to better define pharmaco-resistance and resolve the controversy over the timing of referral, ILAE proposed a consensus definition for drug resistant epilepsy in 2009(5).

Despite these developments, surgical treatment for TLE remains underutilized even in developed countries.(6, 7) Furthermore, studies have not shown a trend towards earlier referral despite guidelines for referral once the patient becomes pharmaco-resistant. The number of epilepsy surgeries in developing countries show an increasing trend, but the reasons related to this increase are still unclear.(8) The temporal trends of referral and the impact of increasing evidence for epilepsy surgery on referral in low and middle income nations has not been investigated. A study of the patterns of referral to an epilepsy surgery centre could give valuable insights into the extent to which existing facilities are being utilised as well as loopholes in the organisational structure. This could influence policy decisions regarding future projects related to epilepsy care. In this study, we analysed the patterns of referral to a tertiary epilepsy surgery centre in India catering to all epilepsy sub-types and the trends in referral patterns over time.

Aims and objectives

1. To study the patterns of referral for TLE surgery centre in a tertiary care centre with all facilities after establishment of definite guidelines on the success of epilepsy surgery in TLE over medical treatment.
2. To investigate any changes in the patterns of referral over time spanning last two decades and compare it with a developed country.

Inclusion criteria

1. Age> 16 years

2. Diagnosed to have intractable TLE as per the latest ILAE guidelines[7] after evaluation by clinical, radiological, video-EEG,SPECT/PET/sphenoidal recording/invasive re cording if necessary.

Exclusion criteria

1. Acute or chronic psychosis on treatment
2. Associated generalized epilepsy or Paroxysmal non epileptic events (PNES) or any other type of epilepsy syndrome.
3. Any associated progressive/degenerative neurological condition
4. Any progressive medical condition precluding surgical candidacy.

Materials and Methods

Data of 10,348 patients who underwent long-term VEEG monitoring in our Institute, as a part of pre-surgical evaluation were analysed from the prospectively maintained records. Patients who fulfilled the above mentioned inclusion and exclusion criteria and were divided into three groups as five year periods during which they underwent pre surgical evaluation, Group 1: Year 2000-2004; Group 2: Year 2005-2009; Group 3: Year 2010-2014.

1364 patients who fulfilled inclusion criteria were included in the study; 389 in Group 1, 487 in Group 2 and 488 in Group 3**.** Patients attending the epilepsy clinic in our Institute are grouped into various categories based on their socio-economic status and per capita income as low(A,B) and high income(C,D) groups. Referral data with particular reference to state of domicile, income category, duration of epilepsy before referral, age at onset of seizures and number of AEDs tried before referral were analysed. Age at onset of seizures was defined as age of first non-febrile seizure, age at evaluation as the age at the time of first admission for VEEG and duration of epilepsy was the age at evaluation subtracted by the age at onset.

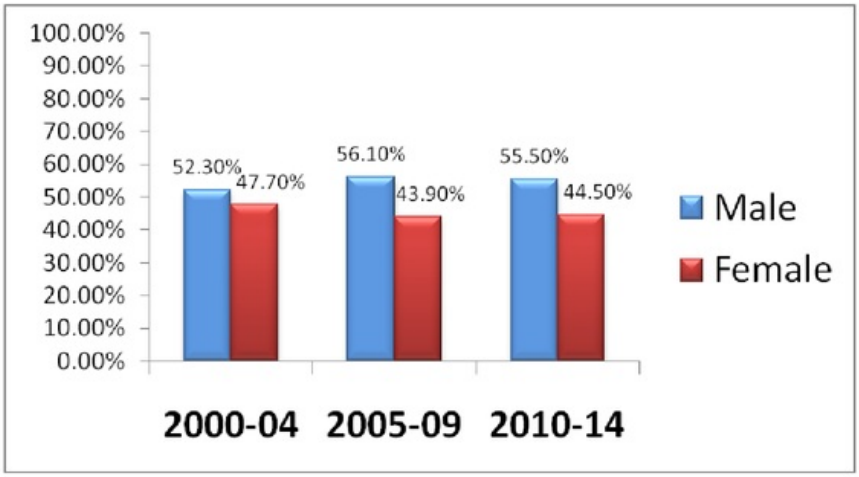
STATISTICAL ANALYSIS

All data were analyzed using SPSS 8, Inc,Chicago, IL,U.S.A. Categorical variables were analyzed in proportions and compared using Chi square test, numerical variables were analyzed using means and SD and compared using ANOVA. As the income group was found to be a potential confounder, the analysis was repeated after weighting for income group. Bonferroni post hoc tests analyzed change in duration of epilepsy over time.

RESULTS

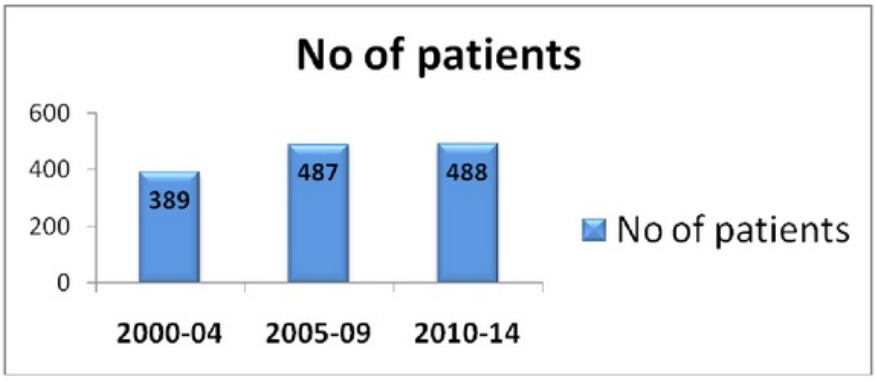
Of the 1364 patients, 747 (54.8 %) were males and 617(45.2 %) were females. There was no significant difference in gender distribution among the groups (p= 0.501). (Figure 1)

Figure 1



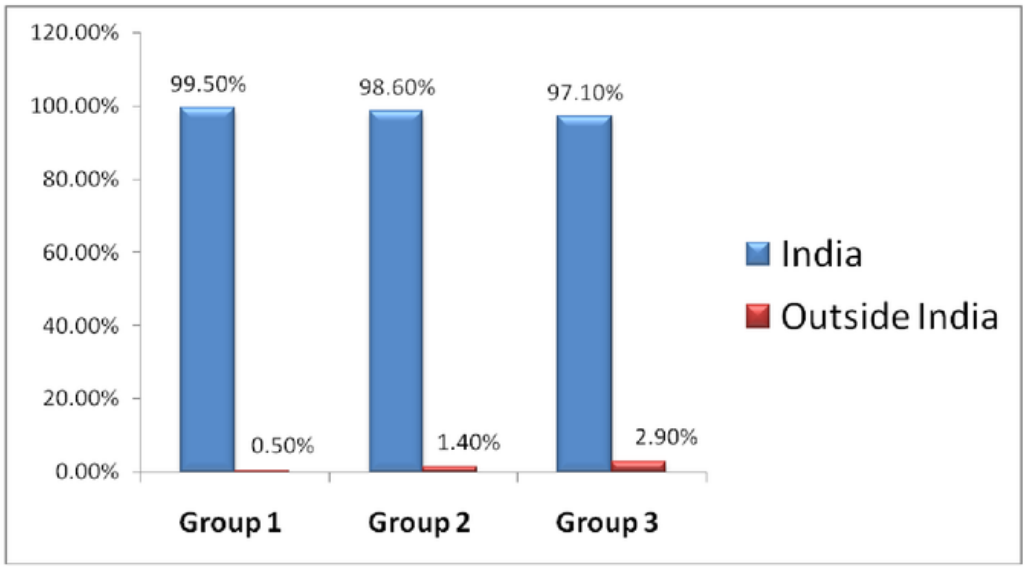
The number of patients referred for presurgical evaluation increased over time from 389 in the Group 1 to 487 and 488 patients in group 2 and group 3 respectively (Figure 2)

Figure 2



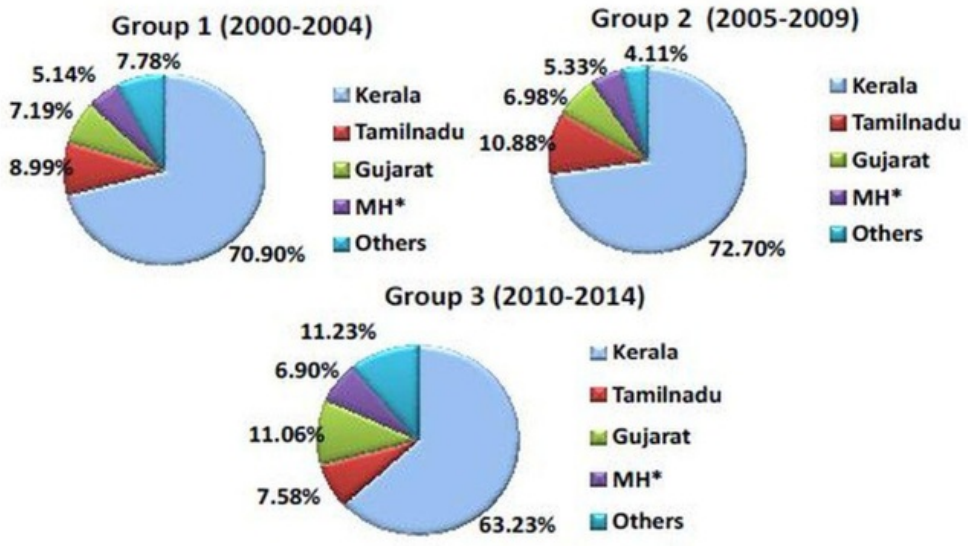
1341 patients (98.35%) were residents of India while 23 patients (1.75%) had their domicile abroad. There was a trend for increase in the number of patients referred from other countries over time: 0.5% in group 1, 1.4 % in group 2 and 2.9 % in group 3 (p= 0.023). (Figure 3)

Figure 3



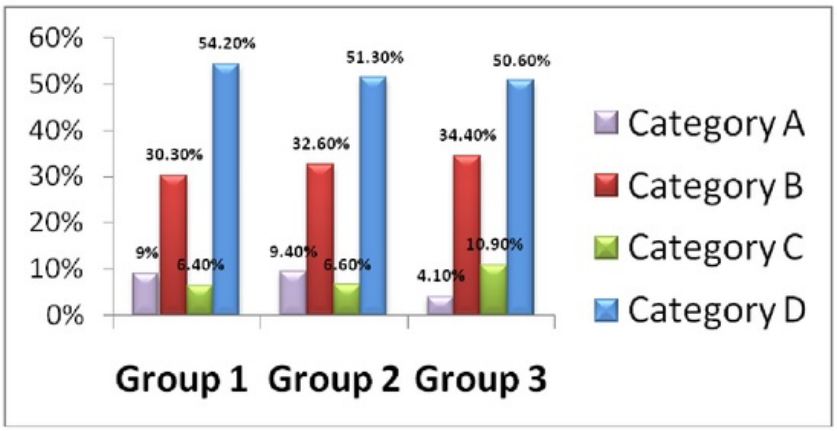
Of 1364 patients, 805 (59.01%) referrals were from within Kerala, 125 (9.16%) referrals were from Tamil Nadu, 116 (8.50%) were form Gujarat and 80 (5.86%) from Maharashtra, 33(2.41%) patients from West Bengal and Madhya Pradesh, 29(2.1%) from Andhra Pradesh, 27(1.97%) patients from Uttar Pradesh, 25 (1.83%) from Rajasthan, 19 from Karnataka (1.39%) .Referrals from within Kerala were 276 in group1, 283 in group 2 and 246 in group 3. The break-up of percentage of patients referred from other states are shown in **Figure 4.**

Figure 4



Majority of the patients belonged to the highest income category-D (51.9%), followed by B (32.6%), C (8.1%) and A (7.4%). (Figure 5)

Figure 5



Data related to educational status was unavailable in 703 (51.3%) patients. A majority of the patients had completed high school- 329 (24.1%), 139(10.2%) patients had completed primary school, 102 (7.5%) patients had completed graduation, 73(5.4%) patients had attended higher secondary school and 2 (0.1%) patients were illiterate. The detailed break-up across the three groups are shown in Table 1.

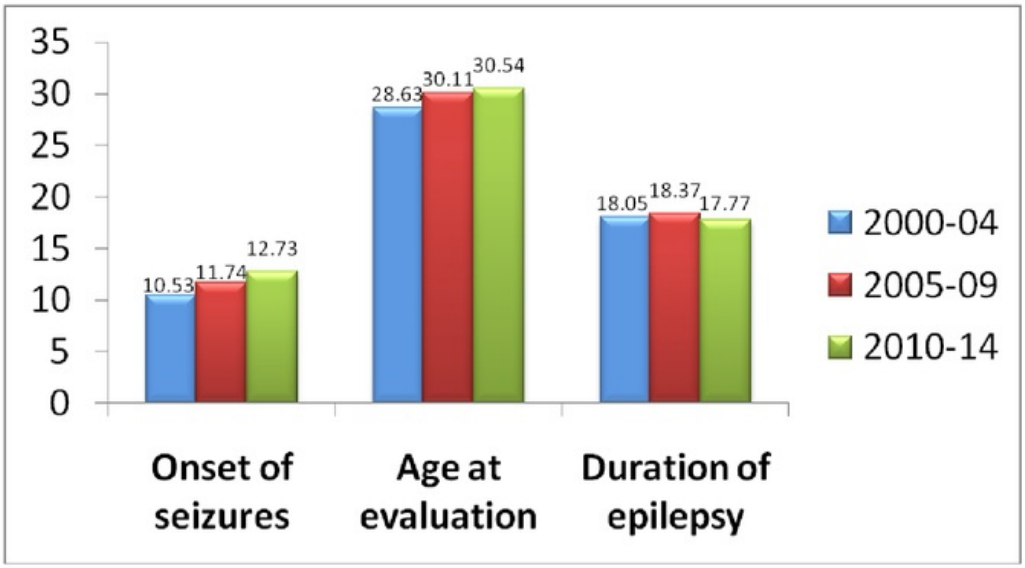
Table 1

Education	Group1	Group 2	Group3	Total

Postgraduate	4	7	5	16
Graduate	21	34	47	102
Higher secondary school	16	28	29	73
High school	84	114	131	329
Primary	61	41	37	139
Illiterate	0	0	2	2

The mean age of onset of seizures was 11.75 ±8.58 years, mean age at evaluation was 29.84 ±9.47 and the mean duration of epilepsy before referral was 18.07 ±9.48 years. There was a significant increase in age at onset of seizures (p=0.001) and age at evaluation (0.009) over time but the mean duration of epilepsy before referral showed no significant change over time (p= 0.612) (Figure 6).

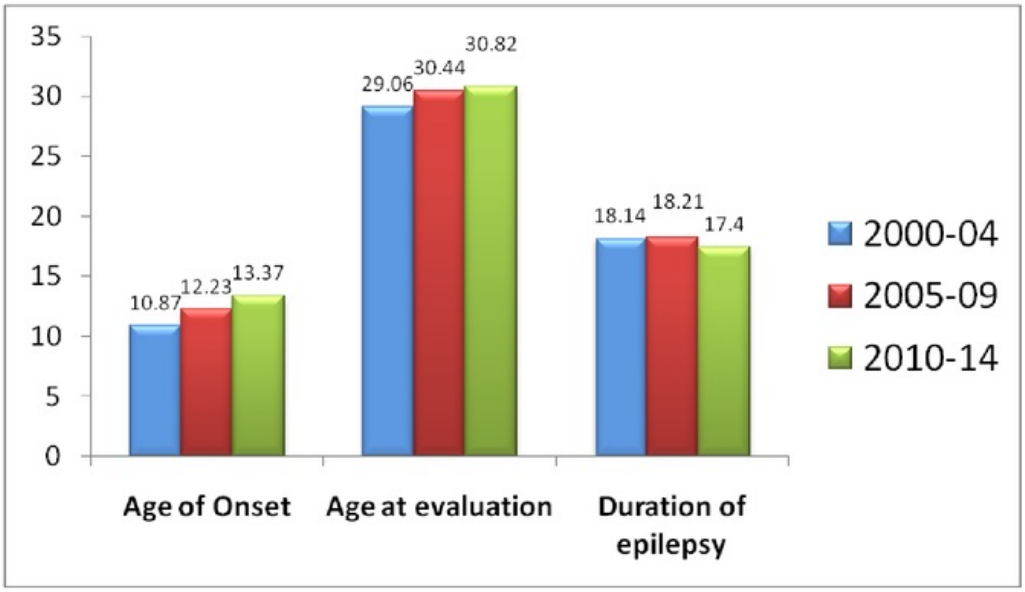
Figure 6



The age of onset, age at evaluation and duration of epilepsy were analysed after weighting for Gender, income and domicile. While other parameters did not show any change in the pattern, on weighting for income, the age at diagnosis (p<0.001) and age at evaluation (p<0.001) continued to

show an increase significantly, but a significant decrease in duration of epilepsy (p=0.045) was also noted (Figure 7).

Figure 7



The age of onset of seizures, age at evaluation and duration of seizures of the entire study population and after weighting for income are shown in Table 2.

Table 2

		Crude			Weighted for income group		
		Mean	SD	ANOVA p value	Mean	SD	ANOVA p value
Age of onset	2000-2004	10.53	6.723	.001	10.87	6.804	<0.001
	2005-2009	11.74	8.853		12.23	9.338	

	2010-2014	12.73	9.461		13.37	9.562	
Age at diagnosis	2000-2004	28.63	9.021	.009	29.06	9.232	<0.001
	2005-2009	30.11	9.331		30.44	9.650	
	2010-2014	30.54	9.890		30.82	10.090	
Duration	2000-2004	18.05	8.995	.612	18.14	9.097	0.045
	2005-2009	18.37	9.420		18.21	9.494	
	2010-2014	17.77	9.907		17.40	10.144	

However, post hoc Bonferroni tests revealed significant increase in age at evaluation and age at diagnosis but did not reveal a significant change in duration of epilepsy. (Table 2)

Table 2

	Groups compared	**P value**
Age of onset of seizures	Group1 & 2	<0.001
	Group 2 & 3	0.001
	Group 1 & 3	<0.001
Age at evaluation	Group 1 & 2	0.001
	Group 2 & 3	0.859
	Group 1 & 3	0.001

Duration of seizures	Group1 & 2	0.99
	Group 2 & 3	0.069
	Group 1 & 3	0.15

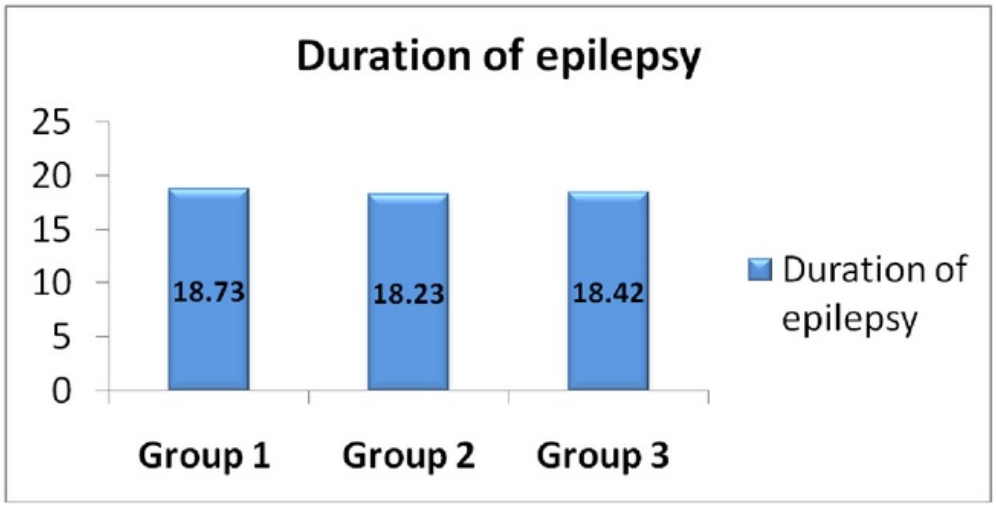
Subgroup analysis: A subgroup analysis of patients with MTS showed a significant increase in age of onset and age at diagnosis but showed no significant change in the duration of epilepsy. A similar trend was seen even after weighting for income (Table 3).

Table 3

					Weighted for income group		
		Mean(years)	SD	p value	Mean(years)	SD	p value
Age of onset	2000-2004	10.45	6.768	0.006	10.85	6.98	<0.001
	2005-2009	11.57	8.66		12.17	9.14	
	2010-2014	12.38	8.96		12.89	8.90	
Age at diagnosis	2000-2004	28.78	9.06	0.018	29.19	9.25	<0.001
	2005-2009	30.31	9.41		30.67	9.78	
	2010-2014	30.62	9.87		30.97	10.04	
Duration	2000-2004	18.27	9.09	0.694	18.28	9.21	.552
	2005-2009	18.73	9.42		18.50	9.53	
	2010-2014	18.23	9.79		18.09	10.07	

The mean duration of epilepsy in patients with MTS did not change significantly over time. (p=0.694)

Figure 8



There was no change in mean number of AEDs tried before referral over time (Table 4).

Table 4

	N	Mean	Std. Error	p value*
2000-2004	389	3.557± 1.204	0.061	
2005-2009	487	3.575± 1.168	0.053	0.680
2010-2014	488	3.626± 1.282	0.0580	

A subgroup analysis of patients on >2 AEDs was made across the groups. 12.9% of patients in Group1, 10.3% in group 2 and 14.4% in group 3 were on 2 or 1 AEDs. When groups 2000-2004 and 2005-2009 are combined, there is a significant difference – the proportion of MTS patients who were treated with >2 AEDs prior to referral have come down from 89.3% to 85.2%. (p=0.043) (Figure 9) (Table 5)

Figure 9

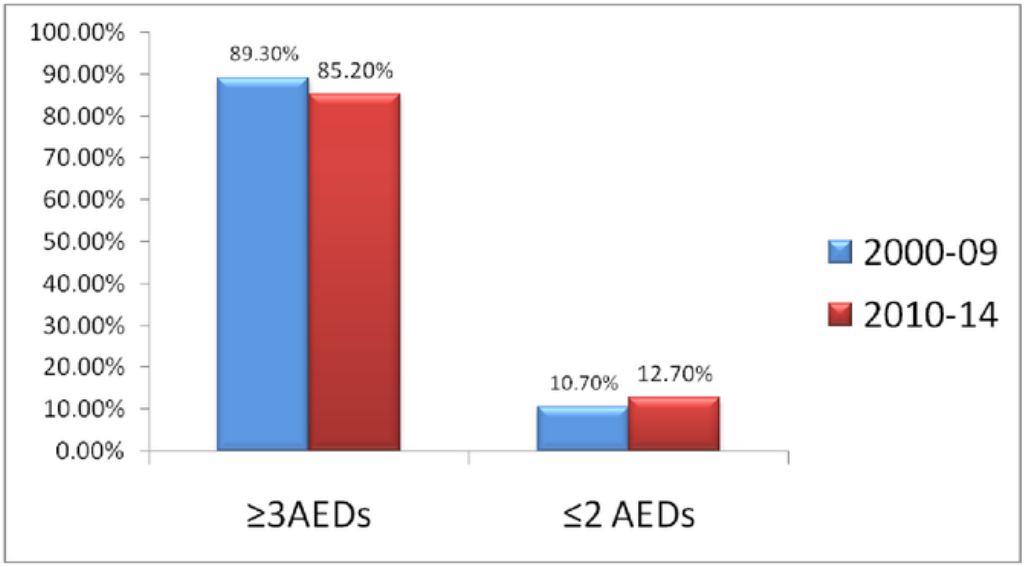


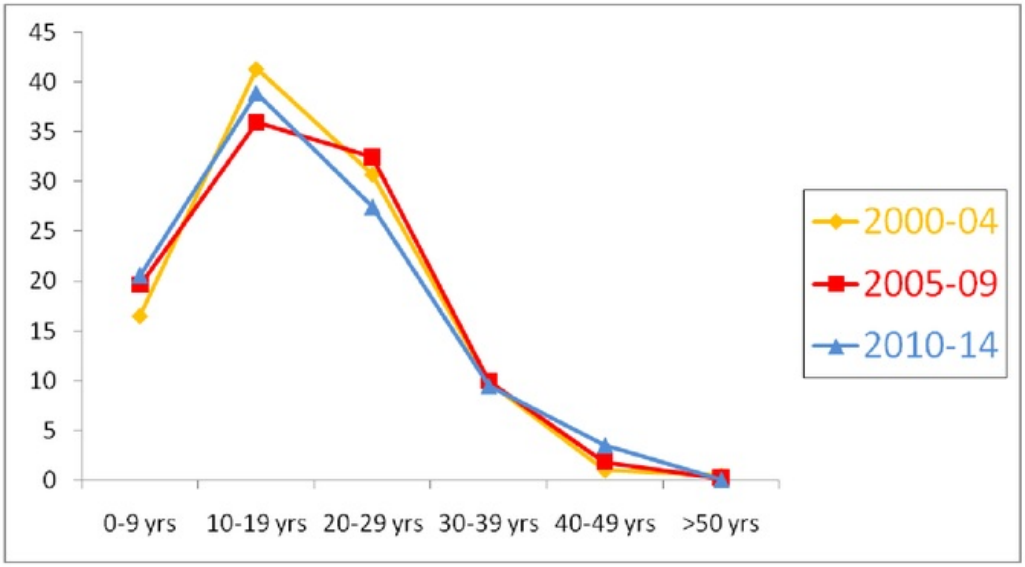
Table 5

More than 2 AEDs			
	No	**Yes**	**p value**
2000-04 & 2005-09	81 (10.7%)	677 (89.3%)	
2010-2014	57 (14.8 %)	328 (85.2%)	0.043

Table 6

	Group 1	**Group 2**	**Group 3**
0-9 years	16.53 %	19.60 %	20.6 %
10-19 years	41.34 %	35.95 %	38.93 %
20-29 years	30.75 %	32.44 %	27.66 %
30- 39 years	9.82 %	9.92 %	9.43 %
40-49 years	1.03 %	1.86 %	3.48 %
>50 years	0.51 %	0.2 %	0

Figure 10:



The most common aetiology was found to be MTS which accounted for 86.7% of the cases.

A similar trend was seen across the groups – 85.6 % in Group 1, 88.04% in Group 2 and 86.1% in Group 3 were diagnosed to have MTS.

Tumours were found to be the second most common cause and accounted for 4.6% of the cases. 3.59% of the cases in Group 1, 5.56 % in group 2 and and 4.68% in group 3 were due to tumours – DNET, ganglioglioma, Fibrillary astrocytomas and low grade gliomas.

Vascular malformations accounted for 1,17% of the cases - 1.29% in group 1, 0.8% in group2 and 1.42% in group 3. The commonest vascular malformation diagnosed was Cavernoma.

Discussion

Despite accounting for 80% of patients worldwide with epilepsy, epilepsy surgery is available in only 13 % of the lower income countries (1). Recent years have seen a rapid growth in epilepsy surgery services in developing countries most prominently in India and China. A recent survey recognized 18 centres offering epilepsy surgery in India, half of which were located in South India (8). The South Indian state of Kerala, where our centre is situated, has a population of 3.33 crores, is ranked 11th in the country in terms of per capita income but has the highest Human development index, which is a composite statistic of life expectancy, education, and income per capita indicators. Kerala's unique feature is how it has leveraged its limited GDP to achieve remarkable outcomes in health, education and quality of life and thus serves as a model state for developing countries.

The epilepsy surgery program in our Institute was started in 1995 and till date 1795 surgeries have been performed. A previous study from our institute in 1996 on referral patterns in epilepsy reported a delay in diagnosis of epilepsy which was significantly more for women and patients from a rural background and revealed that the organization and delivery of neurological services for epilepsy was inadequate (25). A multi-centric study on epilepsy care in 6 Indian cities in 2001 revealed that services for epilepsy are urban-based and that epilepsy services were underutilized (26). However, the temporal trends of referral were not examined in these studies.

In our study, the number of patients admitted for pre-surgical evaluation for TLE steadily increased in the first epoch (387 in group 1, 487 in group 2) but remained stable therafter (488, group 3). The number of patients being referred from states other than Kerala increased in the third epoch (29.1% in group 1 to 36.8% in group 3) as did the number of patients being referred from other countries (0.5% in group 1 to 2.9% in group 3).

In contrast to an increasing awareness and therefore establishment of more centres for epilepsy surgery in India (8), a decreasing trend in epilepsy surgery is seen in developed countries including U.S., U.K, Germany etc (21). This was previously attributed to a lack of definite guidelines for epilepsy surgery. However, a recent study from U.S. by Haneef et al showed that despite adequate recommendations, no significant earlier referrals for pre-surgical evaluation could be identified (31). All evidence points to increased risk of recurrence after focal surgery when the duration of preoperative epilepsy is >20 years.(38) Recent evidence also points to lower probability of seizures following early resective surgery especially in childhood, thus highlighting the importance of early referral for pre-surgical evaluation(18).

Although the number of surgeries for drug-resistant epilepsy in India has risen modestly in the last 1-2 decades with 18 centres doing at least 20 surgeries per year, there is still dearth of adequate number of centres leading to a huge surgical treatment gap (9). All the more, the average duration of epilepsy before referral we found was 18.42 ± 9.46 years. This is similar to the average duration of epilepsy before evaluation or intervention reported worldwide **(Table 6)**. Thus no significant trend for an earlier referral to an epilepsy surgery centre was seen in our study over the last 2 decades despite class I evidence and guidelines for early referral.

Table 6

Author	Year of study	Place of study	No of patients	Duration of epilepsy(yrs)
Benbadis et al	2000-2001	Tampa	36	18
Choi et al	1996-2007	New York	213	21.1-22.6
Haneef et al	1995-98, 2005-08	California	185	17.1- 18.6
Helmstaedter et al	1998-2008	Multicentric, Germany	2812	23±13
Present study	2000-2014	India	1384	18.07 ±9.48

We noticed that age at onset and age at evaluation of TLE was seen to increase i.e. more number of patients had their habitual seizures starting at a later age, but still they reach a surgical care centre very late. This also warrants attention. Helmstaedter et al (39) reported an increasing age at surgery and duration of seizures in patients with histologically proven hippocampal sclerosis which was absent in other etiologies like FCD, gliosis and vascular malformations. Possible explanations suggested include changing incidence of MTS due to better treatment of infections and febrile convulsions, vaccination and better seizure control with newer AEDs which may be applicable in our setting too. Helmstaedter et al also called for studies from developing countries to identify any change in trends. Our study, being the only study from a developing country thus assumes importance in understanding any changes in epidemiology of MTS over time. The findings of our study, which mirror global studies on duration of epilepsy before referral, point to a change in incidence of MTS. However, this needs to be corroborated with population based studies.

Similarly, the increasing age at evaluation over the years appears to be counter-intuitive. Increasing number of epilepsy surgery centres may lead to more number of patients being evaluated in smaller centres before being referred to a large volume center. However, in our study, patients with prior pre-surgical evaluation were excluded and cannot be the reason for increasing age at evaluation. The distribution of duration of seizures shows a higher percentage of patients with duration of epilepsy between 40- 49 in group 3 (3.48%) as compared to group 1(1.03%) and 2 (1.86%) and could more patients with a longer duration of seizures undergoing pre-surgical evaluation could be a reason. (Figure 10) Haneef et al in their study of referral data between 1995-98 and 2005-08, reported a higher percentage of patients with a longer duration of epilepsy among the latter group. They proposed a tendency to operate on older patients, better awareness among older patients of surgical options which could have counterbalanced the effect of some earlier referrals resulting in no significant difference in the overall results between the groups in the study.(31)

Importantly, early referrals are still low with the proportion of patients referred before 10 years being 16.53 % in group 1, 19.60 % in group 2 and 20.60% in group 3.

While the availability of increasing number of AEDs and ambiguity in definition of drug resistance could partly explain the delay in referral, our study did not reveal any change in the number of AEDs tried before referral over time. Further, the ILAE proposed a consensus definition for drug-resistant epilepsy in 2009 as inefficacy of 2 AEDs to control seizures (5). We also analysed the number of

patients referred after a trial of more than 2 AEDs across the three groups, but found no significant difference although a trend towards usage of fewer AEDs before referral was noted in Group 3.

Jehi et al summed up the reasons for delayed referral as "knowledge gap" and "feasibility gap" (32). Knowledge gap refers to the attitude of treating physicians and neurologists towards epilepsy surgery. Studies from U.S, Italy and a recent one from Canada have recognized that a substantial proportion of neurologists and treating physicians are unaware of the recommendations for epilepsy surgery.(18, 19, 20) Though there are no studies on the attitude of Indian neurologists/ physicians towards epilepsy surgery, the situation is unlikely to be any different. "Feasibility gap" refers to the physical and temporal barriers to epilepsy surgery and could play a particularly important role in developing countries.

This study is the first of its kind from the continent and provides insights into patterns of referral over the last two decades from a developing country. Despite recommendations for early surgery in drug resistant TLE, no significant trend for an earlier referral for pre-surgical evaluation was seen in this study. This calls for intensification of efforts to increase awareness about benefits of early surgery in drug resistant TLE amongst neurologists, medical practitioners as well as patients and caregivers to ensure timely referral and pre-surgical evaluation.

Limitations of the study:

Our study has a few limitations-the duration of pharmacotherapy before referral would have been a better measure of pharmaco-resistance but could not be assessed given the retrospective nature of the study. Further, details about the designation of the referring doctor, the nature of treatment received before referral and the dose of AEDs were not available in all patients.

CONCLUSIONS

- There is an increase in number of referrals for temporal lobe epilepsy between 2000-05 and 2006-15.
- There was a trend for increase in number of referrals from outside India over time.
- A majority of references were from within Kerala but over time an increasing proportion of referrals from other states was noted.
- A majority of patients belonged to high income category (51.9%) and only a minority of them (7.4%) belonged to lowest income category.

- Of the available data on education, a majority of patients had completed high school and only a minuscule number were illiterate.
- The mean age of onset of seizures was 11.75 ±8.58 years, mean age at evaluation was 29.84 ±9.47 and the mean duration of epilepsy before referral was 18.07 ±9.48 years.
- There was a significant increase in age at onset of seizures and age at evaluation over time but the mean duration of epilepsy before referral showed no significant change over time.
- On weighting for income, there was a significant increase in age at onset of seizures and age at evaluation over time and a significant decrease in mean duration of epilepsy before referral. However, the post hoc Bonferroni tests showed no significant decrease in mean duration of epilepsy before referral.
- A subgroup analysis of patients with MTS alone showed a mean age of onset of seizures of 11.54 ± 8.30 years, age at evaluation of 29.98 ± 9.50 years and mean duration of seizures before referral of 18.43 ± 9.46 years.
- In patients with MTS, the age of onset of seizures in patients significantly increased over time, the age at evaluation increased significantly over time and the duration of seizures did not change significantly over time. A similar trend was seen even on weighting for income.
- Mean number of AEDs tried before referral was 3.60 ± 1.2
- There was no significant change in the number of AEDs tried over time.
- There was a trend for a decrease in proportion of patients tried on > 2 AEDs before referral over time.

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