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PROJECT REPORT

NAME : Dr. HARIPRASAD K.V
PROGRAMME : D.M. NEUROLOGY
MONTH & YEAR
OF SUBMISSION : 2000 NOVEMBER

PROJECT REPORT

TITLE OF THE PROJECT : NATURAL HISTORY AND PROGNOSIS
OF INTRACTABLE EPILEPSY IN CHILDREN. A FIVE – YEAR
FOLLOW UP STUDY FROM A TERTIARY REFERRAL CENTRE IN
S. INDIA

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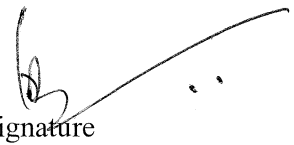
CERTIFICATE

I, Dr. HARIPRASAD. K.V hereby declare that I have actually performed all the procedures listed/ carried out the project under report.

Signature... 

Place : Name in Dr. HARIPRASAD K. V capital letters

Date : 11/11/2018 Forwarded. He has carried out the minimum require & procedures / etc


Signature

Head & Department

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ACKNOWLEDGMENT

I sincerely thank Professor K. Radhakrishnan, Head of Department of Neurology, SCTIMST for inspirational guidance.

I am very grateful to Dr.Sanjeev V. Thomas, Assoc. Professor of Neurology for guiding me through every stage of the study.

I wish to thank Dr.P.Sankara Sharma, Asst. Prof. Of Biostatistics for his immense help in the statistical analysis of the study.

I thank the staff of Medical Records Department, for their co-operation.

I thank M.S.Vishnu who was of great help during the course of the study.

I thank Dr.K.Mohandas, Director, SCTIMST for having allowed me to under take this Study.

Last but not the least, I also take this opportunity to thank all the patients who were part of this study for their co-operation and good will.

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***NATURAL HISTORY AND PROGNOSIS
OF INTRACTABLE EPILEPSY IN
CHILDREN: A FIVE-YEAR FOLLOW
UP STUDY FROM A TERTIARY
REFERRAL CENTRE IN S.INDIA***

Natural history and prognosis of intractable epilepsy in children: A five-year follow up study from a tertiary referral center in South India

Introduction.

The management of children with intractable epilepsy is a major problem in pediatric neurology, which necessitates frequent OPD visits and acute ward admissions. Occasionally the children may require ICU care because of status epilepticus (SE). Certain factors are well known predictors of resistance to antiepileptic drug (AED) treatment. These factors are onset in infancy, organic brain damage (mental impairment, neurological signs), seizure type (tonic, atonic, myoclonic), multiple seizure types, high seizure frequency, long duration of uncontrolled seizures, failure of previous treatments and pathologic EEG. The long term outcome in children with epilepsy is associated with brain pathology which makes etiological considerations important. Some epileptic syndromes are known to have a poor intellectual or neurological outcome eg: Infantile spasm (IS) and Lennox Gastaut Syndrome (LGS). With modern neuro imaging techniques (CT, MRI, SPECT and PET) the localization and extent of brain pathology can be explored. This study was hospital-based study of children below 15 years with active epilepsy. The objectives of this study were

- 1.To identify the predictors of intractability in childhood epilepsy, on long term follow up.
- 2.Classification of epileptic seizures to epileptic syndromes based on International League Against Epilepsy (ILAE) classification¹.
- 3.To ascertain whether referral to a tertiary referral center improves the outcome in children with frequent seizures.

The main objective of the study was to determine the predictors of intractability in childhood epilepsy. Population based studies reports 70-80% of children eventually become seizure free¹. Nearly 20-30% of children have a malignant course and continued to get frequent seizures and sustain severe mental handicap as they grow. Age more than 1year at onset, absence of gross organic brain damage, high initial seizure frequency and family history of seizure in second degree relatives appear to be associated with favourable prognosis. However only few long term studies have addressed risk factors for poor outcome. Only very few population or hospital based long-term outcome study of childhood epilepsy came from developing countries. So far from India, to the best of our knowledge, no long-term follow-up study of childhood epilepsy was published.

The second focus of this study was categorizing the epilepsy types into epileptic syndromes. Unlike seizure types, which are simply symptoms, epileptic syndromes are essentially specific disease diagnosis. Although seizure types contribute to the diagnosis of the syndrome, it is only one piece of information .EEG characteristics, age of onset, presence of underlying neurological abnormalities (including those detected by imaging) and in some instances, the diurnal pattern of seizure occurrence are also a key to determine the seizure syndrome. Syndromes are acknowledged to be essential

to optimal diagnosis and treatment. Modified form of ILAE (1989) was taken as the basis for syndromic classification. Only few ILAE based studies on syndromic classification of epilepsy in general ² and childhood epilepsy in particular ³ were published from India.

Many children with intractable epilepsy in addition have mental retardation as a result of underlying brain abnormalities. However in some children the mental retardation appears to be secondary to intractable epilepsy. Several reports suggest that control of seizure does alter the outcome. The primary purpose of treatment is to allow the opportunity for more normal intellectual development and thus decrease or possibly eliminate the MR that is a complication of persistent 'Catastrophic Seizures'.

The third objective of the study was, whether appropriate drug selection, intense monitoring and providing comprehensive care under the guidance of a territory care center would influence the seizure outcome. There was no randomized controlled trial from India comparing the efficacy of different AEDs in different epileptic syndrome. Only one population based randomized controlled trial comparing the acceptability of Phenobarbital Vs Eptoin for treating childhood generalized and partial seizures, in a rural Indian population has been published so far ⁴.

Materials and Methods.

Children with frequent seizures below 15 years of age referred to SCTIMST for evaluation and management in the year of 1994 were taken as a Cohort .49 children with frequent epilepsy were enrolled in the epilepsy clinic in 1994 and 36 children were completed 5year follow up .The data of this 36 children were included in the final

analysis. 12 children, who did not complete 5 year follow up were excluded from the study. A final review was carried out on all the patients in the year of 1999. Data on clinical characteristics, investigations and treatment were obtained from personal interview and supplemented with medical records. The data extracted includes the details about child's unprovoked seizures (including seizure semiology), child's medical and developmental history, about seizure precipitated by fever, status epilepticus (SE), family history of seizure disorder as well as past and present AED profile. The EEG and neuroimaging findings were extracted from the medical records.

Definitions

In this study following parameters were defined as follows.

Epilepsy

Epilepsy was defined as two or more epileptic seizures, unprovoked by any immediate, identifiable cause and excluding neonatal seizures (NS) i.e., seizures appearing before one month of age⁵.

Seizure frequency

Engel's seizure frequency scoring system was utilized for objective assessment of seizure frequency at the beginning and at the end of the study⁶

Seizure types

Seizures were classified according to the International classification of epileptic seizures based on their clinical manifestations. Since seizure classification was

based on clinical symptomatology (described by parents), the epileptic spasms (IS) and myoclonic seizures were included in one category.

Epileptic syndromes.

The cohort was categorized into various epileptic syndromes on the basis of ILAE (1989) criteria.

Status epilepticus

SE was defined on a seizure or series of seizures lasting more than 30 min or if recurrent seizure lasting more than 30min without full return of consciousness (Hauser,1983,1990;Dunn1988; Meytal etal. 1989)

Seizure with fever

Any episode of seizure triggered by fever in this study group of children Was defined as a seizure with fever.

AED profile

The AED profile of the patient during the beginning of the enrollment in1994 and on the final follow-up in 1999 was compared. AEDs were prescribed by the treating physician's judgment, cost and availability of AED at various point of time. The investigators have no control over AED therapy.

Terminal remission

Terminal remission was defined as a minimum of 2year complete seizure free period at the time of last follow-up in the hospital. Most relapses occur in the first 2 year of follow-up.(Shinnar etal,1985; Reynolds 1987). For children with intractable epilepsy, the main target is to reduce the seizure frequency, than total seizure remission.

Age of onset of epilepsy (AOE)

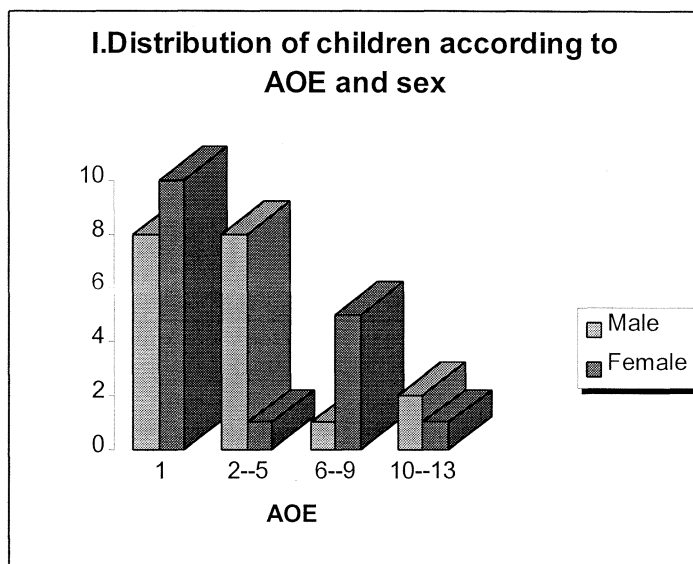
For all children with onset of first unprovoked seizure between one month and 12 months, AOE was considered as first year. For all children above one year the completed year was taken as AOE. Children below one month (NS) were not enrolled in this study.

RESULTS

Forty nine children below 15 years with frequent seizures were registered in the epilepsy clinic in the year of 1994. Complete 5year follow up data was available for 36 children. The age group of the study population varies from one month to 14 years. Mean age at registration was 5.53yrs(SD 4.18) . Mean age of onset of epilepsy was 3.5years(SD 3.49). A mean difference of 2.03 years was there between the onset of epilepsy and referral to SCTIMST.

I. Distribution of children according to AOE and Sex.

AOE	Male(n)	Female(n)	Total(n)
1	8	10	18
2-5	8	1	9
6-9	1	5	6
10-13	2	1	3



Maternal or perinatal riskfactors

In 50% of children the AOE was 1 year. Maternal risk factors (MRF) presumably contributing to epilepsy was identified in 6 (16.6%) children. 2 children were born off by LSCS. Three children were delivered at preterm. In one child the mother was diabetic at the time of epilepsy. Perinatal risk factors (PRF) were identified in 7 (19.4%) children. Five children had evidence of asphyxia at the time of delivery and 2 were hypoglycemic. Developmental delay in milestones was seen in 20(55.5%) children. Mental retardation was seen in 10(27.77%) at the time of registration. Seven out of 10 children with MR had AOE 1 year. Hydrocephalus was seen in one child. Craniofacial anomaly was detected in one child and 2 children had tuberous sclerosis (TS).

II Distribution of seizure type in major epileptic syndrome

Seizure type	Overall(n=36)	LRE(n=13)	WS(n=5)	LGS (n=9)
Generalized				
Tonic clonic	15	2	3	4
Tonic	1	0	0	0
Typical absence	0	0	0	0
Atypical absence	0	0	0	0
Myoclonic and absence spasms	14	0	5	6
Partial				
Simple partial	4	4	0	0
Complex partial	6	1	0	2
Partial seizure with secondary generalization	9	9	3	7

LRE- Localization Related Epilepsy

WS –West Syndrome

LGS-Lennox Gastaut Syndrome

III Classification and coding of epilepsies and epileptic syndromes (modified from ILAE 1989)

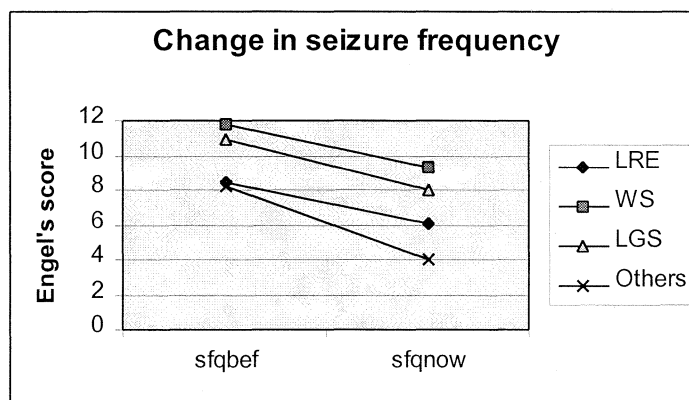
Epilepsy type	n
1.2.Symptomatic localization related epilepsies	
1.2.1.TLE	4
1.2.1.FLE	3
1.2.2 PLE	1
1.3 Cryptogenic localization related epilepsy	
1.3.1. TLE	2
1.3.2. FLE	2
1.3.3. PLE	1
2.Generalised epilepsies and syndromes	
2.1.6. JME	2
2.2.1. West syndrome	5
2.2.2. Lennox Gastaut t Syndrome.	8
2.2.4. Eilepsy with myoclonic absence	1
2.3. Symptomatic generalized epilepsies	
Other symptomatic generalized epilepsies not defined above	2

EEG Profile

EEG showed generalized epileptiform abnormalities in 14 children and focal in 13 children in rest of the children the EEG abnormalities were not specific. Twelve children underwent second EEG examination and 1 child underwent third EEG examination, either for clarification of syndromic classification or to assess the ongoing seizure activity.

IV Major epilepsy types, their seizure frequency at the time of registration and on follow up

	LRE	WS	LGS	Others
	n=13	n=5	N=9	N=9
AOE	4.4(4.07)	1.6(1.34)	1.66(1.0)	5.0(4.06)
SFQBEF	8.38(3.57)	11.8(0.44)	10.88(1.16)	8.22(4.9)
SFQNOW	6.07(3.50)	9.25(4.19)	8.0(3.04)	4.0(3.7)



V. The EEG profile of major epilepsy types

	LRE	WS	LGS	Others
EEG	10	4	8	6
Abnormal				
Normal	2	0	0	3
Nonspecific	1	1	1	0

Mental retardation and epilepsy

Ten children in the study population had MR. Seven children with MR the AOE was one year. Five children with MR had LGS and 2 children had West syndrome (WS).

VI Epilepsy types in children with MR and their seizure frequency at the time of registration and on 5yrar follow up

Sl No	AOE	Sex	Epilepsy Syndrome	SFQBEF	SFQNOW
1	1	M	WS	12	4
2	1	M	WS	11	3
3	1	F	LGS	11	7
4	1	M	LGS	12	8
5	1	F	LGS	9	7
6	1	F	LGS	11	11
7	2	M	LGS	11	8
8	1	F	Partial Epilepsy (FLE:symptomatic)	11	6
9	4	M	Epilepsy with myoclonic absence	12	11
10	9	M	Undetermined epileptic syndrome	2	2

LRE – Localization Related Epilepsy

SFQBEF – Engel's Seizure frequency Score at the time of registration

SFQNOW – Engel's Seizure frequency score at the time of 5year follow up

The mean seizure frequency score of children with MR at the time of registration was 10.2 and on final follow-up it was reduced to 6.7 .In WS the MSFS reduced from 11.5 to 3.5.For children with LGS, MSFS reduced from 10.6 to 6.1.

Family history of epilepsy

Family history of epilepsy was identified in 7 (19.44%).

VII. The Characteristics of epilepsy in children with positive family history (1st/2nd degree relative)

Sl No:	AOE(year)	SEX	Epilepsy syndrome	SFQBEF	SFQNOW
1	1	F	TLE	12	10
2	1	M	LGS	12	8
3	4	F	LGS	12	8
4	4	M	WS	12	12
5	6	F	TLE	6	2
6	8	F	TLE	2	1
7	11	M	TLE	8	8

TLE- Temporal Lobe Epilepsy

LGS-Lennox Gastaut Syndrome

WS-West Syndrome

SFQBEF – Engel's Seizure frequency Score at the time of registration

SFQNOW – Engel's Seizure frequency score at the time of 5year follow up

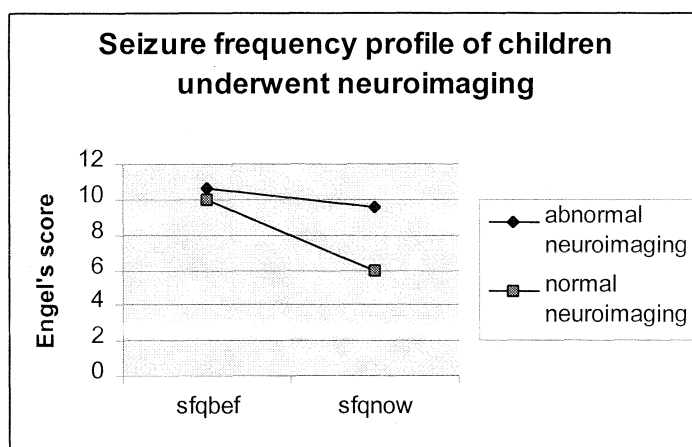
Partial epilepsy (temporal lobe epilepsy-TLE) was the commonest type (4/7) of epilepsy with positive family history (at least one first or second degree relative was affected by the seizure disorder).

Neuroimaging

Neuroimaging was done for 27 children. Focal abnormalities were seen in 12 children.

VIII. The seizure frequency score, at the time of registration and on follow-up of children underwent neuroimaging.

Imaging	No: children had imaging	SFQBEF	SFQNOW	p
Normal	11	10	5.9	$p < 0.01$
Abnormal	12	10.6	9.61	$p < 0.01$
Total	23			



IX. Neuroimaging

Neuroimaging abnormality	No:
Normal	11
Cerebral atrophy	1
S/o Tuberos sclerosi	3
S/o Encephaliti	3
S/o Infarct	1
NMD	1
Ganglio glioma	1
Uncertain	2

NMD- Neuronal Migration Disorder

Epilepsy types with history of “seizures with fever”

History of seizure with fever was obtained in 7 children. Out of 7 children having seizure associated with fever, 3 had west syndrome and 2 had localization related epilepsy and 1 each had LGS and Epilepsy with myoclonic absence.

Status Epilepticus (SE)

Fourteen patients had status epilepticus, at least one during the entire period of illness.

X STATUS EPILEPTICUS

SI No:	AOE	Epilepsy syndrome	Number of Status	SFQBEF	SEQNOW
1	1	Special syndrome	1	2	1
2	1	LGS	2	11	1
3	1	LGS	1	11	8
4	5	TLE	2	6	6
5	1	WS	1	12	1
6	4	WS	2	12	12
7	1	FLE	2	11	6
8	1	LGS	1	11	7
9	1	Symptomatic generalized epilepsy	1	12	1
10	1	LGS	2	12	8
11	01	WS	1	11	10
12	11	TLE	1	9	9
13	02	LGS	1	12	1
14	06	Unclassified	1	11	6

MSFS of children with SE was 10.18(SD3.12) which reduced to 6.93(SD3.75) at the end of the study.

AED profile

At the time of registration 27 children (75%) were on polytherapy. At the end of 5 year follow up 12(33.3%) were on polytherapy.

XI. The AED profile of the cohort on registration and on final follow-up.

	No: children, at the time of registration	No: children, at the time of final follow-up
No AED	0	4
Monotherapy	9	17
Polytherapy	27	15

XII. AED PROFILE

Individual AEDs	Number of children on specific AED on 5 year follow up
VPA	18
CBZ	13
PB	11
DPH	3
CLZ	6
Others	2
MYS	2

The commonest AED used in the childhood epilepsy at the time of registration was VPA. VPA continues to be commonest AED in monotherapy and at the end of 5-year follow up

Discussion

Seizure disorders in the young children follow a dichotomous course. Seizures are either benign and relatively inconsequential or catastrophic. Overall, a quarter of children experience either uncontrolled seizures or serious adverse events. Despite this very few patients are referred to tertiary centers for systematic evaluation of uncontrolled epilepsy. Recent survey in the UK revealed that general practitioners who usually manage childhood epilepsy tend not to follow management guidelines and standards of care were poor. Only 33% of children with poor control of seizure were referred to specialist⁷. The situation is even worse in India and many other developing countries, where nearly 85% are not receiving any medical treatment. The prognosis of seizure disorders have been examined since the beginning of epileptology and only recently has the realization emerged that, ultimately, prognosis depends on causation; which in turn determine whether a condition is self limited or progressive.

Predictors of intractability

The term intractability could be defined as either seizures that remain uncontrolled despite relevant therapy or as being related to seizure frequency as well. No absolute seizure number establishes the condition of intractability. Resistance to control by different modes of treatment, appropriate drug selection and dose, patient age and duration of drug trials must be taken into account. One or more seizure per month is

commonly defined as intractable epilepsy. However by and large in pediatric refractory epilepsies the seizure recurrence rate will be high compared to adults. Thus the MSFS of our cohort was 8.3(SD2.21) at the time of registration. At the end of five year follow up the MSFS has reduced to 6.7(SD1.42). Sillanpaa identified favorable factors guiding good outcome are one type of seizure, good short-term control with AED, no SE, and normal mental development⁸. Seizure remission is less likely in symptomatic epilepsies caused by defined acquired brain damage or less well defined prenatal or perinatal causes manifested by gross neurological deficits or mental retardation. Many other factors frequently reported as predictive of chronic or intractable epilepsy. Age of onset of epilepsy(Annergers et al 1979⁹ , Okuma and Kumashira 1981¹⁰) , Combined seizure types

(Okuma and Kumashira 1981, Brorson and Wranre 1987¹¹) , high seizure frequency , long duration of epilepsy and MR¹². In the present study the relation between previously established predictors of intractability and seizure frequency was confirmed.

Maternal and perinatal risk factors.

In children exposed to maternal or perinatal risk factors, the mean seizure frequency at the time of registration was 11.6(SD 0.5). For children without exposure to the above risk factors, the initial seizure frequency was only 8.7(SD 3.8) . At the end of the study period, the final SFS of the cohort with risk factor was 7.4(SD 3) in comparison with children without risk factor of 6.0(SD 3.9).

Antenatal and intrapartum risk factors associated with seizures in term newborn. Various studies confirmed a strong association between seizure and factors that increase

the risk of fatal asphyxia Patterson.C.A. etal. (1989), studied 40 infants who had seizures within 72hrs of birth when compared with 400 controls using logistic regression analysis¹⁹. The risk factors identified in that study were antepartum anemia, antepartum bleeding, asthma, meconium-stained amniotic fluid, presentation other than occiput anterior, fetal distress and shoulder dystocia. However we did not include neonatal seizures in this study, hence their long-term outcome cannot be predicted from this study.

Nelson.K.B. etal did a prospective study, analyzing whether late obstetric complications were a risk factor for seizure disorder in childhood²⁰. This study did not show any statistical association between late obstetric complication and development of nonfebrile seizure.

In our study, the seizure frequency of group exposed to risk factor's and not exposed to the above were same. Hence the maternal and perinatal risk factors may not be an independent contributor for long-term epilepsy in childhood (barring neonatal seizures)

Initial seizure frequency

In this study children with very high initial seizure frequency (ES =12), at the time of registration continued to have high seizure frequency at the end of 5 Year follow up. For Children with initial seizure frequency (ISF) of ES –12 at the end of 5year follow up, the SFS was 8.14(SD 3.68); however with children with initial seizure frequency ES below 12, the final ES was 5.24(SD3.52)

Sillanpaa et al studied the predictive factors for intractability in long-term follow up for 10 years. On logistic regression analysis the predictors of intractability were identified. High initial frequency (OR 4.6; 95% CI 1.1-9.3) was identified as one of the important predictors of intractability⁸. Our study was in consistent with the observation of Sillanpaa.

Age of onset

Age of onset appears to be a predominant predictor of intractability. In this study the initial seizure frequency score of children with AOE by one year, was 10.18(SD3.26). For children with AOE above one year SFS was 8.69(SD4.01) at the time of registration, however at the end of five year follow up period the final SFS was similar in both groups i.e. 6.5(SD3.68) for AOE by one year and 6.4(4.02) for AOE more than one year.

Anne.T.Berg et al by multiple logistic regression analysis identified that AOE is a independent predictor of intractability, decreasing risk with increasing age of onset of epilepsy⁹.

Seizure with fever.

‘Seizure with fever’ (SWF) defined as any seizure in any child with fever of any cause. Precipitation of seizure in children with severe neurological disorder and /or MR

came under this category. Most of the children in this study were MR and AOE were around 1 year.

In this study, the initial SFS of children with SWF (n=5) were compared with children without SWF (n=31). The initial SFS of children with SWF was 9.5(SD3.5) and SFS of children without SWF was 9.8(SD1.64). However on final analysis the SFS of children with SWF continued to be high compared to the children without SWF ie. 8(SD3) Vs 5.96(3.8). Being a univariant analysis, the strength of association cannot be very certain. The cerebral development of children in whom the fever precipitated the seizure may be poor compared with children in whom fever did not trigger the seizure.

Mental retardation and Intractability

The long-term outcome of intractable epilepsy in children with MR is considered to be poor than children with normal mental development (Ulf Steffen berg et al 1988)¹². The structural or metabolic brain abnormality that causes seizure will inevitably causes MR. The seizure themselves lead to MR and without the occurrence of the seizures the child could develop normally.

In this study 10 children were severely retarded. The MSFS at the time of registration for mentally retarded children was 9.2(SD3.88), which was reduced to 6.4(SD3.470) at the end of 5year follow up. Meanwhile for children without MR, the MSFS at the beginning were 9.47 (SD3.31), which reduced to 5.95(SD4.26) at the end

of 5year .The terminal seizure frequency of both group were same. MR may not be a predictor for intractability. The principle limitation of the study was small number of the cohort. Another factor that may be contributing to better seizure control in children with MR could be the intense supervised therapy from the territory care center.

Polymorphic seizure and intractability

In this study 14 children presented with Polymorphic seizures,(4 children with three seizure types and 11 children with two seizure type). The MSFS of children with polymorphic seizures at the beginning was 11.35(SD 1.08). For children with monomorphic seizure the MSFS was 8.05(SD4.02) At the end of 5year follow up period the MSFS of children with polymorphic seizure was reduced to 8.14(SD 2.93). For children with monomorphic seizure the final seizure frequency score was 5.23. Hence comparing children with polymorphic children at presentation, children with monomorphic seizure has better long-term outcome.

Ulf Steffen burg etal on the basis of population based study of intractable epilepsy in mentally retarded children identified that the number of seizure types were the best predictor of high seizure frequency (multivariate analysis). Among children with only one seizure type, 23% had intractable epilepsy the figure, which increased successively to 100% among the children with 4 or more seizure types

Polytherapy and intractability.

27 children were on polytherapy at the time of registration. However at the end of five year only 12 children were on polytherapy. The seizure frequency of the children

on polytherapy was higher at the beginning, as well as at the end of the study. The MSFS of children on polytherapy was 10.79(SD5.29), at the beginning of the study. However it reduced to 7.96 (SD2.84) at the end of five year. Contrary to that children on monotherapy had MSFS of 5.37(SD4.48) which reduced to 2.00(SD 2.49) at the end of the study.

SE and intractability

In this study SE occurred in 14 children (38%) .The initial seizure frequency score of these children with SE was 10.14(SD3.12) which reduced to 6.93(SD3.75) at the end of the study, however for children without history of SE even though the initial seizure frequency score was 8.7(SD3.86) the final frequency score was almost same as that of children with SE ie.6.93(SD3.4).

Anne.T.Berg⁹and Sillanpaa⁸ noted that SE and intractability were strongly associated. Children who had remote symptomatic epilepsy were more likely to have an episode of SE.

The final seizure frequency of children with and without history of SE was same in this study, which means that even in children with history of SE, aggressive antiepileptic therapy do bring the seizure burden considerably.

EPILEPTIC SYNDROMES

Only few reports were available regarding the syndromic classification of childhood epilepsy from the developing countries. Shah.K.N. etal (1989)¹⁷from Mumbai

classified the epilepsies in 493 children according to ILAE guidelines. Predominant epileptic syndromes were partial, seen in 55.3% of patients. Twenty-seven percentage had generalized epilepsy and 4.1% were special syndromes. Recently Murthy.J.M et al¹⁸ from Hyderabad analyzed the data of 2531 patients with epilepsy using ILAE classification. Symptomatic localization related epilepsy (62.7%) were the commonest type of epilepsies seen in that study.

Following major epileptic syndromes were identified in this study

Infantile spasm

Infantile spasm is by far the most common catastrophic epilepsy of childhood, occurring in about 9% of all children in whom epilepsy has been diagnosed. Defining characteristics are onset of flexor spasms in the first year of life (peak age of onset is 5 months) and hypsarrythmia on EEG. Some patients have multiple independent spike discharges on EEG rather than hypsarrythmia. IS is associated with many different causes. Essentially, any disorder that affects the developing brain has been associated with IS, including neurocutaneous disease (especially tuberous sclerosis) metabolic disease such as PKU or MSU disease, cortical dysplasias, tumor, porencephalic cyst, trauma, birth hypoxia, CNS infections and stroke. The developmental outcome of children with IS is generally poor. Most have MR. However the patients who are developmentally normal are the patients whose IS were controlled. Thus, control of seizure is a very high priority.

In this study there were 5 children with IS. 4 of them had MR. Three patients underwent neuroimaging. Two of them showed abnormalities. The seizure frequency at the time of registration was very high 11.8(SD0.44). There was only 2-point reduction in SF at the end of 5year. Four out of 5 children were on polytherapy at the time of registration. The final AED profile showed only 2 patients were on polytherapy. Even though none of these patients achieved remission, the ‘active ‘ treatment do reduced the seizure frequency, which in turn might have helped the cognitive development of these children.

. Natural history of IS is influenced by several factors, such as underlying etiology, delay in diagnosis and the type of treatment administered. The first and largest long-term outcome study of WS was done by Riikon et al.(Epilepsia,1996)⁶. 214 children born between 1960 and 1997, who had been followed for 25-30 years or until death at three months to 30 years of age. The mortality in that study was 31%(67 of 214 patients). Two-year seizure freedom was seen in 48(33%) children. Twenty-six (18%) patients had continuous daily seizures.

Lennox Gastaut Syndrome

Lennox Gastaut Syndrome is a relatively common seizure syndrome comprising about 1.5% of children with epilepsy. Defining characteristics are multiple seizure types(tonic, atonic,atypical absence, partial and /or generalized tonic-clonic seizure and a slow spike and wave (1-2.5Hz) EEG abnormality. LGS often follows IS and usually begins at between 1 and 3years of age . The etiology is similar to IS, and a full laboratory evaluation to identify evaluation of the course. The seizures associated with

LGS are difficult to control. The standard AEDs such as CBZ or DPH are not helpful and may exacerbate seizures. VPA and benzodiazepines are usually helpful. Most patients with LGS have MR, but an occasional child will develop normally if seizures are controlled.

There were 9 children with LGS in this study all of them showed some improvement in seizure control. SFS reduced from 10.88 to 8. LGS has poor prognosis in terms of control of seizure and mental development. Prognosis for normal development is very poor. Only 21% of the patient observed over 12 year period were attending regular school or engaged in some occupation¹⁵. In a study of 72 patient with LGS 19 followed up for >10 years seizure tend to persist on a daily or weekly basis in more than 2/3 of the patients. Five out of 9 children with LGS in this study were mentally retarded.

Partial Epilepsy

ILAE recognizes 5 symptomatic localization related epilepsies, 4 of which are anatomically defined: Temporal lobe epilepsies, frontal lobe epilepsies, parietal lobe epilepsies and occipital lobe epilepsies. In syndromic classification studies of childhood epilepsies, the partial epilepsies were the commonest type of epileptic syndrome.

In our cohort of 36 patients, by electro-clinical characteristics we were able to identify 13 (36%) with partial seizures (localization related epilepsy). Both symptomatic and cryptogenic partial epilepsies were identified. Comparison with children having west syndrome and LGS the initial seizure frequency as well as terminal seizure frequency was less for children with LRE. ISFS was 8.38, which reduced to 6.07 at the end of the study.

Jorge Eslava et al. (1988)¹⁶ from Colombia classified the seizure types of children, attending pediatric epilepsy clinic, using ILAE (1981) classification into various epileptic syndromes. Out of 191 cases, 121 (70 %) were partial seizures. Of 121 patients with partial onset syndrome, only 3 had idiopathic forms.

Intractability and abnormal neuroimaging

One highly significant observation of this study was children with abnormal neuroimaging (MRI/CT) the seizure remains to be more refractory than children with normal neuroimaging. The initial seizure frequency of children with and without abnormal neuroimaging was almost same. However at the end of five-year, children with abnormal neuroimaging continued to have high seizure frequency compared to children with normal imaging ($p < 0.01$).

Tertiary care improves the outcome.

T.Okuma et al. (1981) did a multi institutional study of prognosis of epilepsy in Japan¹⁰. 1868 cases were grouped into 3 subtypes and followed up for different period of time, 10, 5 and 3 years respectively. The rate of remission of seizure in all groups was 58.3%. The following factors were identified as favorable pointers for seizure remission.

- a. Idiopathic epilepsy than symptomatic epilepsy.
 - b. In patients with onset before 10 years of age than with onset after 10 years.
 - c. In patients with less frequent seizures.
 - d. Sleep epilepsy than waking and diffuse epilepsy.
 - e. In patient with standard treatment within 1 year of onset of seizure
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- f. In patients with single-type partial seizures than in those with partial seizures combined with tonic clonic seizures.
- g. Single type of seizure
- h. Patient without neurological symptoms, personality disturbance and intellectual deficit.

In this study there were multiple risk factors for poor seizure remission. Twelve out of 27 (44.44%) children had focal abnormalities in neuroimaging, 14 out of 36 (38.88%) children were mentally retarded. In spite of all these negative prognostic factors 33% of children in this study achieved 2-year terminal seizure remission. Attaining of remission or significant reduction in the final seizure frequency for the entire cohort was seen in this study. This could be because of following reasons.

- a. accurate syndromic classification.
- b. proper AED selection.(both the drug and dosage).
- c. regular follow up and consistent assurance of drug compliance.

In this study the number of children on monotherapy has increased from 9 to 24 at the end of 5 year. The general principal in the management of epilepsy in children is to use the appropriate AED in monotherapy. An additional AED may be required whenever the seizure are not controlled with primary drug. Indiscriminate use of multiple AEDs , particularly benzodiazepines and phenobarbital may aggravate drowsiness or hyper kinetic behavior of the child. Systematic evaluation and treatment appropriate to epileptic syndrome at tertiary referral center was associated with better control of seizures or remission of epilepsy in children with frequent seizures.

Limitations

This cohort consisted of only 36 children and we undertook only univariant analysis. The significance of predictors of intractability as well as factors influencing the final seizure remission has to be further validated by studying a larger cohort with longer follow up

Conclusions

In this cohort of children with catastrophic epilepsy, risk factors for intractable epilepsy were identified in some children. Many of them were MR. Localization related epilepsy was the commonest type of epileptic syndrome. AED treatment under close supervision improved the seizure outcome in all types of epilepsy.

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Appendix I

III classification and coding of epilepsies and epileptic syndromes(modified from ILAE 1989)¹

Epilepsy type

1 Localization related epilepsies and syndromes

1.1 Idiopathic localization related (i.e. Age related onset) epilepsies.

1.1.1 Benign childhood epilepsy with centrotemporal spikes (BECT)

1.1.2 BECT in brain damaged children

1.1.3 Childhood Epilepsy with occipital paroxysms

1.1.4 Benign frontal epilepsy of childhood

1.1.5 Benign psychomotor epilepsy of childhood

1.2 Symptomatic localization related epilepsies.

1.2.1 TLE

1.2.1 FLE

1.2.2 PLE

1.2.4 Occipital lobe epilepsy.

1.2.5 Rasmussen's Syndrome.

1.3 Cryptogenic localization related epilepsy

1.3.1 TLE

1.3.2 FLE

1.3.3 PLE

1.3.4. OLE

2. Generalised epilepsies and syndromes

2.1. Idiopathic generalised(with age related onset)

2.1.1. Benign neonatal familial convulsions

2.1.2. Benign neonatal convulsions

2.1.3. Benign myoclonic epilepsy of infants

2.1.4 Childhood absence epilepsy

2.1.5. Juvenile absence epilepsy

2.1.6. JME

2.1.7. Epilepsy with GTCS on awakening

2.1.8. Other generalised idiopathic epilepsy not defined above

2.1.9. Epilepsies with specific mode of seizure precipitation

2.2. Cryptogenic or symptomatic generalised epilepsies (in order of age)

2.2.1. West syndrome

2.2.2. Lennox Gastaut t Syndrome.

2.2.3. Epilepsy with myoclonic –astatic seizures

2.2.4. Eilepsy with myoclonic absence

2.3. Symptomatic generalized epilepsies

2.3.1. Nonspecific etiology

Early myoclonic encephalopathy

Early infantile epileptic encephalopathy with suppression burst

Other symptomatic generalized epilepsies not defined above

2.3.2 Specific syndromes

3.Epilepsies undetermined whether focal or generalized.

3.1.With both generalized and focal seizures

3.1.1 Neonatal seizures

3.1.2 Severe myoclonic epilepsy in infants

3.1.3 Epilepsy with continuous spike and waves during slow wave sleep

3.1.4 Acquired epileptic aphasia (LKS)

3.1.5 Other undefined epilepsies not defined above.

3.2.Without unequivocal generalized or focal seizures

4. Special syndromes

4.1..Situation related seizures

4.1.1 Febrile convulsions

4.1.2 Isolated seizures or isolate status epilepticus

4.1.3 Seizures associated with acute metabolic or toxic events

5 Differentiation between epileptic and non-epileptic events uncertain

Appendix II

Engel's seizure frequency score

		Engel's score
Seizure free	offAED	1
Seizure free	need for AEDnot known	2
Seizure free	require AED to remain so	3
Non disabling simple partial seizures(aura) only		4
Non disabling nocturnal seizures only		5
1-3 per year		6
4-11 per year		7
1-3 per month		8
1-6 per week		9
1-3 per day		10
4-10 per day		11
More than 10 per day		12