East African Medical Journal Vol. 88 No. 12 December 2011
EPILEPSY FOLLOWING SIMPLE FEBRILE SEIZURE IN A RURAL COMMUNITY IN TANZANIA
W. B. P. Matuja, MBChB, MRCPsy, MRCP, Professor (Neurology), Department of Internal Medicine, Muhimbili University of Health and Allied Sciences (MUHAS) and M. Fataki, MD, MMed, Senior Lecturer, Department of Paediatrics and Child Health, Muhimbili,University of Health and Allied Sciences

EPILEPSY FOLLOWING SIMPLE FEBRILE SEIZURE IN A RURAL COMMUNITY IN TANZANIA

W. B. P. MATUJA and M. FATAKI

ABSTRACT

***Objective*: To study the outcome of subsequent epilepsy following a single uncomplicated febrile seizure in a cohort of children aged six months to six years followed up for a ten year period.**
***Design*: Observational prospective cohort study**
***Setting*: Mahenge epilepsy clinic, Ulanga District, Morogoro region, Tanzania.**
***Subjects:* Children aged six months to six years living in Ulango District, Morogoro Region, Tanzania.**
***Results*: A total of 6522 children aged six months to six years lived in the study area. Of these 213 (3%) had experienced one uncomplicated febrile seizures within six months of the commencement of the study. At the end of ten years follow-up period 145(65%) were still living in the study area. Of these 44 (30%) had developed epilepsy giving an equivalent of cumulative incidence rate of 3.8 per 100 person years. The age of onset of first uncomplicated FS between the ages of two to five years was significantly associated with the development of later epilepsy in comparison to other ages X^2 26.43; P<0.001. This difference was significantly accumulative with time of follow-up. The number of recurrent febrile seizures significantly influenced the development of later epilepsy. X^2 = 32.3; p =<0.001 with relative risk (odds ratio 5.4, 95% CI 2.6-11.41 P<0.001). A positive family history of FS significantly influenced the development of later epilepsy. X^2 P<0.001 with relative risk (odds ratio 3.2, 95% CI 2.0-5.1; p<0.001. A positive family history of epilepsy did not significantly influence the development of later epilepsy X^2 = 38.1; P <0.212.**
***Conclusion*: Cumulative incidence of epilepsy in rural Tanzanian children following a single uncomplicated FS was small but higher than that reported in developed countries. This risk was influenced independently by the number of recurrent FS, family history of FS, and the age of onset of the first ever FS.**

INTRODUCTION

Febrile seizure (FS) is the most common neurological disorder among children worldwide. Febrile seizures occur in two to four percent of all children between the age of six months and six years in developed countries (1-4). Population based studies in developing countries are scanty, the few available studies report higher percentage of 15-20% children experience febrile seizure between the age of six months to seven years (5, 6). FS account for 20-25% of all childhood admission in Africa (7-9). Population based studies in developed countries report children with first ever febrile seizures will have a recurrence in 23-38% (2,4,10) and a small proportion (about 2-10%) of these children can expect to have one or more subsequent unprovoked seizures (2, 4, 11, 12). The few studies conducted in African have reported a higher incidence of subsequent epilepsy of 20-40% in children after FS (6, 13-15). These studies were cross-sectional in nature and relied on retrospective enquiry into the previous history of childhood FS and most were hospital based and only a few were community based.

Children who experience first ever febrile seizures with complex symptomatology are more at risk of experiencing two or more unprovoked seizures than those without complex symptomatology (4, 11, 16,17).

In developed countries childhood simple febrile seizures are considered benign events and are rarely followed by subsequent unprovoked seizures. However, the subsequent risk of developing epilepsy after first ever-simple febrile seizure in African children is not well studied.

Hence, we conducted a prospective community based study in a cohort of children aged one year to six years for a period of ten years to study the

outcome of recurrence febrile seizures and subsequent two or more unprovoked seizures (that is, epilepsy), following a single simple febrile seizure.

MATERIALS AND METHODS

The study was conducted in Mahenge Division, a rural area in Tanzania with a total population of 20284 inhabitants.

The design and method used in the study has been described in previous publications (l5, 18). Following an informed consent obtained from divisional leader, village leaders and head of household, a team of trained health workers conducted a door-to-door interviews. The interviews identified all children between the age of one year to six years in each household and registered those who have had single febrile seizures in the last six months. These children were latter seen by a Neurologist and Paediatrician to characterise the features of the febrile seizure through a detailed interview of parents or guardian. If the parent did not witness the seizure, an adult who witnessed the seizure was contacted and was interviewed. Duration of the FS was estimated either less than ten minutes or more. Parents/guardian or children with FS estimated the duration during the interview of ten minute interval and were requested to recall if the timing was less or more than the ten minutes. If the estimated duration was less than ten minutes. These were further characterised by interview to exclude those with focal signs who were then excluded the study Duration of the FS was estimated either less than ten minutes or more. Parents/guardian children with FS whose duration less than of ten minutes were further characterised by interview to exclude those with focal signs who were then excluded. Medical records of those children who had been treated at the district hospital were scrutinised whenever this information was available. Further information on the family history of febrile seizures, level of education of the parents or guardian, history of developmental delay or other neurological abnormalities was obtained from the parents or guardian. FS children were also examined for evidence of neurological dysfunction. The time interval from the first ever FS to the time of enrolment into the study was between six months to three years with an average of one years six months. The study was carried out from 1st July 1998 to 31st June, 2008.

Definitions: Febrile seizure (FS) was defined as convulsion with fever in the absence of any hint of intracranial infection.

Simple or uncomplicated febrile seizure was defined as a single tonic-clonic convulsion lasting less than ten minutes per episode of fever.

Recurrent febrile seizures was defined as convulsion (focal or generalised) in more than one episode of fevers which could be uncomplicated generalised tonic clonic seizure or complicated if seizures lasted for more than ten minutes or was focal or multiple seizures per episode of fever.

A family history of febrile seizure was defined a history of convulsive seizures with fever between the ages of six months to seven years of age in two or more first degree relatives.

A family history of epilepsy was positive if there were one or more first degree relative with epilepsy. Epilepsy was defined as the development of more than one non-febrile seizures occurring on different days in the absence of acute medical illness.

Inclusion criteria were children who had single febrile seizure without focal or multiple episodes and was estimated to last for less than ten minutes without residue neurological deficit and with no previous history of neurological dysfunction and had no neurological dysfunctions during examination at the beginning of the study. Children who had experienced a single uncomplicated seizures were registered in the study. A total of 6522 children aged one to six years lived in the study area. Among these 213 (3%) satisfied the criteria and were registered for follow-up.

Follow-up: Families with children who were included in the study were invited to visit the district hospital twice a year or whenever a FS occurred and were seen by the Senior Nursing Officer in charge of the epilepsy clinic who was well trained in obtaining a detailed description of the type of seizure and referred the child to the clinical officer for further examination in the presence of fever.

The neurologist and paediatrician classified the various seizure episodes as either recurrent febrile seizure or unprovoked seizure. Recurrent FS was reclassified into uncomplicated generalised tonic clonic convulsions, complex or unclassified by the neurologist.

Follow-up at home was made every six months for those children who did not report at the health facility to ascertain whether the child did not experience further seizures, or had migrated or had died. Follow-up was terminated by migration or death or the development of two unprovoked seizure on separate days (were referred to the epilepsy clinic) or at the end of ten years. Of the 213 children registered at the beginning of the study 181(85%) were still being followed-up at the end of four years and 145(65%) at the end of ten years. Characteristics of FS was obtained from parents/guardian only in 128(60%) and in 85(36.9%) the characteristics of FS from parents was supplemented by scrutinising medical records at the district hospital.

During detailed interview parents/guardian were enquired about the use of prophylactic therapy at the time on enrollment and during the whole

follow up period. None of the children received prophylactic anti-convulsants during the whole period of study. However the use of traditional interventions was not recorded.

The primary end-point was the development of two or more unprovoked seizures and secondary end-point was the number of recurrence of FS at the end of the ten years follow- up period.

Data analysis : Data coded on a primary data sheet were entered into the computer using SSPSS and primarily analysed by the Chi-square test and Chi-square for trend univariate associations. Logistic regression was used for multiple variables, which were significant at 10% level. Kaplan-Meier method was used. Variables significant by log-rank test were included in the Cox's proportional hazard mode for evaluating their simultaneous effect of the factors under study.

RESULTS

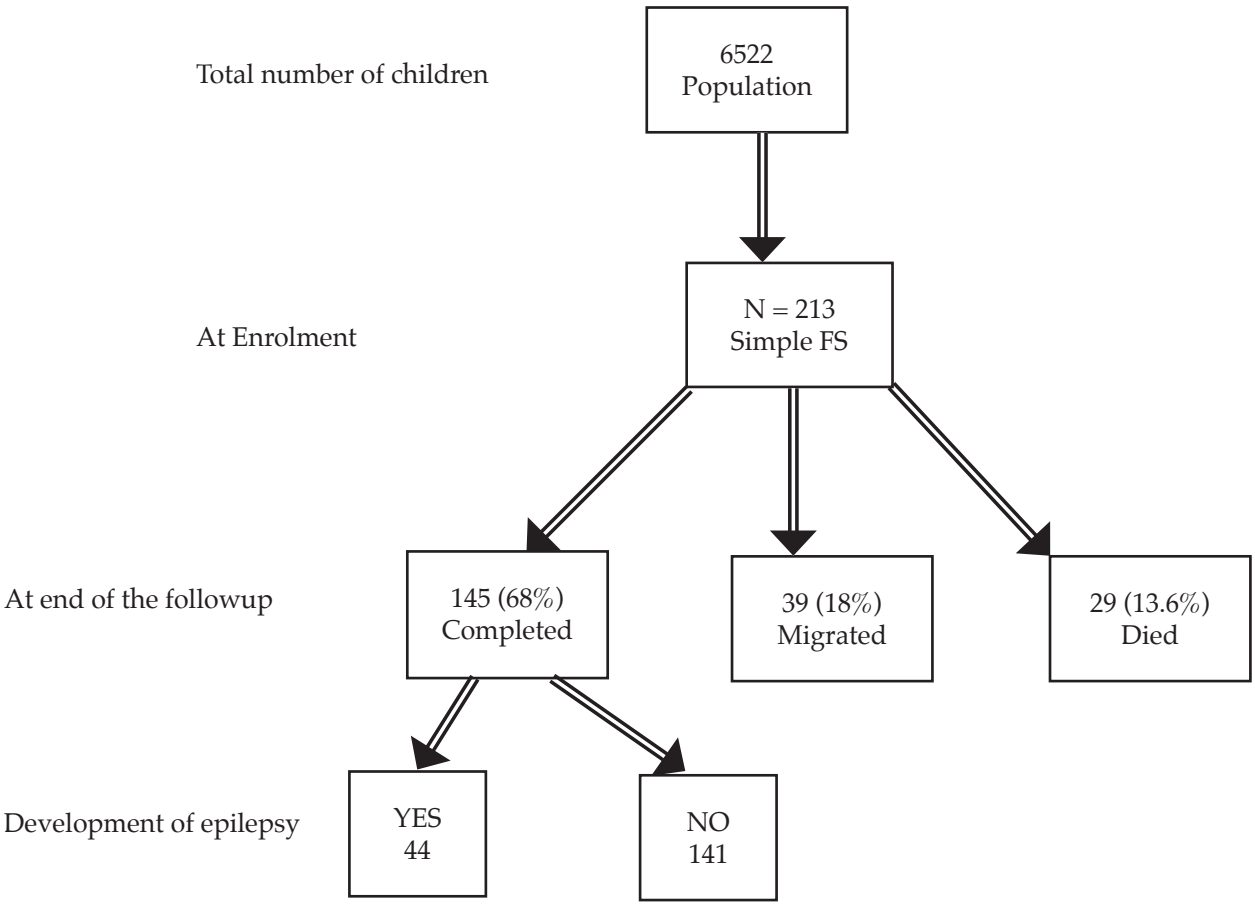
Table 1

Characteristic of children with first ever simple febrile seizure n=213

	Males N=97(%)	Females N=116(%)	Total N=213 (%)
Age 1-	65 (87)	76 (66)	141 (66)
4-6	32 (34)	40 (34)	72 (24)
+FHFS	33 (34)	47 (40)	80 (37.6)
++FHEp	27 (28)	36 (31)	63 (29.6)

+FHES Family history of febrile seizure
++FHEP Family history of epilepsy

Figure 1
Number of children with simple FS at enrolment and at follow up



Of the 6522 children who live in Mahenge division, 213(3%) had had one uncomplicated febrile seizure. The majority of whom 141(66%) were between one and three years old. Eighty children (37.6%) had a positive family history of febrile seizures and 63(29.6%) had a family history of epilepsy. There was no significant difference between sexes and age distribution, family history of epilepsy or family history of febrile seizures.

Of the 213 children who had experienced one uncomplicated febrile seizure, 145(65%) completed the ten year follow-up and 68 (32%) were lost to follow-up before they had developed two or more unprovoked seizures. Of these 39 (18%) had migrated and 29 (13.6%) had died.

Table 2 shows the characteristics of those children who completed the ten year follow up. Of 145 children 44(30%) had developed at least two or more unprovoked seizures (Epilepsy). This is an equivalent of cumulative crude incidence of 3.8 per 100 person years. There was no significant difference in age and sexes for those who completed the ten year follow up between those who developed epilepsy and those who did not develop epilepsy X^2=1.94; p<0.164 and X^2 =0.62; p<0.43 respectively.

Table 2
Characteristics of Children at the end of 8 years study

	Epilepsy N=44	No Epilepsy N=101	P-value Univariate analysis
Sex M/F	18/26	48/52	0.29
Age 9<10	20	58	0.16
11+>	24	43	0.16
+RFS	37	34	0.00
2 or>RFS	23	16	0.000
TRFS	N=37(%)	N=34(%)	
UGTC	21 (61.8)	13(38.2)	0.18
CFS	11(57.9)	10(43)	0.18
Uncls	5(35.3)	11(64)	0.02
FHFS	25	17	0.000
FHEP	18	45	0.201
P/G/EDUC			
Nil	8	15	0.16
Primary	24	55	0.2
Secondary	12	30	0.17
Higher	0	1	

RFS = Recurrent febrile seizure
TRFS = Type of Recurrent febrile Seizure
UGTC = Uncomplicated Generalized tonic-clonic
CFS = Complex febrile seizure
FHFS = Family history of febrile seizure
FHEP = Family history of epilepsy
Uncl = Unclassified febrile seizures
P/G/EDUC = Parents or Guardian level of education

The highest cumulative risk for developing epilepsy was found in children who had experienced their first ever-uncomplicated seizure between the ages of two to five years. This was statically significant than in children who had their ever first uncomplicated seizure below two years of age or those who were above five years log-rank hazard ratioX^2=26.43; p<0.001

Recurrent FS was common in children who developed epilepsy 37(84%) of 44 than those who did not develop epilepsy 34 (34%) of 101. Significantly more children who had recurrent rather than single febrile seizure developed epilepsy (7/73(9.6%) with single versus 37/72(51.3%) with recurrences; X^2= 32.3, p<0.0001, with a significant relative risk (odds ratio 5.4,95%CI 2.6-11.4 p<0.001)

The risk of developing epilepsy of was more significant in children who had more than one recurrent febrile seizures and this was cumulatively significant (log rank X^2 = 28.6 p<0.0001.

The type of recurrent FS did not influence the risk of developing epilepsy. Twenty-one (61.8%) of37 of those who had recurrent seizures developed epilepsy with generalised tonic-clonic febrile seizures in comparison to 11 (60%) with focal seizures. This difference was not significant X^2 = 23.34 p<0.188 (Table 1).

A positive family history of FS was found to be statically significant in those who developed epilepsy than those who did not develop epilepsy, 25(56.5%) of 44 who developed epilepsy in comparison to 17 (68.8%) of 101 who did not develop epilepsy X^2 =23.45 p<0.0200.

A positive family history of FS was an independently significant factor and the probability of developing epilepsy was also significant cumulatively X^2 =18.34 p<0.000. However, a positive family history of epilepsy was not significantly different from those who developed epilepsy and from those who did not develop epilepsy at end of the study X^2 = 38.1 p<0.212.

Of the 44 children who developed epilepsy 21 had recurrent uncomplicated FS. Of these eight (38%) out of twenty one had a febrile complex partial seizures in comparison four (36%) out of eleven who had recurrent complex FS. This difference was not significant X^2 = 3.34; p(<0.1889).

The level of education of the parents or guardian was not significantly different from children who developed epilepsy than those who were epilepsy free at the end of the study.

DISCUSSION

Two to five percent of children will experience at least one febrile seizure before age of five years in

western world (2-4). It is difficult to compare our study with others because of the differences in design and definition in febrile seizures. For instance our study-included only of children who had one uncomplicated FS, giving a prevalence rate of 3% of children in Mahenge had one uncomplicated seizure before the age of six years. This prevalence is the same as that reported in western world but studies in western world included all types of febrile seizures (2-4). Therefore, the prevalence of all types FS must be higher in Mahenge if all types of FS could have been included in the study, which would be a true reflection the situation in Tanzania in general and for other developing countries.

In this study 44 (30%) children developed epilepsy at the end of the eight year follow-up giving a crude cumulative incidence of 3.8 per 100 person years. This is slightly higher than other populations based studies in developed countries with incidence rate of 2.4 to 2.7% although there were differences in study design (12,17).

It has been reported that the incidence of epilepsy following febrile convulsions are higher at age of seven and ten years (2.0% at seven years, 2.5%, at age of ten years) (2,12). Although, this was not directly addressed in our study, however, we found that the risk of developed epilepsy was independently associated with first ever-febrile seizure occurring between the age of two years to five years. Supporting the finding that younger children at the onset of febrile seizures are more likely to develop epilepsy (16). The cumulative risk of a later febrile seizure increased with age from 3% at the age of ten versus 3.8% at age fourteen. This finding is consistent with the findings of other studies (10,12).

We found the number of subsequent febrile seizures following a single uncomplicated seizure was independent significant risk factor for later development of epilepsy supporting the hypothesis that recurrent febrile seizures may lead to brain cell injury that may be a source of later unprovoked seizures. We did not, however find significant differences in the risk of developing epilepsy between children who had recurrent (more than two) uncomplicated febrile seizures from those who had complicated recurrent febrile seizures, negating the concept of cause-and-effect relationship. Our finding is contrary to other studies that reported complex febrile seizures being significantly associated with later epilepsy rather than uncomplicated febrile seizures (2,11,12). It is almost an established fact that prolonged episodes of febrile seizures in children can injure brain cells particularly those in the hippocampus and other medial temporal structures with apparent source of unprovoked seizures. This has been reported in animal studies (19) and in retrospective studies of patients with epilepsy (20-22) and in imaging studies in children who suffered focal seizures (23-25). However, the association between FS and temporal lobe epilepsy although has been recognised, it is still controversial from quantitative point of view even in children with febrile seizures (26).

A family history of epilepsy in children who had uncomplicated FS was not apparently related to later epilepsy in our study contrary to other population based studies where a family history of epilepsy influenced the later development of epilepsy (12,17). This difference could be explained by the differences in study designs, in the definitions of family history and the inclusion criteria used. Nevertheless, our study supports the complex heterogenecity of familial clustering in epilepsy as has been reported by familial studies (27). In our study, the population of children was from Mahenge where genetic analysis had been carried out in over 1500 members of 20 families of 20 epileptic pro-bands, which found a strong familial clustering but there was no evidence for specific gene (28). Our finding supports the probable complex familial clustering in epilepsy.

In this study we found the presence of positive family history of FS to be significant and independent risk factor for later epilepsy. Our findings supports previous family population based studies which indicated a double sibling when both parents had FS (55.6%) compared with when only one parent is affected (21.7%), or when both are unaffected (5.5%) (29). Also, twin studies have demonstrated a higher concordance rate in monozygotic twins than dizygotic twins (30). However, genetic studies by two-point linkage analysis by assuming dominant mode of inheritance have revealed possible genetic heterogenecity for FS (31).

We did not find an association between occurrence of recurrent complex FS and later development of unprovoked complex partial seizures. The ratio between children who had had recurrent febrile seizure was almost the same as that in children who had a single uncomplicated febrile seizure. However, the number of children with previous single uncomplicated FS was too small (seven of fourty four children) for statistical analysis. Our findings are similar to other studies supporting the hypothesis that FS do not appreciably contribute to the occurrence of unprovoked partial complex seizures (12, 17, 31).

Limitations of the study: We relied our characterisation and duration of the first ever FS on parents / guardian recall which may have biased the study. Nevertheless the duration of the first ever FS was estimated during the interview by real timing of less or more than ten minutes.

The follow up interval was rather long which may have resulted in some further seizures being unreported by parents / guardian.

The use of prophylactic anti-convulsants during the study time could have influenced the frequency of recurrent FS. Nevertheless the use of prophylactic anti-convulsant in FS is not a national or policy in study area

We conclude that the cumulative incidence of epilepsy in children who had single uncomplicated febrile seizure may be higher in a rural area in Tanzania than in developed countries. The number of recurrent febrile seizures, family history of febrile seizures, and the age of onset of the first ever-febrile seizure influenced independently the risk for later epilepsy. This underscores the need for recognition of recurrent FS and early interventions that need to be taken in lowering episodes of fever so as to prevent further FS in children at risk for later epilepsy in developing countries.

REFERENCES

1. Hauser, W. A. and Kurland, L. T. The epidemiology of epilepsy in Rochester Minnesota 1935 through 1967. *Epilepsia* 1975. **16**: 1-66.
2. Nelson, K. B. and Ellenberg, J. H. Predictors of epilepsy in children who have experienced febrile seizures. *N. Engl. J. Med*. 1976; **259**: 1029-1033.
3. Offringa, M., Hazebroek-Kampschreurt, A. A. J. M. and Derek-Lubsen, G. Prevalence of febrile seizures in Dutch School children. *Paedtr. Perinatal Epidemol* 1991; **5**: 181-188.
4. Verity, C. M., Butler, N. R. and Golding, J. Febrile convulsions in a national cohort followed up from birth. 1. Prevalence and recurrence in the first five years of life. *Br. Med. J*. 1985; **290**: 1307 -1310.
5. Stanhope, J. M., Brody, J. A., Brink, E., *et al*. Convulsions among the chamorro people in Guam, Mariana Islands II. Febrile convulsions. *Am. J. Epidemiol*. 1972; **95**: 299-304.
6. Familusi, J. B. Febrile convulsions in Ibadan Nigeria. *Afr. J. Med. Sci.* 1971; **2**: 134 -149.
7. Akped, G. O. and Sykes, R. M. Convulsions with fever among preschool children in developing countries: Dev. Med. Child. *Neurol*. 1992; **34**: 524-529.
8. Obi, J. O., Ejeheri, N. A. and Alakija, W. Childhood febrile seizures (Benin City Experience*). Ann. Trop. Paediatr.* 1994; **14**: 211-214.
9. Birbeck, G. H. Seizures in rural Zambia. *Epilepsia* 2000, **41**: 277-281.
10. Annegers, J. F., Blacley, S. A., Hauser, W. A. and Kurland, L. T. Recurrence of febrile convulsions in a population based cohort. *Epilepsy Res*. 1990; **5**: 209-216.
11. Annergers, J. F., Hauser, W. A., Elveback, L. R. and Kurland, L. T. The risk of epilepsy following febrile convulsions. *Neurology* 1979; **29**: 297-303.
12. Verity, C. M. and Golding, J. Risk of epilepsy after febrile convulsions: a national cohort study. *Br. Med. J*. 1991; **303**: 1373-1376.
13. Ogunniyi, A., Osuntokun, B. O., Bademosi, O., *et al*. Risk factors for epilepsy. A case controlled study in Nigerians. *Epilepsia.* 1987; **28**: 280 - 285.
14. Bademosi, O., Ogunninyi, A. and Osuntakun, B. O. Febrile convulsions as a risk factor for epilepsy in Nigeria. A case control study. *Afr. J. Neurol. Sci.* 1989; **8**: 20-23.
15. Rwiza, H. T., Kilonzo, G. P., Matuja, W. B. P., *et al*. Prevalence and incidence of epilepsy in Ulanga, a rural Tanzanian District. A. Community based study. *Epilepsia* 1992; **33**: 1051-1056.
16. Wallace, S. J. The child with febrile seizures. *London John Wright*. 1988: 109-126.
17. Annegers, J. F., Hauser, W. A., Shirts, S. B. and Kurland, L. T. Factors prognostic of unprovoked seizures after febrile convulsions. *N. Engl. J. Med*. 1987; **38**: 493-498.
18. Matuja, W. B. P., Kilonzo, G., Mbena, P. *et al*. Risk factors foe epilepsy in Rural Area in Tanzanioa: A community based case-control study. *Neuroepidemiology*. 2001; **20**: 242-247.
19. Meldrum, B. S. Secondary pathology and experimental convulsions, In Brazier MAB, Coceani F, eds. "Brain dysfunction in infantile febrile convulsion, New York: Raven 1976 : 213-222.
20. Falconer, M. A., Serafetinides, E. A. and Corsellis, J. A. N. Etiology and pathogenesis of temporal lobe epilepsy. *Arch. Neurol*. 1964; **10**: 233-248.
21. Sagar, H. J. and Oxbury, J. M. Hippocampal neuronal loss in temporal lobe epilepsy: Correlation with early childhood convulsions. *Ann. Neurol*. 1987; **22**: 334-340.
22. Cendes, F., Andermann, R., Gloor, P., *et al.* Atrophy of mesial structures in patients with TLE: Cause or consequence of repeated seizures. *Ann. Neurol*. 1993: **34** 795-801.
23. Van Landinghan, K. E., Heinz, E. R. and Cavaros, J. E. Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile convulsions. *Ann. Neurol*. 1998; **43**: 413-426.
24. Stafstrom, C. E., Tien, R. D., Montine, J. J., *et al*. Refractory status epileptics associated with progressive MRI signal change and hippocampal neuronal loss. *J. Epilepsy.* 1996; **9**: 253-258.
25. Maher, J. and McLachlan, R. S. Febrile convulsions: is seizure duration the most important predictor of TLE? *Brain* 1995; **118**: 1521-1528.
26. Knudsen, F. U. Febrile seizures. Treatment and prognosis (Progress in Epilepsy Research). *Epilepsia.* 2000; **41**: 2-9.
27. Ottman, R., Annegers, J. F., Risch, N., *et al*. Relations of Genetic and Environmental Factors in the etiology of epilepsy. *Ann. Neurol*. 1996; **39**: 442 - 449.
28. Neuman, R. J., Kwon, J. M., Jilek-Aall., *et al*. Genetic analysis of Kifafa: a complex familial seizure disorder. *Am. J. Human Gen*. 1995; **57**: 902-910.
29. Hauser, W. A., Annegers, J. F., Anderson, V. E., *et al*. The risk of seizure disorder among relatives of children with febrile convulsions. *Neurology* 1985; **35**: 1268-1273.
30. Corey, L. A., Berg, K., Pellock, J. M., *et al*. The occurrence of epilepsy and febrile seizures in Virginian and Norwegian twins. *Neurology* 1991; **41**: 1433-1436.
31. Rachachol McLachlan, R. S., Ebers, G. C., *et al*. Evidence favouring genetic heterogeneity for febrile convulsions. *Epilepsia* 2000; **41**: 132-139.
32. Lee, K., Diaz, M. and Melchior, J. C. Temporal lobe epilepsy not a consequence of childhood febrile convulsions. *Acta. Neurol. Scand*. 1988; 231 - 236.