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Heterogeneity of prevalence and risk factors for Active Convulsive Epilepsy in a rural district of Kenya

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Abstract

Background—There are few large-scale studies of epilepsy in sub-Saharan Africa. We estimate the prevalence, treatment gap and risk factors for active convulsive epilepsy (ACE) in Kenyans aged 6 years in a rural area.

Methods—A three-phase screening survey of 151,408 individuals followed by a nested community case-control study.

Findings—The overall prevalence of ACE was 2.9 per 1000 (95%CI: 2.6 to 3.2 per 1000) and after adjustment for non-response and sensitivity, 4.5 per 1000 (95%CI: 4.1 to 4.9). There was substantial heterogeneity in the prevalence, with evidence of clustering.

The treatment gap was 70.3% (95%CI: 65.9 to 74.5) with weak evidence of a difference in sex and residential division.

Adjusted odds of ACE for all ages were increased for family history of non-febrile convulsions (OR 3.3, 95%CI: 2.4 to 4.7), family history of febrile convulsions (OR 14.6, 95%CI: 6.3 to 34.1), history of both seizure types (OR 7.3, 95% CI: 3.3 to 16.4) and previous head injury (OR 4.1,

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95%CI: 2.1 to 8.1). In multivariable analyses in children, adverse perinatal events increased odds (OR 5.7, 95%CI: 2.6 – 12.7) as did paternal orphanhood (OR 5.1, 95%CI 2.4 to 11.0).

Interpretation—This survey demonstrates significant heterogeneity in the prevalence of ACE in large population in Africa and identifies subgroups in greatest need of targeted interventions through assessment of prevalence, treatment adherence and demographic variation in screening response. Adverse perinatal events, febrile illness and head injury are potentially preventable risk factors of epilepsy in this region.

Keywords

epilepsy; prevalence; door-to-door; sub-Saharan Africa; treatment gap; risk factor

Introduction

The World Health Organization (WHO) estimates that of the 50 million people with epilepsy in the world, 80% live in developing countries¹ but this estimate is based upon few studies. A recent review of epilepsy in sub-Saharan Africa (SSA) suggested that small studies provide widely varying, and imprecise estimates of disease burden². Larger studies may underestimate prevalence due to under-reporting from stigma². Furthermore, definitions of epilepsy vary across studies, as do methods for screening and data collection³. Door-to-door surveys are thought to be the most effective screening method in areas with poor resources for capture and maintenance of medical history. Such studies detect mainly convulsive epilepsies, due to limited resources and low awareness of non-convulsive epilepsy. Nine case-control studies have been reported from SSA to determine risk factors with limited investigation of confounding effects². Many people with epilepsy in this region do not access treatment⁴.

We report the results of a large screening survey in a rural, malaria endemic area of Kenya. We estimate the prevalence of, the treatment gap and risk factors for active convulsive epilepsy (ACE) in individuals aged 6 years and above.

Methods

Study Setting

This study was conducted in Kilifi District, a rural area on the coast of Kenya, in which Kilifi District Hospital (KDH) is located in the administrative centre. An area of 891 km squared has been mapped and forms part of a demographic surveillance system (DSS) including re-enumeration of the population every 4 months (births, deaths, migration). This study area is divided administratively into 6 divisions and within these divisions into 15 locations, 40 sublocations and 185 enumeration zones. Mijikenda are the indigenous people of coastal Kenya and consist of the Giriama, Chonyi and Kauma ethnic groups and some other small groups. Kilifi is the second poorest district within Kenya⁵; literacy amongst adults is low, access to sanitation facilities is poor and subsistence farming is the main source of income. The life expectancy at birth is 57 years for females and 51 for males⁵. Malaria is endemic with two peaks in transmission during May to August and December to

January⁶. Infectious diseases such as malaria, pneumonia or bacteraemia are common causes of admission to KDH^{7,8}.

Three-phase survey

The door-to-door survey was conducted during the population re-enumeration between August and November 2003.

Phase I: The head of each household was asked two questions by the census team, regarding *each* person within the household, to identify those who had experienced convulsions (Appendix A). The second question was 100% sensitive in detecting active epilepsy in children when asked of the parents in a previous study in this area⁹.

Phase II: Individuals identified in Phase I were visited by the epilepsy field team who interviewed the individuals or their guardians in person (Appendix A).

Phase III: Individuals suspected of having epilepsy in Phase II were invited to attend for formal assessment and diagnosis at KDH, within one week of the Phase II interview. One clinician, fluent in the local languages, Kigirima and Kiswahili, obtained a detailed medical history from which to make a diagnosis and record a description and frequency of seizures. A panel of neurologists (authors: TK, GM, BN, LS, CN,) reviewed case notes to confirm diagnoses.

Active Convulsive Epilepsy was defined as two or more unprovoked convulsions, with one convulsion occurring within 12 months prior to Phase III, based on the most recent International League Against Epilepsy (ILAE) definition of active epilepsy at the time of study design and the criteria for offering anti-epileptic drugs (AED) to patients in Kenya^{10,11}. Individuals under 6 years were excluded in Phase II due to difficulty in differentiating between febrile seizures and epilepsy in younger children¹².

Individuals with epilepsy were asked if they were currently taking or had previously taken any AED and shown the actual tablets to aid recognition. A blood sample was taken from consenting individuals to test for Phenobarbitone, the only AED available in the peripheral clinics. Samples were tested for Phenytoin if use was reported. Drug levels were measured with TDxFLx® fluorescence polarization immunoassay (Abbott Laboratories, Diagnostics Division, Abbott Park IL, USA) which detects concentrations of at least 10 mg/L in Phenobarbitone and Phenytoin. For study purposes, an optimal level of Phenobarbitone was defined as 10 – 30 mg/L and for Phenytoin, 10 – 20 mg/L¹³.

The seizure treatment gap is the proportion of people with active epilepsy whose seizures are not being appropriately treated, where ‘appropriate treatment’ includes diagnosis and therapeutic treatment¹⁰.

Case-control study: Recruitment of controls

To control for confounding and to minimise recall bias, controls were randomly selected from the DSS and frequency-matched to ACE cases by age, in five strata; 6-12, 13-17, 18-28, 29-49 and 50 years or more. Data on children was often obtained from parents.

Recall of previous events may decrease with age and ascertainment of true age is problematic in older adults in a rural population.

Potential Risk factors

Participants and guardians were asked about convulsive seizure history among their first-degree relatives (siblings and parents) and extended relatives, febrile seizures in all relatives and serious head injury. We classified early seizures with fever and full recovery as febrile seizures. For children under 18 years, mothers were questioned regarding adverse perinatal events (history of prolonged labour and postnatal difficulties, such as convulsions in the first week of life and, or difficulty in establishing breathing or breast feeding)¹⁴. Socio-demographic factors included sex, ethnic group and location of residence.

Statistical Analysis

Data were double-entered and verified using Visual FoxPro v9.0 (Microsoft, USA) and statistical analyses carried out using STATA v8, (StataCorp 1984-2006).

Unadjusted prevalence and exact binomial 95% confidence intervals (CIs) were calculated overall and by age and sex, per 1000 people. Associations between socio-demographic characteristics and overall prevalence were tested using chi-squared, as were associations with AED adherence in diagnosed cases. Adjusted prevalence by geographical area was derived at enumeration zone, sublocation and location level from a binomial regression model, adjusted for age and sex, to examine evidence of heterogeneity.

Sensitivity and specificity¹⁵ were estimated for Phase II screening questions and self reported AED use as a means of determining current AED use.

Logistic regression was used to investigate individual risk factors for ACE, after adjustment for the frequency matched variable age¹⁵. Subjects with complete data were included in multivariable regression model building using a forward stepwise strategy (inclusion $p < 0.1$ and exclusion $p > 0.1$) for factors relating to medical histories. Adjustment was also made for underlying socio-demographic variation identified in overall prevalence analyses to improve model fit. A subgroup analysis in children (aged < 18 years) investigated the effect of perinatal events using the same multivariate modelling strategy. Regression models were compared using the likelihood ratio test (LRT).

The National Ethical Review Committee of Kenya, Institute of Child Health Ethics Committee and London School of Hygiene and Tropical Medicine Ethics Committee approved the study. Written informed consent was obtained from participants. In the case-control study, cases were consenting survey participants with ACE.

Results

Population Screening

In Phase I, household heads provided responses for 151,408 residents aged 6 and above. Numbers screened and subsequent results are presented in Figure 1. Non-response in Phase II was not associated with age or sex ($p > 0.3$) but was higher in non-coastal ethnic groups

and Malindi, Bahari and Kikambala divisions ($p < 0.001$). Non-response in Phase III was weakly associated with age ($p = 0.075$), strongly with division ($p < 0.001$) (higher in Bahari and Kikambala) but not with sex or ethnicity ($p > 0.6$). Diagnosis of ACE was made in 445 individuals; 442 directly and 3 following detection of AED in a blood sample (Figure 1).

Of the 1,283 Phase II negative participants, 1,174 were re-interviewed with 70 screening positive and attending Phase III assessment. In addition to the 442 diagnoses through Phase III assessment of Phase II positive subjects prior to blood testing, a further 24 diagnoses were made in subjects originally Phase II negative. Sensitivity and specificity estimates were 94.8% (442/466, 95% CI 92.4 – 96.7) and 52.3% (46/88, 95% CI 41.4 – 63.0), respectively.

Prevalence of ACE

The overall prevalence of ACE was 2.9 per 1000 people (95% CI: 2.6 – 3.2). Unadjusted prevalence varied with age ($p < 0.001$) and sex ($p = 0.036$), with higher prevalence in males and in those aged 13 – 28 years (Table 1). There was little evidence of a difference by ethnicity ($p = 0.166$). Based on a 5 year cut off for date of last seizure, unadjusted prevalence of active epilepsy was estimated as 3.1 per 1000 (2.8 – 3.4 per 1000).

Taking non-response and Phase II sensitivity into account, the estimated prevalence of ACE was 4.5 per 1000 (95% CI: 4.1 – 4.9) assuming 100% sensitivity in Phase I, using the formulae in Appendix B.

Geographical variation of ACE

The median number of eligible individuals screened in Phase 1, per enumeration zone, was 959 (IQR: 679 to 1275). After adjustment for age and sex, there was strong evidence of heterogeneity in the prevalence of ACE across zones within the large study area ($p < 0.001$). Heterogeneity was also present at location and sublocation levels ($p < 0.001$). Adjusted prevalence by enumeration zone is presented graphically on a map of the study area (Figure 2).

Anti-Epileptic Drugs & Treatment Gap

Of the 445 cases of ACE, blood samples were taken from 408 (91.7%) consenting patients. There were detectable levels in 132 samples and optimal levels in 63 providing minimum treatment gap estimates of 70.3% (95% CI: 65.9 to 74.5) and 85.8% (82.3 to 88.9), respectively. Age was associated with non consent for blood samples with children under 12 years less likely to have a sample ($p < 0.001$). Sex, ethnicity and location were not associated with consent ($p > 0.3$).

Current use of any AED was self-reported by 127 with Phenobarbitone and/or 121 with Phenytoin. Self reported and blood sample results concurred in 307 patients; 76 for AED and 231 without AED. The sensitivity and specificity of self reporting were 57.8% (95% CI 48.7 – 66.1) and 86.7% (78.8 – 87.9), respectively.

There was weak evidence that males were less likely to adhere to AED ($p = 0.057$) and of an association between non-adherence and division ($p = 0.074$) but no evidence of an association with age, ethnicity or seizure frequency ($p > 0.1$).

Risk Factors for ACE

Recruitment of controls was based on immediate results from Phase II. Consequently the number of controls exceeded the number of cases, however, frequency matching was upheld (Table 2).

Analyses of individual potential risk factors were adjusted for age. Results supported evidence of a geographical association with odds of ACE and also suggested increased odds for head injury, family history of febrile seizures and family history of convulsions in subjects of all ages (Table 2). There was evidence of an interaction between history of febrile convulsions and convulsive seizures ($p=0.008$) when considered in four categories. The final multivariable model adjusted for these factors and also underlying demographic characteristics (sex, division and ethnicity) in order to obtain a better model fit to the data (Table 3).

The final multivariable model in children under 18 identified adverse perinatal events and mother's marital status as risk factors, after adjustment for seizure histories and socio-demographic factors (Table 3), with higher odds of ACE if mothers were widowed rather than married. After adjustment for perinatal event, head injury was no longer significant in children ($p=0.161$).

In both final models, family history of convulsions was collapsed into a binary variable for increased power and the interaction term included with results suggesting increased odds of ACE in those with a history of either febrile or non-febrile convulsions or both types, compared to no history of either.

Discussion

This is the largest community survey of epilepsy in Africa and estimated overall prevalence to be 4.5 per 1000, adjusted for non-response and screening sensitivity. A previous study, conducted when the DSS was one third of the size, estimated a similar prevalence of ACE and that 3.5% of deaths in a 2 year period were epilepsy related¹⁶. In addition, the current study found strong statistical evidence of variability in prevalence across small geographical areas suggesting clustering of people with ACE. It highlighted differences within smaller divisions in response rate and awareness of epilepsy; findings suspected by others but not supported by available data until now². Variation could be due to clustered exposure to environmental or genetic risk factors. Access to medical care may also account for the clustering, since people living closer to KDH are treated more frequently¹⁷ although visual inspection of the prevalence map provided little evidence of a prevalence gradient surrounding the hospital.

Other large studies in SSA, surveying more than 15,000 people found the prevalence of ACE to range from 5.2 to 12.5 per 1000¹⁸⁻²⁰. Prevalence of studies including non-convulsive epilepsies in 3 studies ranged from 10.2 to 18.2 per 1000^{20,21}. Estimates from smaller studies are especially variable². Cross-sectional prevalence estimation is thought to underestimate the prevalence of life-time epilepsy by more than 75%²². Non-convulsive epilepsies may constitute 50% of all epilepsies in community based studies²². Therefore, the

life-time prevalence of epilepsy in Kilifi could be more than double the prevalence of ACE measured in this study.

Our findings also demonstrate negligible difference in prevalence estimates based on a 1 or 5 year cut-off for most recent seizure, justifying cautious comparison of large published studies using either definition. Complexities of comparisons between studies are probably more influenced by difficulties in capture of persons at risk during early screening phases and identification of aetiologies, than differences in definitions of active epilepsy.

Higher prevalence was found in adolescents and young adults. Studies in the West have shown peaks in incidence among young children and the elderly (>65 years)^{22,23}. Inter-regional comparisons without comparable age standardisation are not so informative given that only 3% of our population was 65 years or older. However, variation in prevalence by age and sex in Kilifi, with a higher prevalence in adolescents and young adults, and lower prevalence particularly in adult women, is similar to that observed in other studies in rural sub-Saharan Africa^{2,24}. A relatively low prevalence of ACE during adult life may be attributable to spontaneous remission, though it may also indicate that those with epilepsy die prematurely, as documented in other developing countries^{16,25}.

The treatment gap was substantial in this high risk group but slightly lower than reported from other areas of SSA^{4,26}. The treatment gap based on self reported AED use would have been similar to confirmed results, but the low sensitivity of self reported use highlights the need for intervention studies to increase awareness of epilepsy and treatment options. Phenytoin use could have been underestimated since samples were only tested in the 2% who reported use, due to financial limitations, although Phenytoin is less widely available. Fewer children gave consent for blood testing and parents reported less use of AED.

Important methodological considerations

This study only detected convulsive epilepsies, but the detection of these epilepsies is a priority in SSA, since they are associated with more comorbidity, injury and mortality, than non-convulsive epilepsies. The detection of non-convulsive epilepsies is much more difficult and would require detailed medical anthropological studies to ascertain the symptoms such as staring episodes and hallucinations that are the manifestations of these types of epilepsies.

Phase I aimed to identify individuals experiencing convulsions with high sensitivity, efficiently screening a large population with only limited interview time available during the census enumeration. Phase II aimed to confirm that the individuals identified in Phase I, had experienced convulsions and determine the timing of recent seizures with higher specificity.

The questions in both questionnaires should detect any persons experiencing convulsions in those wishing to divulge such information (Appendix B). Negative responses should only be due to lack of awareness of convulsions in family members on the part of the household head or stigma related bias, the latter reason thought to be more likely to occur. Assuming 100% Phase I sensitivity leads to the most conservative prevalence estimate (Appendix B). It is known that stigma is widespread within communities in this area¹² and even within health care workers in developing countries^{12,28}. An important reason for high non-response

could be beliefs that epilepsy is caused by bewitchment so treatment with modern medicine is inappropriate^{12,28}. The high sensitivity for Phase II suggests, in those reporting convulsions, the questions asked are extremely effective for detection of people with convulsive epilepsies although these results are also susceptible to stigma related bias.

After controlling for underlying demographic variation, family history of febrile and non-febrile convulsions and head injury in adults were important, preventable associated factors. In children, perinatal events and possible paternal orphanhood were associated factors. Mortality is higher in epilepsy²⁵ and the observed association between children with ACE and convulsions in first degree relatives could suggest paternal orphanhood is a marker for fathers with epilepsy or increased risk through poverty. Of nine case-control studies in SSA, only two used multivariate methods to control for confounding, and they identified febrile and convulsive family seizure history and perinatal events². Interviewers tried to distinguish between the convulsive epilepsy and febrile convulsions in the family history but it is likely there was dependence in many cases, due to long recall. This may explain the unusual interaction observed in which, compared to no history of either febrile or non-febrile convulsions, odds of ACE were higher for those with a history of only febrile convulsions, than for a history of both when it might have been expected that an increase in odds would be higher in those exposed to both types of convulsive history. Also, low power for investigating these effects in this sample led to low precision. A case-control study in Indian children estimated similar odds ratios for age-adjusted effects of febrile illness and first-degree family history of convulsive seizures²⁹.

Epilepsy is most prevalent in adolescents and young adults in this rural area with considerable geographical variation in prevalence. Intervention is required to increase awareness of epilepsy as a treatable condition and treatment seeking in rural areas in order to detect those in need. The identification of adverse perinatal events, febrile illness leading to seizures and head injury as risk factors suggests that much epilepsy is preventable.

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Appendix A: Screening questions

Phase I

1. Do you/this member of the household have fits or has someone ever told you that you/they have fits?
2. Do you/this member of the household experience episodes in which your/their legs or arms have jerking movements or fall to the ground and lose consciousness?

Phase II

The questions in Phase I were asked again for clarification. The following additional questions were also asked:

1. Have you/this member of the household ever been told by a doctor that you have epilepsy or epileptic fits?
2. Have you/ this member of the household ever been told by someone else that you have epilepsy or epileptic fits?
3. Have you/ this member of the household ever fallen to the ground without a reason and experienced twitching?
4. Have you/ this member of the household ever fallen to the ground without a reason and wet yourself?
5. Have you/ this member of the household ever fallen to the ground without a reason and bitten your tongue?

Appendix B: Formulae for adjusted prevalence estimate and corresponding standard error

$$p = \frac{d}{R_1 \left(\frac{R_2}{R_1^+} \right) \left(\frac{R_3}{R_2^+} \right) \text{sens}_{\text{phaseII}}}$$

and

$$\text{s.e.}(p) = \sqrt{p(1-p) / R_1 \left(\frac{R_2}{R_1^+} \right) \left(\frac{R_3}{R_2^+} \right) \text{sens}_{\text{phaseII}}}$$

where p = prevalence, d = number of cases of ACE at phase 3, R_i = number who responded at phase i , R_i^+ = number with positive result for tool at phase i , $\text{sens}_{\text{phaseII}}$ = sensitivity of Phase II questionnaire. 95% confidence intervals were constructed assuming normal approximation; limits = $p \pm 1.96 \times \text{s.e.}(p)$.

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Figure 1. Screening Survey Flow

* Individuals aged 6 years and over resident during the previous census round

† ACE = Active Convulsive Epilepsy defined as 2 or more unprovoked seizures with the most recent within last 12 months

‡ History of epileptic seizures.

¶ AED = Anti-epileptic drugs. Confirmed by testing of blood sample

Figure 2. Prevalence (per 1000) of Active Convulsive Epilepsy by enumeration zone and boundaries of administrative divisions within the study area in Kilifi District, adjusted for age and sex

Table 1
Unadjusted prevalence (per 1000) of ACE by age and sex with 95% confidence bounds

Age in years	Male				Female				All	
	Screened in Phase I	Active Convulsive Epilepsy	prevalence per 1000	95% CI	Screened in Phase I	Active Convulsive Epilepsy	prevalence per 1000	95% CI	prevalence per 1000	95% CI
6-12	21,165	71	3.4	2.6 - 4.2	20,562	53	2.6	1.9 - 3.4	3.0	2.5 - 3.5
13 - 17	13,383	45	3.4	2.4 - 4.5	11,898	48	4.0	3.0 - 5.3	3.7	3.0 - 4.5
18 - 28	13,912	55	4.0	3.0 - 5.1	18,077	62	3.4	2.6 - 4.4	3.7	3.0 - 4.4
29 - 49	13,490	33	2.4	1.7 - 3.4	20,560	39	1.9	1.3 - 2.6	2.1	1.6 - 2.5
50	8,074	21	2.6	1.6 - 4.0	10,287	18	1.7	1.0 - 2.8	2.1	1.7 - 2.7
All ages	70,024	225	3.2	2.8 - 3.7	81,384	220	2.7	2.4 - 3.1	2.9	2.6 - 3.2

Table 2
Age-adjusted odds ratios for socio-demographic and medical history risk factors

Characteristic *	Controls N = 636	Cases N = 445	Odds Ratio [‡]	95% CI
Age				
6-12, n (%)	170 (26.7)	115 (25.9)	1	
13 - 17, n (%)	146 (23.0)	98 (22.0)	1.0	0.7 - 1.4
18 -28, n (%)	155 (24.4)	117 (26.3)	1.1	0.8 - 1.6
29 - 49, n (%)	112 (17.6)	77 (17.3)	1.0	0.7 - 1.5
50, n (%)	53 (8.3)	38 (8.5)	1.1	0.7 - 1.7
Sex				
Female, n (%)	353 (55.5)	220 (49.4)	1	
Male, n (%)	280 (44.0)	225 (50.6)	1.3	1.0 - 1.7
Division				
Bahari, n (%)	308 (48.4)	196 (44.1)	1	
Chonyi, n (%)	138 (21.7)	90 (20.2)	1.0	0.7 - 1.4
Ganze, n (%)	25 (3.9)	26 (5.8)	1.6	0.9 - 2.9
Kikambala, n (%)	83 (13.1)	107 (24.0)	2.0	1.4 - 2.8
Malindi, n (%)	31 (4.9)	11 (2.5)	0.6	0.3 - 1.1
Vitengeni, n (%)	51 (8.0)	15 (3.4)	0.5	0.3 - 0.8
Family history of non-febrile convulsions				
none, n (%)	540 (84.9)	297 (66.7)	1	
first degree relatives, n (%)	12 (1.9)	15 (3.4)	2.3	1.0 - 5.1
both 1 st degree & extended relatives, n (%)	7 (1.1)	15 (3.4)	3.9	1.6 - 9.8
extended relatives only, n (%)	76 (11.9)	115 (25.8)	2.8	2.0 - 3.8
Family history of febrile convulsions				
no, n (%)	617 (97.0)	381 (85.6)	1	
yes, n (%)	16 (2.5)	63 (14.2)	6.5	3.7 - 11.4
Previous head injury				
no, n (%)	611 (96.1)	408 (91.7)	1	
yes, n (%)	14 (2.2)	35 (7.9)	3.7	2.0 - 7.0
<i>Children only</i> [†]	N = 315	N = 213		
History of perinatal events				
No, n (%)	303 (96.2)	171 (80.3)	1	
yes, n (%)	11 (3.5)	32 (15.0)	5.4	2.7 - 10.9
Mother's marital status				
Married, n (%)	260 (82.5)	150 (70.4)	1	
Never married, n (%)	19 (6.0)	3 (1.4)	0.3	0.1 - 0.9
Divorced / Separated, n (%)	17 (5.4)	17 (8.0)	1.7	0.9 - 3.5
Widowed, n (%)	14 (4.5)	35 (16.4)	4.4	2.3 - 8.4

* 3 records were missing values for sex, 4 for convulsive seizure history and febrile seizure history and 13 for head injury.

[†] Of 528 children, 7 had missing values for birth trauma and 13 for mother's marital status

[‡]Odds ratios for individual characteristics adjusted for age since cases and controls were frequency matched by age within intervals shown

Table 3
Risk factors for Active Convulsive Epilepsy: adjusted odds ratios from the final multivariable model

Risk Factor		Adults and Children		Children	
		Adjusted OR*	95% CI	Adjusted OR*	95% CI
Family history of febrile convulsions	Family history of non-febrile convulsions				
None	None	1.0		1.0	
None	In any family member	3.3	2.4 – 4.7	3.6	2.1 – 6.0
In any family member	None	14.6	6.3 – 34.1	18.4	5.6 – 60.2
In any family member	In any family member	7.3	3.3 – 16.4	5.5	1.9 – 15.9
Previous head injury		4.1	2.1 – 8.1	-	-
Perinatal event		-	-	5.7	2.6 – 12.7
Mother's marital status					
Married		-	-	1	
Never married		-	-	0.4	0.1 – 1.5
Separated or divorced		-	-	1.5	0.7 – 3.5
Widowed		-	-	5.1	2.4 – 11.0

* OR for all subjects also adjusted for age, sex, division and ethnicity