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# Risk Of Seizures In First Degree Relatives Of Probands With Epilepsy.

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## SUMMARY

**Objective:** To determine the risk of seizures in first degree relatives of epileptic patients. To relate the risk to several clinical characteristics in the probands. Such information is useful for genetic counselling.

**Methods:** A prospective case-control study of 648 FDR of 88 probands attending the neurology out-patient clinic of a tertiary hospital in Lagos, Nigeria, and 308 FDR of 44 age and sex-matched controls was carried out. History of seizures in all FDR was sought using a survey questionnaire either directly filled by the FDR, probands or both. The risk of seizures in FDR was related to some clinical variables in the probands.

**Results:** Overall risk of seizures was slightly but insignificantly higher (3.6%) in FDR of probands with epilepsy compared to controls (2.3%) (chitest; $p > 0.05$). Risk of seizures was highest in offspring of probands (4.3%), and FDR of female probands (4.0% compared to 3.1% in males), probands with seizure onset below 10 years (5.1% compared to 3.1% >10years) and probands with complex partial seizures (4.9% compared to 3.9% for generalized tonic-clonic seizures). The differences did not however reach statistical significance in comparison to the control group (chitest; $p > 0.05$).

**Conclusion:** The risk of seizures in FDR of Nigerian probands with epilepsy has a similar profile with that in other environments such as Europe and North America in that it is marginally higher but not significantly different from the risk in the normal population.

## INTRODUCTION

The epilepsies have been bedevilled with misconceptions regarding aetiology, from Shakespearean implications of Caesar being inflicted by a god, to the widespread (mis)belief in Africa of the contagious nature of the disease. Stigmatization as a result of ignorance has been well documented amongst patients as well as medical personnel [1, 2]. Advances in scientific knowledge, have, however, lent reasonable clarity to the role of genetics in epilepsy. Pioneering works of note include those of Conrad in 1935, and Lennox between 1939 and 1951. The latter concluded that although a genetic factor in epilepsy was unquestionable, its nature and extent were still uncertain[3].

Epilepsies are currently considered as either genetically transmitted (idiopathic epilepsies) or consequences of specific cerebral disturbances (symptomatic epilepsies) [4]. Genetic factors can have an impact on the appearance of an epileptic condition in at least three ways: (a) the susceptibility of any given brain to an epileptogenic disturbance is, predominantly, genetically determined; (b) the idiopathic epilepsies are specific inherited syndromes associated with characteristic seizure types but no structural or biochemical abnormalities and no other neurological deficits; and (c) several genetic disorders, such as tuberous sclerosis, are characterized by structural or biochemical disturbances of the brain which in turn cause seizures, constituting the familial symptomatic epilepsies [5]. Some epilepsy syndromes appear to have clear-cut patterns of inheritance, but the vast majority appear to be multifactorial, involving an interaction between polygenic disorders and environmental factors [6]. In the latter, the risk of seizures in first degree relatives of the probands does not follow a simple theoretical proportion.

Studies aimed at determining the risk of seizures in relatives of probands with epilepsy have been family and population based, utilizing criteria such as presumed aetiology of epilepsy, drug response, seizure characteristics, detailed family histories, EEG studies of available parents, siblings and offspring, as well as age at onset of seizures [7, 8]. More recently, advances in molecular biology have facilitated the identification of genetic loci if abnormality in a few inherited epilepsies such as Unverricht-Lundborg disease and autosomal dominant nocturnal frontal lobe epilepsy [9, 10].

The present study is directed at determining the role of genetic factors in the aetiology of the epilepsies in Nigerians, by describing the risk of seizures in first degree relatives (FDR) of probands with epilepsy, comparing this to the risk of seizures in FDR of non-epileptic controls, and relating some clinical variables of the probands to risk of seizures in their FDR (parents, siblings or offspring). The finding will be of value in genetic counselling of close relatives of epileptic patients in this environment.

## METHODOLOGY

### Probands and FDR

A total of eighty eight probands with epilepsy attending the neurology out-patient clinic of the Lagos University Teaching Hospital (LUTH) were recruited into the study and verbal informed consent obtained. The study protocol was approved by the ethical committee of the hospital. Selection was by recruitment of all consecutively attending probands

with sufficient information to enable classification of seizure type and epilepsy syndrome (i.e. seizure description and electroencephalographic characteristics). Diagnostic criteria were in conformity with the International League Against Epilepsy criteria for classification of epileptic seizures and epilepsy syndromes [4]. Only those patients who were in close enough contact with their FDR (same domicile, telephone contact or same locality) and able to question them as to the occurrence of seizures were included. For underage probands and FDR, history obtained from parents was accepted as being accurate. To limit the likelihood of false declarations, FDR were assigned serial alphabetic codes preceded by the probands serial number so as to assure them of confidentiality and privacy of all information. Forms were filled and returned at a subsequent contact visit one to four weeks later.

### Controls and FDR

Forty-four age and sex-matched controls were recruited into the study. The controls were either medically normal subjects or patients attending other out-patient clinics for disorders completely unrelated to epilepsy. The method of obtaining information from FDR was uniform with that used for the probands.

### Methods

A uniform questionnaire was used for the following purposes:

a) To document basic information about the probands, including age at onset of seizures, gender, seizure type, and epilepsy syndrome.

b) To obtain information regarding the occurrence of two or more unprovoked seizures in FDR of probands (see details in Figure 1).

On this basis, the seizure history of 648 (six hundred and forty eight) FDR of 88 probands and 308 FDR of 44 age and sex-matched controls was documented.

### Statistical analysis

The baseline characteristics of probands were reported as mean ± SD for continuos variables. $\div^2$ test (uncorrected or Yates corrected) was used to compare differences in categorical variables.

## RESULTS

### Demography of probands and controls

The demographic characteristics of the 88 probands (47 males and 24 females) and the 44 controls (24 males and 20 females) is as illustrated in Table 1. The age range of probands at the onset of seizures was 3 months to 65 years (mean age 16.3 ± 12.5 years).

### Risk of seizures in FDR

The total number of FDR of epileptics with a history of seizures was 23 (see Table II). The overall risk of seizures in FDR of epileptics was 3.6% and did not vary significantly from the risk in FDR of controls (2.3%) (chitest, p value >0.05). The highest risk of seizures in FDR of epileptics occurred in offspring (4.3%).

### Clinical Variables

The risk of seizures based on various clinical characteristics of probands was determined by comparing the total number of affected FDR in a category to the total number of FDR (unaffected and affected) in the same category (Table III).

For probands aged below 10years at onset of seizures, risk of seizures in FDR was 5.1%, compared to 3.3% and 3.0% respectively for those with adolescent (>10 – 15 years) and adult (>15 years) -onset seizures. The differences in the values did not however reach statistical significance (chitest; p value > 0.05). In comparison to other clinical variables in probands, risk of seizures in FDR appeared to be highest in FDR of female probands and those with complex partial seizures (Table III). There was however no significant difference when compared to overall risk of seizures in FDR of controls (chitest; p > 0.05).

**Table I**

**Demography of Probands with Epilepsy and controls**

| Characteristic | Probands | Controls |
|---|---|---|
| Sex distribution | | |
| Male to Female ratio | 1:1.15 | 1:1.2 |
| Age range (years) | 6-68 | 6-69 |
| Mean age (years) | 23±15.7 | 24.7 ± 16.0 |
| Distribution of FDR | | |
| Parents | 170 (26.2%) | 80 (26.0%) |
| Siblings | 385 (59.4%) | 186 (60.4%) |
| Offspring | 93 (14.4%) | 42 (13.6%) |
| Total number of FDR | 648 | 308 |

**Table II**

**Overall risk of seizures in FDR of probands compared with controls**

| category | Probands | | Controls | | Statistics | |
|---|---|---|---|---|---|---|
| | Total | No. with seizures | Total | No. with seizures | x2 | P value |
| Parents | 170 | 3 (1.8%) | 80 | 1 (1.2%) | 0.06 | 0.81 NS* |
| Siblings | 385 | 16 (4.2%) | 186 | 5 (2.7%) | 0.4 | 0.52 NS |
| Offspring | 93 | 4 (4.3%) | 42 | 1 (2.4%) | 0 | 0.96 NS |
| Overall | 648 | 23 (3.6%) | 308 | 7 (2.3%) | 0.74 | 0.39 NS |

*NS Not statistically significant

**Table 3**

**Risk of seizures in FDR compared to clinical variables in the probands**

| Clinical Variable | Risk of Seizures in first degree relative | | | | | |
|---|---|---|---|---|---|---|
| | N1* | N2+ | (%) | $X^2$ | Statistics P value | |
| AGE AT ONSET OF SEIZURES | | | | | | |
| Paediatric age (0-10 years) | 8 | 156 | 5.1 | 0.95 | 0.34 | NS |
| Adolescent or adult age (>10 years) | 15 | 492 | 3.1 | | | |
| GENDER | | | | | | |
| Male | 11 | 350 | 3.1 | 0.15 | 0.69 | NS |
| Female | 12 | 298 | 4.0 | | | |
| SEIZURES TYPE | | | | | | |
| Primary Generalized seizures | 15 | 412 | 3.6 | 0 | 0.96 | NS |
| Partial seizures | 8 | 236 | 3.4 | | | |
| • Generalized tonic-clonic | 15 | 383 | 3.9 | | | |
| • Complex partial | 4 | 81 | 4.9 | 0.67 | 0.96 | NS |
| • Secondary generalized | 4 | 143 | 2.8 | | | |
| EPILEPSY SYNDROME | | | | | | |
| Generalized epilepsy | 15 | 412 | 3.6 | 0 | 0.99 | NS |
| Localization-related epilepsy | 8 | 240 | 3.3 | | | |

N1* Total number of affected FDR in category
N2+ Total number of FDR in category (affected and unaffected FDR).
NS Not significant

**I: PERSONAL DATA**

**i) Serial Number:** _____ **ii) Age (years)** _____ **iii) Sex: 1) Male 2) Female**

**iv) Relationship to proband/control: 1) Parent 2) Sibling 3) Offspring**

**v) Age (years) at onset of seizures (where applicable):** _____

II: a) Have you ever lost consciousness for at least 1 minute or longer? 1) YES 2) NO

b) If YES: Have you had such loss of consciousness up to two times or more? 1) YES 2) NO

c) IF YES: how many times have you lost consciousness in the past one year? _____

III: a) Have you ever had an episode when you lost contact with your surrounding for a brief period and you were not conscious of your whereabouts or what you were doing? 1) YES 2) NO

b) If YES: Have you had such loss of contact two times or more? 1) YES 2) NO

c) If YES: how many times in the past one year? _____

IV: a) Have you ever had an episode when either your leg or arm suddenly started jerking for some minutes and you could not control it? 1) YES 2) NO

b) IF YES: Was the episode followed by loss of consciousness or convulsions? 1) YES 2) NO

c) Have you had such an episode twice or more? 1) YES 2) NO

d) If YES: How many times did you have such in the past one year? _____

V: a) Have you ever had convulsions? 1) YES 2) NO

b) If YES: Have you had convulsions up to two times or more? 1) YES 2) NO

c) If YES: How many times have you had convulsions in the past one year? _____

VI: When you were a young child (below 5 years), did you have convulsions when you had fever?

1) YES 2) NO 3) DON'T KNOW

VII: a) Does any of your brothers/sisters suffer from convulsions or loss of consciousness or involuntary twitching of the limbs?

1) YES 2) NO 3) DON'T KNOW

b)If YES: How many? Brothers _____ Sisters ____

**Fig. 1: Sample Questionnaire for Seizure History in FDR of Probands and controls**

## DISCUSSION

The uncertainties surrounding a family with a member who has epilepsy make it imperative that the actual risk of seizures in other family members of the patient be defined. This would serve as a guide in counselling FDR in an attempt to reassure them and allay their personal fears.

In the present study, the overall risk of seizures in FDR was 3.6%, being highest in offspring (4.3%), and least in parents (1.8%). A similar trend was noted in earlier studies. In a study conducted in Rochester, Minnesota, United States of America, on probands with onset of idiopathic epilepsy before age of 15 years, the frequency of seizures was 3.6% in siblings (as compared to 1.7% in the general population). The risk in offspring was found to be between 2- 4% [3]. Annegers et al, more recently, found that the standardized morbidity ratio for unprovoked seizures in relatives of individuals with idiopathic childhood-onset epilepsy was 2.5% in siblings and 6.7% in offspring [11].

The strongest indicator of tendency to have seizures in FDR in this study (when age at onset of seizures in probands is considered) appears to be onset of seizures below the age of 10 years, with a progressive decline above that age. The highest risk of seizures in FDR (5.1%) was when the age at onset of seizures in probands was below the age of 10 years.. This finding tallies with that of Lennox, who, in 1951, studied 20,000 near relatives of 4,231 epileptic patients. He found that irrespective of epilepsy aetiology, the incidence of epilepsy among relatives decreased progressively with a later age at onset of seizures [3].. Lennox reported that risks progressively increased with declining proband age at onset, being highest in relatives of probands with onset before 5 years of age, intermediate between 5-19 years and lowest with older age at onset [13]. Several other studies have shown that relatives of patients with early-onset epilepsy have a higher risk of seizures than relatives of those with epilepsy of later onset [8, 12, 13]. The role of age at onset in determining risk of seizures in FDR may be related to the fact that those subtypes of epilepsy that are more strongly genetic may have an earlier age at onset (a heterogeneous hypothesis) or, alternatively, that probands with early onset of seizures may have a stronger genetic predisposition with a correspondingly higher risk for siblings and offspring (a multifactorial hypothesis) [5, 8].

With respect to gender, the risk of seizures in FDR appeared to be higher in probands of the female gender (4.0%), compared to males (3.1%) even though the difference was not statistically significant. A similar finding was that in the Rochester study which showed an increased risk of seizures in offspring of female probands [14]. The exact relationship between gender and a higher risk of seizures is as yet undetermined. Hauser et al found that for each class of seizure disorder, risk was substantially higher in offspring of affected mothers than in those of affected fathers, the latter's risk being similar to that in the general population [14].

Considering the seizure type in the probands, despite the fact that overall, the risk of seizures was marginally higher in the FDR of probands with primary generalized seizures (3.6% compared to 3.4% for partial seizures), the single seizure type with the highest risk in FDR was complex partial seizures (4.9%). This is not entirely surprising considering the association between complex childhood febrile convulsions (with its genetic associations) and mesial temporal sclerosis resulting in complex partial seizures in later life [15]. The possibility exists that genetic predisposition may increase the risk of seizures following an identified brain insult [8]. Some studies have shown that if the proband has partial seizures, the risk to siblings is in the order of 2-3%, but rises to 5-6% if the proband has absence or generalized tonic-clonic seizures or generalized spike and wave discharges on the EEG [3, 8]. An earlier review of 402 cases of epilepsy in the LUTH between 1968 and 1974 reported that 26% of patients with grand mal epilepsy had a history of seizures in their parents, siblings and near-relatives, whereas 9% of patients with temporal lobe epilepsy had a similar history [16]. The lower value for temporal lobe epilepsy may be related to the age range of the subjects in that study who were children, as that form of epilepsy is less common in the paediatric age group, tending to occur more often as a later sequel of complex febrile convulsions with mesial temporal sclerosis. In a recent study to characterize the seizures in family members of patients with refractory temporal lobe epilepsy and hippocampal sclerosis, family history of seizures (particularly febrile convulsions) was significantly higher in patients than controls [17]. The distribution of risk of seizures as regards the epilepsy syndrome closely followed the seizure type in the present study, being overall marginally higher in the generalized epilepsies. Lennox found that incidence of seizures in relatives of his patients was 3.6% if the probands seizures were idiopathic, and 1.8% if symptomatic. Twin studies have also shown that the concordance for seizures is much higher in monozygotic twins with idiopathic epilepsy than in their dizygotic twins or twins with symptomatic epilepsy [5].

## CONCLUSION

The present study provides data for comparison with other populations as well as a basis for counselling FDR in this environment. In general, the overall risk of seizures in FDR of epileptics is not appreciably higher than that in FDR of normal controls. The findings here are similar to observations in other populations.

## LIMITATIONS

One of the greatest limitations of studies based on family history is widespread non-disclosure by probands due to the stigma still attached to epilepsy, as well as non-recognition of various types of seizures. This was addressed by cross-checking family history obtained from FDR within a family, maintaining anonymity in personal data by using serial numbers, and using descriptive terminology in asking about seizure types.

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