AN INVESTIGATION INTO THE GENETIC RELATIONSHIP BETWEEN BIPOLAR AFFECTIVE DISORDER AND (IDIOPATHIC) EPILEPSY IN A SUB-SAHARAN AFRICAN POPULATION

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ABSTRACT

Background: Bipolar affective disorders and epilepsy have been linked by investigations concerning their phenomenology, neuro-biology and pharmacotherapy. One large Epidemiological study revealed that bipolar symptoms occurred in 12% of community-based epilepsy patients, a rate of about seven times higher than normal controls. Little is known however, if these observations are epiphenomena of an underlying genetic substrate, the establishment of which is an important step in the understanding of these disorders, such that we can predict, prevent and effectively manage them.

Objective: To determine if there is a probable genetic relationship between bipolar affective disorder and epilepsy.

Method: A case control study assessing the prevalence of epilepsy among the first degree relatives of patients with bipolar affective disorder and the prevalence of bipolar disorder among first degree relatives of patients with epilepsy compared to normal controls.

Results: A total of 150 patients attending the outpatient clinic between March and July 2006 were recruited for the study (40 bipolar, 60 epileptics and 50 health controls). It revealed a significantly high prevalence of epilepsy among the first degree relatives of bipolar patients compared with healthy controls; 15.2% vs. 2.0% (χ^2 = 46.08, $p<0.001$). There was similarly high and significant prevalence of bipolar affective disorder in first degree relatives of patients with epilepsy compared with normal control; 14.5% vs. 2.1% ($\chi^2 = 31.2, p<0.001$).

Conclusion: The biological links already noted by earlier studies between bipolar disorders and epilepsy seem to be strengthened by this findings of familial predisposition. This may be a prelude to other similar or more advanced studies to establish definite genetic link between these two important disorders.

Keywords: Genetic, Bipolar affective disorder, Epilepsy, Sub-Saharan Africa

INTRODUCTION

Bipolar affective disorders and epilepsy have been linked by investigations concerning their phenomenology, neuro-biology and pharmacotherapy. Bipolar symptoms occurred in 12% of community-based epilepsy patients, and at a rate higher than in other medical disorders (Etinger, 2005). Bipolar symptoms were found to be 2.2 times common in patients with epilepsy compared to those with migraine head ache and bipolar symptoms were 6 times more likely to occur in epileptics than in a healthy control group. Randomized controlled trials of potential psychiatric indications for antiepileptic drugs have shown evidence of efficacy. Evidences have accumulated to warrant the inclusion of antiepileptic agents in

the management of bipolar affective disorders (NICE Guideline, 2008). A number of studies have demonstrated that affective disorders in epilepsy represent a common psychiatric co-morbidity; however, most of the classic neuropsychiatric literature focuses on depression, which is actually prominent, but little is known about bipolar depression, and very little about mania, in epilepsy. Biochemical, structural, and functional abnormalities in primary bipolar disorder could also occur secondary to seizure disorders (Mazza, 2007).

The kindling paradigm, invoked as a model for understanding seizure disorders, has also been applied to the episodic nature of bipolar disorder. In bipolar patients, changes in second-messenger systems, such as G-proteins, phosphatidylinositol, protein kinase C, myristoylated alanine-rich C kinase substrate, or calcium activity have been described, along with changes in c-fos expression. Common mechanisms at the level of ion channels might include the antikindling and the calcium-antagonistic and potassium outward current-modulating properties of antiepileptic drugs. All these lines of research appear to be converging on a richer understanding of neurobiological underpinnings between bipolar disorder and epilepsy.

Despite these links between epilepsy and bipolar affective disorders little is known however, if these observations are epiphenomena of an underlying genetic substrate, the establishment of which is an important step in the understanding of these disorders such that we can predict, prevent and effectively manage them.

Objective: To determine if there is a probable genetic relationship between bipolar affective disorder and epilepsy

MATERIALS AND METHOD

Study setting: The study was conducted at the out-patient department of the federal neuro-psychiatric hospital Maiduguri.

Study design: A case control study assessing the prevalence of epilepsy among the first degree relatives of bipolar patients and the prevalence of bipolar disorder among first degree relatives of patients with epilepsy compared to normal controls.

Materials: The instruments used include the mood disorder questionnaire, international league against epilepsy criteria for clinical diagnosis of epilepsy and a socio-demographic questionnaire.

The socio-demographic questionnaire was designed to capture socio-demographic variables such as age sex, occupation etc.
The mood disorder questionnaire is a standardized questionnaire used for the assessment of mood disorders particularly bipolar affective disorders. The questionnaire is based on the ICD 10 and DSM V diagnostic criteria. It was back translated into Hausa language for use in patients who do not speak English. It was examiner administered.

Ethical Considerations: Ethical clearance was obtained from the ethical committee of the federal neuropsychiatric hospital Maiduguri and consent was sought and obtained from the patients.
Inclusion criteria: Literate patients residing within Maiduguri metropolis with either epilepsy or bipolar disorder, having no co morbidity and stable enough (not psychotic or severe disturbed) to participate in the study.

Procedure: Using a simple random sampling technique, patients with epilepsy who meet the inclusion criteria were identified, (n= 60) and patients with bipolar disorders (n=40).
The first degree relatives of the epilepsy respondents who had bipolar were invited to the clinic and the mood disorder questionnaire administered to confirm the diagnosis of

bipolar disorder. The first degree relatives of the bipolar respondents who had epilepsy were invited to the clinic and the international league for epilepsy criteria for clinical diagnosis of epilepsy was administered to confirm clinical epilepsy.

The prevalence of epilepsy among the first degree relatives of the bipolar respondents and the rate of bipolar disorder among the first degree relatives of the epileptic respondents were determined. This was compared with the rate of either of the two disorders among the first degree relatives of a normal control (n=50). The normal control was chosen from among hospital staffs.

RESULTS

A total of 140 patients attending the outpatient clinic between March and July 2008, were recruited for the study (58 bipolar, 82 epileptics) and 50 healthy controls. At the end of the study 40 bipolar and 60 epileptics completed the study which is a response rate of 71%. The reason for the drop out included withdrawal of consent, lack of transportation to come for interview and traveling out of town.

Socio-demographic characteristics of respondents

Age:

Table 1: The mean Age of respondents

Category	Epileptic	Bipolar	Control
Mean age	24.5	27.9	32.6
Standard Deviation	15.0	12.5	8.0

Table 1 above shows the age distribution between the epileptic and the bipolar respondents is quite similar.

Sex: The male sex ratios for the three categories are; Epileptics (n=35, 59%), Bipolar (n= 24, 60%) and control (n=35, 68%).

Occupation: 60% epileptics, 73% bipolar and 35% healthy controls were unemployed.

Rate of epilepsy among first degree relatives of bipolar respondents:

The study revealed a significantly high prevalence of epilepsy among the first degree relatives of bipolar patients compared with healthy controls; 15.2% vs. 2.0% ($\chi 2$= 46.08, p<0.001).

Rate of Bipolar among first degree relatives of epileptic respondents:

There was a similarly high and significant prevalence of bipolar affective disorder in first degree relatives of epileptic patients compared with normal control; 14.5% vs. 2.1% (χ^2= 31.2, p<0.001).

Figure 1: Showing the rate of Bipolar disorder among the first degree relatives of epileptics and the rate among the first degree relatives of the Control

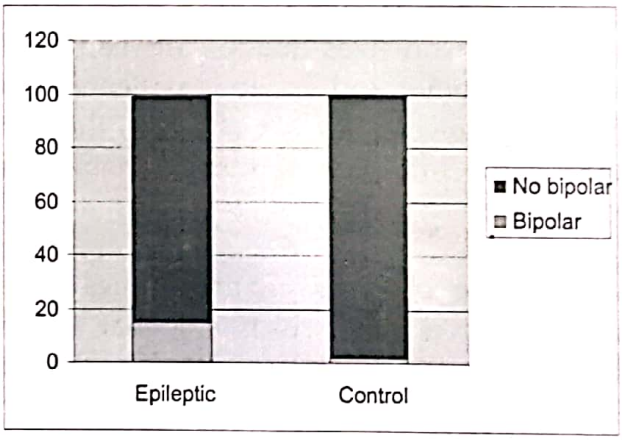
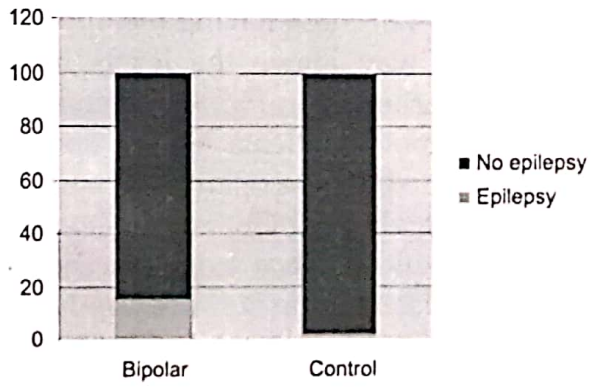


Figure 2: Showing the rate of epilepsy among the first degree relatives of bipolar respondents and the rate of epilepsy among the first degree relatives of the control



Relationships between familial tendency and other important variables

There were no significant relationships between the age of onset of epilepsy and having a family member with the disease χ^2=23.3; p=0.49

No significant relationship between maximum therapeutic dose in control of epilepsy and epileptic having a family member with bipolar disorders χ^2=6.67; p=0.5 nor with relapse rate in the last 1 year: χ^2= 2.96; p=.39

DISCUSSION

Family studies are the most basic of genetic studies and often serves as the basis upon which more refined and complicated genetic studies may be conducted. First degree family members share about 50% of similarity in genetic composition.

The comparison was made between two groups of bipolar and epileptic patients who were well matched for sex and age, thereby reducing the influence of these variables as confounders.

The prevalence of epilepsy in the families of the control group is 2.1% which is similar to the general population figure of 3% (Goodridge and Shorvon, 1983). The rate of bipolar disorders among the first degree relatives of epileptic patients is 2.0% which again is almost the same as 1.5% -2.5% prevalence rates in the general population (Akiskal et al, 2000).

The prevalence of the disorders in the first degree relatives of those having the opposing condition are way above the levels in the general population. With 15.2% of first degree relatives of bipolar patients having epilepsy and 14.5% of first degree relatives of epileptic patients having a bipolar illness, this show that a strong familial tendency exists for the two disorders to cluster within the same family.

The possibility of a family member having one disorder when the patient has the other disorder is strikingly similar (15.2% vs. 14.5%). Other environmental factors it may be argued, that interfere with the development of the growing brain may co-exist in the settings of these patients and thus account for the similarity in prevalence of the conditions within close family members, rather than the purely genetic attribution being arrived at.

However, the absence of significant relationships between the other important variables such as age of onset of the illness and maximum therapeutic dose required to achieve remission of symptoms in a patient, with having a family member with the opposite disorder and the link in terms their phenomenology, neuro-biology and pharmacotherapy further makes the case for a genetic link between epilepsy and bipolar affective disorder. Although it does not entirely answers the question concerning the environmental factors as being partly responsible for the picture that has emerged in the light of this small study.

CONCLUSION

Family studies are the most basic of genetic studies. The biological links already noted by earlier studies between bipolar disorders and epilepsy seem to be strengthened by this findings of familial predisposition.

This may be a prelude to other similar or more advanced studies to establish definite genetic link between these two important disorders. It may also help to determine the effect if any, of environmental factors to the relationship between bipolar disorder and epilepsy.

Limitation of the study

The study has the following limitations

1. Sample size is small making generalization of findings rather difficult to justify
2. No EEG was done to diagnose epilepsy

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