

EPILEPSY IN THE CONSANGUINEOUS FAMILIES AT TRIBAL SOCIETY OF KHYBER PAKHTUNKHWA-PAKISTAN

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ABSTRACT

Objective: To determine the association between epilepsy disease (ED) and consanguinity in the tribal society of Khyber Pakhtunkhwa-Pakistan.

Material and methods: Approximately, 150 clinically diagnosed epileptic patients of consanguineous families with ages ranging from 3 to 70 years were included during the period of (2018-19). Children in this study were aged 7-10 years and male to female ratio among the patients was 1:1.5. The target familial cases were included on the basis of sex, age, parental consanguinity, seizure type, cause of epilepsy, and family history. The parents were interviewed to collect the required information after informed consent. Non-consanguineous families, patients with acquired causes, and those who were not willing to participate were excluded from the study.

Results: In the current study, the consanguinity in parents of the epileptic patients was compared with the general population and we found significant results ($P < 0.01$). Generally, 56 (37.33%) of the patient's parents were first cousins with ($OR=3.245$ and $95\%-CI=2.26-4.645$ and $P<0.0001$), 24 (16.00%) were second-degree cousins with ($OR=3.269$ and $95\%-CI=2.032-5.258$ and $P<0.0001$) and 70 (46.66%) were unrelated.

Conclusion: The overall results in this study clearly indicate the potential role of heritage lineage/consanguinity in epilepsy within consanguineous families. The present retrospective study supports genetic counselling prior to marriages. More significant genotype-phenotype correlation is also needed to minimize the risk of epilepsy disease.

Key words: Consanguinity, Epilepsy, Tribal society

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INTRODUCTION

Epilepsy is a common neurological disorder characterized by recurrent seizures affecting more than 70 million people around the world and nearly 80% of epileptic patients are living in developing countries¹. Seizure is defined by an excessive, abnormal neuronal firing in the brain. Clinically, an epileptic patient has at least 2 or more unprovoked seizures with duration of 24 hours apart².

According to the published guidelines of the international league against epilepsy (ILAE) for the classification of epilepsy (2017), epileptic seizures are divided into

three groups i.e. generalized onset, focal onset, and unknown onset seizures. In Generalized seizures, the whole cerebral hemispheres of the brain are involved from the onset whereas, in focal onset seizures, an electrical discharge occurs in specific parts of the brain. Unknown seizures have no defined cause and therefore, are also called unclassified seizures^{3, 4}.

Approximately 20–30% of epilepsy is due to defined causes such as brain tumor, head injury, stroke, CNS infection, metabolic disorders, and neoplasm but the remaining 70–80% cases are believed to be due to one or more genetic factors⁵. Some of the individuals with intellectual disability (ID), depression, mood disorder, autism, or schizophrenia have epilepsy as a co-morbid condition⁶. The overall prevalence of epilepsy in Pakistan is approximately 10 per 1000 while the prevalence of epilepsy is 64.70% and 35.50% in urban and rural areas of Pakistan respectively and the female (10.9%) are affected more than males (9.2%)⁷.

Consanguinity means shared DNA resulting from the union of biologically related persons whose offspring

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are at higher risk of certain genetic disorders while the risk of epilepsy with consanguinity has been increased many folds⁸. Worldwide, millions of people have consanguineous marriages, and up to 50 % of marriages in Arab and Middle Eastern countries are also consanguineous⁹. Consanguineous marriages are very common in Pakistan (~63%) but almost (70%) in the province of Khyber Pakhtunkhwa leading to higher rates of genetic disorders¹⁰. In consanguineous marriages, inherited diseases were found to be twice common as compared to non-consanguineous marriages¹¹. Educational background, socio-economic status, conserved attitudes in people, and size and location of the area have been found as the cornerstone for consanguineous marriages^{12, 13}.

The majority of the population studies reveal an increased familial history of epilepsy, particularly where the couples are first and second-degree cousins/relatives¹⁴. A number of risk factors have been linked to epilepsy but the fact about epilepsy and consanguinity is little known. This work was carried out to trace the epilepsy lineages in the tribal society of KP-Pakistan with consanguineous marriages, a common social practice of the studied region. Tribal societies are located in the north-western of Pakistan usually called the Federally Administered Tribal Areas (FATA) that existed from 1947 until being merged with the neighbouring province, Khyber Pakhtunkhwa in 2018. It consisted of seven tribal agencies (districts) and six frontier regions (F.Rs). The territory is almost exclusively inhabited by the Pashtun. The current study may help in providing a better understanding to implement proper interventions in order to minimize this serious health problem.

MATERIAL AND METHODS

The retrospective data review was conducted in the tribal society of Khyber Pakhtunkhwa-Pakistan. The epileptic patients were registered for the study by visiting Hospitals and they were traced back to their dwellings for collecting the required information regarding the history of epilepsy within the family. The sampling criteria were based on the presence of at least two epileptic patients in the family, as well as their parent's cousin's marriage. A total of 150 patients with consanguinity in their parents were identified and selected among the total toll of 5000 patients. A larger part of the patients denied sharing their family information and willingly participating in such studies as per the common practice of the tribal norms. Informed consent of the involved families and all the necessary information were collected after the approval from the ethical committee and board of studies of the Institute of Biotechnology and Genetic Engineering (IBGE), the University of Agriculture Peshawar under project no. 2013-Agr-U-3179.

ENROLMENT OF PATIENTS

A total of 150 epileptic patients were enrolled with an age range of (3-70 years). Patients, who experienced two or more unprovoked seizures with a time interval of more than 24 hours apart, were considered epileptic patients². The epileptic patients suffering since their birth or childhood but mostly at young ages were enrolled for the study who were referred as outpatients in the Department of Neurology, Lady Reading Hospital (LRH), Peshawar during the period of (2018-19).

Only the target familial cases were included in the study and the inclusion criterion was comprised of sex, age, parental consanguinity, seizure type, cause of epilepsy, and family history. The required information was obtained through interviews of patients, their parents, or close relatives and by reviewing their medical records, after getting the informed consent in the local language. Patients whose parents were not in consanguineous marriages or had definitive acquired causes and those whose parents were not willingly participated were excluded from the study.

Statistical analysis using the odds ratio (OR), the Z-test, and the Chi-Square, with a P value of less than 0.01 considered significant. The Odds Ratio and its 95% confidence interval (CI) were calculated for first and second-degree relatives.

In the current study, the classification of seizures was carried out as generalized onset, focal onset, and unknown onset according to the recent guidelines published by the international league against epilepsy (ILAE)³.⁴. The seizures with no defined cause were classified as idiopathic.

Consanguinity in parents was classified as first-degree and second-degree cousins^{15,16}. The patient's parental consanguinity was compared to the general population of the same geographical region. In the general population, the consanguinity percentage was collected through a survey of over 5000 patients inhabiting tribal society in Khyber Pakhtunkhwa.

RESULTS

Male to female ratio was 1:1.5 with age range (3-70 years) among the studied patients, demonstrating clear etiology in 45 (30%), whereas 105 (70%) were assigned to genetic generalized epilepsy (GGE) formerly called idiopathic. The potential risk factors for epilepsy found in the patients are shown in (Table I).

SEIZURES CLASSIFICATION

According to the ILAE classification (2017), epilepsy in the patients was classified as generalized onset, focal onset, and unclassified (Table II).

Consanguinity in epileptic families was found common in the idiopathic (GGE) patients. The percent consanguinity in epileptic families is shown in (Table III).

When patients with generalized seizures (118) were considered, 62 (52.54%) patients had consanguineous parents (OR=3.151, 95%-CI =2.183-4.547 and $P<0.0001$) as compared to the general population. Similarly, in these patients, 42 (67.74%) were first cousins (OR=3.042, 95%-CI=2.026-4.569, and $P<0.0001$). The second cousins in these patients were 20 (32.25%) with (OR=3.076, 95%-CI=1.838-5.147, and $P<0.0001$). The remaining 56 (47.45%) were non-consanguineous parents.

In the remaining (19) patients expressing partial/focal epilepsy phenotypes, there was no significant statistical difference in the relation of married couples of the affected families and the general population on the basis of consanguinity. Only (8) consanguineous marriages (42.01%) were found in this category with (OR=2.06, 95%-

CI=0.83-5.15, and $P=0.11$).

DISCUSSION

Epilepsy is a neurological disorder characterized by recurrent seizures. Worldwide, it has a prevalence of 4–8 per 1,000 and a lifetime risk of seizures is 3% in the general population¹⁷. Consanguinity means the union of couples having close genetic relations and is a well-known tradition in the tribal society. About 700 million consanguineous marriages have been reported all around the world where about 50% of couples are consanguineous in the Middle East including the tribal society of KP⁹. The offspring of consanguineous marriages are at a greater risk of numerous genetic disorders including epilepsy and the intensity of risk increases if the married couples are first-degree cousins than second-degree cousins⁸. The current study is the very first attempt to find the association of consanguinity with epilepsy in the tribal society of Pakistan. In this study, the couples among the epileptic families were more consanguineous as compared to the general population which strongly suggests that consanguinity is one of the potential risk factors for epilepsy

Table 1: Epileptic risk factors in the patients in current study

Risk Factor	Number of Patients	%age
GGE (Idiopathic)	105	70
Intellectual Disability	15	10
Mood Disorder	11	7.33
Developmental Delay	05	3.33
Down syndrome	03	02
Head Trauma	06	04
Others	05	3.33

Table 2: Seizures classification in 150 epileptic patients in current study

Category	Epilepsy	Number of Patients	%age
Generalized	Generalized Tonic-clonic (GTC)	70	46.66
	Myoclonic	21	14
	Infantile Spasm	11	7.33
	Atonic	09	06
	Absence	07	4.66
Partial/Focal	Simple Partial	11	7.33
	Complex Partial	08	5.33
Unclassified	Unclassified Epilepsy	13	8.66

Table 3: The comparison of parentage consanguinity with general population

Parameters	First Cousins	Second Cousins	Unrelated	Total
Patient's Family	56 (37.33%)	24 (16.00%)	70 (46.66%)	150
General Population	912 (18.24%)	388 (7.76%)	3700 (74%)	5000
OR, 95%-CI	2.33, 1.61-3.37	2.86, 1.79 - 4.56	-	-
P-Value	0.0001	0.0001	-	-

which can be supported by the increased homozygosity in the inbred families up to many folds. Parental consanguinity of epileptic patients was shown to be a potential risk factor for epilepsy¹⁸. Similarly, in Iran, the percentage of consanguinity in parents of epilepsy patients was significantly higher in comparison to the general population (OR 2.6, 95% CI: 1.9-3.5, $P < 0.0001$), indicating that consanguinity is a risk factor for epilepsy¹⁹. Another study carried out by Ramasundrum and Tan has reported an increased risk for epilepsy in children whose parents were in blood relation²⁰. The study, conducted in Abha and Khamis, Kingdom in Saudi Arabia found that 19.4% of epileptic children had consanguineous marriages between their parents²¹. Consanguinity was suggested to be a potential risk factor for epilepsy and reported up to 20% in the patients suffering epilepsy²². The rate of epilepsy in the current study (53.33%) is much higher than in previous studies which are probably due to the higher consanguinity rate. It was found that epilepsy patients had an increased rate of consanguinity than those suffering random seizures. However, all these mentioned studies have confirmed a significant role of consanguinity in epilepsy. Keeping in view, the situation, the youth at schooling and the parents at their homesteads may be educated through genetic counselling regarding expected couples prior to their marriages. The model of Pre-marriage counselling in couples expecting thalassemia has proved successful recently in the tribal society of the frontier region in KP. It resulted in an approximately 19% decrease in cousin marriages prone to a high risk for thalassemia during the past 20 years i.e. from 65% in 1998 to 43% in 2018 (organization, Jihad for Zero Thalassemia JZT). In the case of partial epilepsy, the lower statistical significance may be due to a decreased influence of consanguinity or may be due to insufficient sample size, however, in the future; this aspect needs further investigation.

The unwillingness of the families to participate in the study, willingness to participate but unwillingness to sign the consent form, inaccessibility to the hard areas, non-consanguineous marriages, and unavailability of family and clinical history were some of our study limitations.

CONCLUSION

The significant results in this study show a potential association between epilepsy and consanguinity. Genetic counselling is suggested prior to marriages within the family to minimize the risk of epilepsy.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Badsha N: Concept, Design, and Proofreading

Ahmad S: Acquisition and critical review

Khan SH: Analysis and interpretation of data

Qurashi SA: Data collection, Final approval

Sarwar MT: Data collection, Final approval

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.