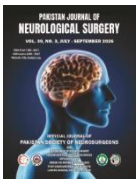

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Original Research

Consanguinity and Epilepsy in Khyber Pakhtunkhwa: A Demographic Analysis

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ABSTRACT

Objective: The purpose of this study was to assess the relationship between consanguineous parenthood and the prevalence and features of epilepsy in those who have it.

Materials & Methods: A cross-sectional study of 541 epileptic patients was carried out. A standardized form was used to collect data on demographics, parental consanguinity, marital status, clinical features (EEG, MRI, and CT scan results), therapy methods, and geographic location. The chi-square test was used to investigate the link between consanguinity and other risk variables.

Results: Of the 541 participants included in the study, 58.78% (n=318) were male, and 41.22% (n=223) were female. As far as parental consanguinity was concerned, 54.71% (296) said that their parents were cousins, while 45.29% (245) said theirs were not cousins. Consanguinity did not show any statistically significant associations with gender, marital status, abnormal EEG, or availability of diagnostic imaging ($p > 0.05$ for all). The most often prescribed medication was Epival (43.4%), followed by Tegral (8.85%). Most patients came from Peshawar (18.9%) and the surrounding areas.

Conclusion: Consanguineous marriage was common among families with epileptic patients, but there was no obvious statistical association with specific clinical characteristics. However, the high family clustering of epilepsy and limited access to diagnosis highlight the need for genetic counseling, improved diagnostic instruments, and additional research into inherited risk factors.

Keywords: Epilepsy, parental consanguinity, consanguineous marriages, genetic predisposition to disease, Hereditary disorders, Seizures.

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INTRODUCTION

There are numerous causes of epilepsy, including genetic, environmental, and social factors. It is a chronic neurological condition. Further research is required to determine the potential genetic influence on epilepsy in regions where consanguineous marriages are culturally common. Consanguineous marriage refers to a union between biologically related individuals, most commonly first or second cousins. Such marriages are associated with an increased risk of inherited genetic disorders and congenital abnormalities in offspring. Pakistan has one of the highest rates of consanguineous marriages worldwide. Consanguineous couplings have been the subject of ongoing scrutiny by medical researchers, social scientists, biologists, and clinicians.[1] Epilepsy is a prevalent neurological illness marked by recurring seizures, impacting over 70 million individuals globally, with almost 80% of those affected residing in poor nations.[2] A seizure is characterized by excessive and aberrant neuronal discharge in the brain. Clinically, a patient with epilepsy has a minimum of two unprovoked seizures occurring within 24 hours.[3]

Idiopathic generalized epilepsy (IGE) is a category of disorders characterized by specific clinical and electroencephalographic symptoms, accounting for about one-third of all epilepsies.[4] Globally, 690 million individuals are consanguineous, and a significant prevalence of consanguineous marriages is historically rooted and culturally embedded in South Asian nations.[6] The electroencephalogram (EEG) displays a generalized bilateral, synchronous, and symmetrical discharge, as delineated in the seizure arrangement for the respective type.[7]

Prior research indicates that genetic transmission from consanguineous unions may result in the development of different health complications, as well as an elevated risk of stillbirth, abortions, congenital malformations, neonatal death, and genetic abnormalities.[8] According to the 2017 International Association against Epilepsy (ILAE) guidelines for the categorisation of epilepsy, epileptic seizures fall into one of three categories: focal onset, generalized onset, and unknown onset seizures. In generalised seizures, cerebral hemispheres are involved from the beginning, but in focal onset seizures, electrical signals occur in specific areas of the brain. Unknown seizures lack a recognized etiology and are hence referred to as unclassified seizures.[9,10] Approximately 20-30% of epilepsy cases have recognised causes, such as brain tumours, head trauma, strokes, infections of the central nervous system, metabolic abnormalities, and neoplasms; the remaining 70 percent to 80 percent are considered to be caused by one or more hereditary factors.[2,11]

Consanguineous marriages are prevalent in Pakistan, around 63%, and reach almost 70% in the region of Khyber Pakhtunkhwa, resulting in an elevated prevalence of genetic diseases.[12] Hereditary diseases were seen to be twofold more prevalent in consanguineous unions than in non-consanguineous marriages.[13] Consanguineous marriages are prevalent in Pakistan, especially in Khyber Pakhtunkhwa, where they lead to a higher incidence of inherited diseases. In previous studies, parental consanguinity has been proposed to be associated with a higher risk of neurological and genetic diseases such as epilepsy. But little information is available on demographic and clinical features of persons with epilepsy from populations with a high proportion of consanguineous marriages. This study was therefore designed to find out the prevalence of consanguinity among epilepsy patients in Khyber Pakhtunkhwa and to correlate consanguinity with

demographic, clinical, diagnostic, and treatment-related parameters. There are several distinct demographic and clinical features of patients with epilepsy with parental consanguinity compared with patients without parental consanguinity.

MATERIALS & METHODS

Study Setting: This cross-sectional study was performed at Hayatabad Medical Complex to examine the association between epilepsy and consanguineous marriages among patients from the Pashtun Population of Khyber Pakhtunkhwa.

Study Design: The present retrospective cross-sectional study was carried out at Hayatabad Medical Complex, Peshawar, Pakistan. Medical records and patient interviews were used to gather data for 541 people who were diagnosed with epilepsy.

Sampling Techniques: Data collection included conducting interviews with patients and their relatives and reviewing medical records where available.

Ethical Standards and Ethical Approval: The ethical standards articulated in the Declaration of Helsinki guided the course of our investigation. The Ethical Review Committee of Khyber Medical University in Peshawar, Pakistan, approved the study (Ref No. 852/HEC/B&PSC/2022).

Inclusion Criteria: Individuals with diagnosed epilepsy, irrespective of age or gender, who gave details about their parental relationship (consanguinity), treatment, and medical history.

Exclusion Criteria: Participants who had undiagnosed or unverified illnesses, lacked critical demographic information, or were unwilling to share their family health history were excluded from the study.[14] Gender, age, number of family members, number of affected family members, parental cousin marital status, known cause of epilepsy, patient marital status, presence of comorbidities, EEG results, neuroimaging status (MRI and CT scan), treatment information, and residential address were among the variables included in the dataset.

Statistical analysis: R (version 4.3.0) was used for all statistical analyses. Data on age were categorized. To capture demographic distributions, descriptive statistics were used. Categorical factors, including consanguinity, EEG abnormalities, and different types of treatment, were examined by frequency distributions and chi-square tests to evaluate relationships. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

Of the 541 participants included in the study, 58.78% (n=318) were male, and 41.22% (n=223) were female. As far as parental consanguinity was concerned, 54.71% (296) said that their parents were cousins, while 45.29% (245) said theirs were not cousins. The marital status of the patients indicated that 74.12% (n=401) were single, 16.45% (n=89) were married, and 9.43% (n=51) had missing responses. Of the participants, 25.88% (n=140) reported a comorbid condition, while data were absent for 401 individuals (74.12%).

Table 1: *Summary of several variables together with their frequency and percentage.*

Variable	Category	Frequency and Percentage
Gender	Female	41.22% (n=223)
	Male	58.78% (n=318)
Parent-cousin marriage	No	45.29% (n=245)
	Yes	54.71% (n=296)
Patient Married	No	74.12% (n=401)
	Yes	16.45% (n=89)
Abnormal EEG	No	19.41% (n=105)
	Yes	47.50% (n=257)
MRI Done	No	18.11% (n=98)
	Yes	4.44% (n=24)
CT Scan Done	No	16.45% (n=89)
	Yes	7.02% (n=38)

Regarding neurological evaluations, 47.50% of patients (n=257) had abnormal EEG findings, 19.41% (n=105) presented normal EEGs, and 33.09% (n=179) had no EEG data documented. A total of 4.44% of patients (n=24) had received an MRI scan, 18.11% of patients (n=98) had not, and 77.45% of patients (n=419) had incomplete MRI data. Similarly, 7.02% of patients (n=38) underwent a CT scan, 16.45% (n=89) did not, and 76.52% (n= 414) had no CT scan data accessible, as shown in Table 1.

The geographic distribution indicates that the largest patient cohort originated from Peshawar, 18.9% (n=101), followed by Bannu, 7.1% (n=38), Charsadda, 6.54% (n=35), and Afghanistan, 5.61% (n=30). Additional significant places comprised Kohat 3.93% (n=21), Swat 3.93% (n=21), Dir 3.18% (n=17), Karak 3.18% (n=17), Dir Lower v(n=15), and Nowshera 2.62% (n=14). This distribution demonstrates a varied geographic representation over multiple districts and adjacent regions, with a focus on metropolitan and semi-urban locales shown in Table 2.

Table 2: *Residence Locations.*

Residence Address	Frequency and Percentage
Peshawar	18.9% (n =101)
Bannu	7.1% (n =38)
Charsadda	6.54% (n =35)
Afghanistan	5.61% (n =30)
Kohat	3.93% (n =21)
Swat	3.93% (n =21)
Dir	3.18% (n =17)
Karak	3.18% (n =17)
Dir Lower	2.80% (n= 15)
Nowshera	2.62% (n= 14)

Age Distribution

The age distribution of epilepsy patients in this study encompassed all developmental stages, with the largest proportion being adults aged 18 years and older, 33.83% (n=183), followed by adolescents aged 10–17 years, 24.39% (n=132), and early school-age children aged 6–9 years, 12.39% (n= 67). The younger age groups comprised infants under 1 year, 11.65% (n= 63), toddlers aged 1–3 years, 11.09% (n=60), and preschool-aged children aged 3–5 years, 6.47% (n=35), as shown in Table 3.

Table 3 Age Group Distribution of Epilepsy Patients

Age Group	Frequency and Percentage
Infant (up to 1 year)	11.65% (n=63)
Toddler (1–3 years)	11.09% (n=60)
Preschool (3–5 years)	6.47% (n=35)
Early School (6–9 years)	12.39% (n=67)
Adolescent (10–17 years)	24.39% (n=132)
Adult (above 18 years)	33.83% (n=183)

Association with Consanguinity

All the associations between parent consanguinity and selected demographic and clinical characteristics were tested using Pearson's Chi-square test (Table 4). No statistically significant association was observed between parental consanguinity and gender (χ^2 = 0.730, df = 1, p = 0.393), marital status (χ^2 = 0.382, df = 1, p = 0.537), abnormal EEG findings (χ^2 = 0.028, df = 1, p = 0.647), MRI performance (χ^2 = 0.062, df = 1, p = 0.803), or CT scan performance (χ^2 = 0.022, df = 1, p = 0.322). Likewise, a significant correlation was not found between comorbidity and parental consanguinity (χ^2 = 14.967, df = 16, P = 0.527).

Management Patterns

The distribution of treatments among epilepsy patients indicated that Epival was the most often given medicine, utilized by 43.4% (n=49) of patients. Subsequently, Tegral was utilized by 8.85% (n=10) of the sample. A combination of Epival and Tegral was observed in 4.42% (n=5) of patients, indicating dual therapy in a subset of cases. Additional drugs comprised Lerace 2.65% (n= 3), Dopoken 1.77% (n= 2), and Phenobarbital 1.77% (n=2). Furthermore, antidepressant drugs

were observed in 0.88% (n=1) of patients, suggesting the potential existence of comorbid psychological disorders or mood-related symptoms in individuals with epilepsy, as shown in the table (5).

Table 4: Association between parental consanguinity and demographic and clinical characteristics among patients with epilepsy.

Variable	Valid Cases (n)	χ^2	df	P-value
Gender	541	0.730	1	0.393
Marital status	469	0.382	1	0.537
Other disease (Comorbidity)	541	14.967	16	0.527
Abnormal EEG	378	0.028	1	0.647
MRI performed	111	0.062	1	0.803
CT scan performed	115	0.022	1	0.322

Table 5: *Drug use by different epilepsy patients.*

Treatment	Frequency and Percentage
Epival	43.4% (n=49)
Tegral	8.85% (n=10)
Combination of Epival, Tegral	4.42% (n=5)
Lerace	2.65% (n=3)
Dopoken	1.77% (n=2)
Phenobarbitol	1.77% (n=2)
Anti-depression	0.88% (n=1)

DISCUSSION

Recurrent seizures are a hallmark of epilepsy, a neurological condition. The global occurrence is 4–8 per 1,000, with a lifetime seizure risk of 3% in the general population (15).[15] Our study showed that epilepsy affects all age groups; adults (33.83%) and adolescents (24.39%) are most affected. Importantly, 45.29% of subjects revealed paternal consanguinity (cousin marriages), suggesting that consanguinity may be an indicator of risk for seizures and pointing to a possible genetic component in its development. The high proportion of family clustering of epilepsy raises concerns, even if consanguineous marriage did not significantly affect gender, marital status, abnormal EEG, or neuroimaging results.

Prior research indicated that the percentage of paternal consanguinity in Pakistan is around 51.353.1% in urban regions and 65.6-66.9% in rural areas. Research has demonstrated that consanguineous couples have an elevated chance of producing babies with genetic disorders.[15] In tribal tribes, consanguinity, the uniting of spouses with deep genetic ties, is a recognised custom. Over 50% of couples in the Middle East, which includes the nomadic civilisation of Khyber Pakhtunkhwa, are consanguineous, with an estimated 700 million consanguineous marriages recorded worldwide.[16,17]

Epival was the most frequently recommended therapy, followed by Tegral and combination therapies in our study. Other antiepileptic drugs were selected depending on the type of seizure, the physicians' preference, and availability of drugs. Some patients may have had psychological issues associated with their use of antidepressants. The absence of EEG in a large number of patients identified a lack of diagnosis and clinical assessment. Some families of patients with epilepsy had higher rates of consanguineous marriage, implying a genetic component to epilepsy. Furthermore, certain patterns of seizures and EEG abnormalities such as generalized spike-wave discharges and polyspike trains were linked to treatment resistance.[18]

According to the study conducted in the state of Saudi Arabia's Abha and Khamis, 19.4% of children with epilepsy had fathers who were consanguineous. Consanguinity has been proposed as a possible risk factor for epilepsy, with reports indicating prevalence rates of up to 20% among people afflicted by the condition.[19] Paternal consanguinity has been evaluated as an indicator of risk factor for unexplained generalised epilepsies in several studies. A case-to-control ratio of 1:1 was used in the study's control of cases design. This study found that the case group had a considerably higher proportion of parental

consanguinity (74.1%) than the control group (54.7%), supporting findings from an Oran study that found consanguinity to be a major risk factor for hereditary epilepsies.[4,20] A significant prevalence of paternal consanguinity has been documented in 31 Jordanian families with familial childhood epilepsy and among Iranian children with epilepsy, in comparison to the general population.[21]

Limitation of the Study

There are some limitations in this study. First, because of its retrospective cross-sectional design, it is not possible to draw cause-and-effect conclusions. Second, there is no control group and, as such, the role of parental consanguinity as a risk factor for epilepsy cannot be assessed directly. Third, a large proportion of the EEG, MRI, and CT scan data were missing, limiting the power in the analyses to detect associations between consanguinity and clinical characteristics. More comprehensive studies in the future with full diagnostic data and adequate control groups are recommended to make an accurate assessment of the genetic role of consanguinity in epilepsy.

CONCLUSION

Over half of the subjects indicated consanguinity of parents. No statistically significant relationships were found, however, between parental consanguinity and sex, marital status, EEG results, MRI results, or CT scan results. The present study, despite demonstrating that consanguinity is present amongst the epilepsy patients in the study population, fails to show a significant association between consanguinity and the clinical characteristics evaluated. Additional controlled studies with genetic analysis would be useful to further explore this relationship.

Recommendation

The results of this study allow numerous suggestions to be made to enhance the management and knowledge of epilepsy in groups where consanguineous marriages are very frequent. Initiatives for community-based genetic counseling should be implemented to raise awareness of the potential hereditary risks associated with cousin marriages. These initiatives could help families make informed choices and potentially reduce the genetic transmission of epilepsy. To enable children and young people with epilepsy to be recognized and treated promptly, early screening and diagnostic programs should be extended, particularly in high-risk populations and rural areas. To enable accurate diagnosis and individualized treatment, underprivileged areas should have more access to diagnostic equipment including CT scans, MRIs, and EEGs. Incorporating psychosocial support services, such as mental health counseling and epilepsy education, may also help patients and their families manage associated psychological challenges and reduce social stigma.

Additional Information

Disclosures: The Authors report no conflicts of interest.

Human Subjects: Written informed consent was obtained from the participants or their legal guardians.

Conflicts of Interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Financial Relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other Relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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