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Brief Communication

Parental Consanguineous Marriages are Associated with Early Age of Onset of Schizophrenia in a Pakistani Cohort

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ABSTRACT Schizophrenia is a complex multifactorial psychiatric disorder. Both environmental and genetic factors are thought to play a role in the development of this condition. Many studies have shown an association between consanguinity and schizophrenia. A study from Iran has examined the association between age at onset and consanguinity. In this study, the researchers found a strong relationship between age of onset of schizophrenia symptoms and parental cousin marriages. There was no effect of positive family history of disease on age of onset.

INTRODUCTION

Schizophrenia is a serious psychiatric disorder which is characterized by hallucinations, delusions, cognitive deterioration and decline in social functioning. Its diagnosis is primarily based on clinical evaluation and both International Classification of Diseases 10th Edition (World Health Organization 1993) and Diagnostic and Statistical Manual 5, have diagnostic criteria for this disorder (American Psychiatric Association, American Psychiatric Association and DSM-5 Task Force 2013: 5). Twin and adoption studies support contribution of genetic factors in its etiology (Kendler 2013). Molecular genetic studies using mainly genome-wide association approach have identified over 100 genetic loci associated with schizophrenia (Ripke et al. 2014). There is evidence of association of consanguinity and schizophrenia from populations with high level of consanguinity (Bener et al. 2012a; Bener et al. 2012b; Mansour et al. 2010; Prasad 1985; Saugstad and Odegård 1986). The age at onset of illness studies in sib-pairs (DeLisi et al. 1987; Kendler et al. 1987; Kendler et al. 1997) and dizygotic twins (Cannon et al. 1998) has a correlation of 0.3 while the one for monozygotic twins has a correlation of 0.7 (Kendler et al. 1987; Cannon et al. 1998). These data are consistent with a genetic contribution to age at onset of illness. Many studies report the influence of genes on age at onset of schizophrenia (Pulver et al. 1991; Kendler et al. 1990). Successive stages of the disease start at different ages; non-specific psychiatric symptoms start to present first at age of 15 years, followed by the positive symptoms which appear between 24-35 years of age and negative symptoms after that (Jablensky 2000).

In this study, the researchers' investigated the association between age at onset of schizophrenia and consanguinity in a sample of patients with schizophrenia. Earlier age of onset is a marker of severity of illness.

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METHODOLOGY

Subjects

One hundred and fifty (150) consecutive patients with schizophrenia from three hospitals in Lahore and one hospital in Gujranwala in 2010 were selected to participate, and were assessed in detail. The study had ethical approval from University of Health Sciences, Lahore and all subjects provided written informed consent to participate in the study.

Inclusion Criteria

All the inpatients in psychiatric wards, and the outpatients who met ICD-10 criteria for schizophrenia were included. The diagnosis was confirmed independently by two senior psychiatrists working in the hospital.

Exclusion Criteria

Patients with organic brain disorders, epilepsy and substance-induced psychotic disorders were excluded.

Data Collection and Assessment

The researchers had ethical approval from research ethics Committee, University of Health Sciences, Lahore and acquired informed written consent from the participants. This research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients were assessed by trained research staff and the information collected included: demographic details; age at onset (age at the first appearance of psychosis); family history of disease; personal history (marital status, education level and socio-economic status) and past treatment history. The researchers collected information about parental relationships whether they were first cousins or not. In addition to direct patient interviews, the research staff also interviewed the primary caregiver of subjects included in the study to obtain collateral information.

Data Analysis

All statistical analyses were performed using R package. For categorical variables the researchers reported numbers and percentages and Chi square test when appropriate. They analyzed the data using ANOVA to examine the effect of different variables on age at onset. Differences were considered significant when $p < 0.05$.

RESULTS

One hundred and fifty patients with ICD-10 based diagnosis of schizophrenia were enrolled in the study. The sample comprised of 98 (65.3%) males and 52 (34.6%) females. Mean age for the total sample was 34.07 (SD 9.51), mean age for men was 35.15 (SD 9.81) and for women it was 31.96 (SD 8.61). Status of parental cousin marriages, family history of schizophrenia and marital status of patients is reported in Table 1.

Comparisons between male and female patients are shown in Table 2. More women were product of cousin marriages than men. The researchers presented the data about the age at onset and its relationship with different variables in Table 3.

The researchers described the results of Analysis of Variance (ANOVA). The mean age at onset was 36.46 (SD 7.9) for married patients, and 25.9 (SD 8.8) years for single/never married patients. There was a highly significant difference between the two groups. Family history of illness did not have any effect on age at onset. Age at onset in patients with a positive family history was 31.5 (SD 9.5) and without family history 32.6 (SD 9.7). The age at onset was 34.3 (SD 9.8) for men and 31.4 (SD 8.5) for women. The p value of 0.08 was not significant. The patients whose parents were cousins had a younger age

Table 1: Status of parental cousin marriages, family history of schizophrenia and marital status of patients

	Positive	*Negative*	*Missing N*
Parental cousin marriage	79 (67.12%)	48 (32.88%)	23
Family history of schizophrenia	49 (44.36%)	74 (55.64%)	27
Single or never married	44 (31.42%)	96 (68.58%)	10

Table 2: Gender differences observed in the sample

	Gender N (%)		*Total N (%)*	*Missing N*	*Analysis Chi-square*	*P value*
	Male	*Female*				
Number	98 (65.3)	52 (34.6)	150		9	**<0.005**
Parents are cousins	39 (51.3)	40 (78.4)	79 (62.2)	23	8.42	**0.003**
Parents are not cousins	37 (48.7)	11 (21.6)	48 (37.8)			
Family history	29 (39.7)	20 (40.0)	49 (39.8)	27	1.4873e-30	1
No family history	44 (60.3)	30 (60.0)	74 (60.2)			
Single or never married	24 (24.5)	20 (38.5)	44 (29.3)	0	2.56	0.1
Married	74 (75.5)	32 (61.5)	106 (70.7)			

Table 3: Age of onset and its determinants

Age at onset years (SD)	*ANOVA F*	*p value*
Married = 36.46 (7.9) (8.8) Single/ never married =25.9	50.76	**4.42e-11**
Family history present=31.5 (9.5) Family history absent =32.6 (9.7)	0.365	0.547
Male =34.3 (9.8) Female =31.4 (8.5)	3.13	0.0789
Parents are cousins =29.6 (8.8) Parents are not cousins = 36.7 (8.9)	18.82	**2.96e-05**

In the first column, the researchers gave the figures for the age at onset of different groups. They compared the groups using analysis of variance. In the last column they reported *p values.*

at onset of 29.6 (SD 8.8) than the patients whose parents were not cousins with 36.7 (SD 8.9). This difference was highly statistically significant p 2.96e-05.

Most of the patients interviewed were either married or previously married (divorced/ widowed), and only a small proportion of patients were identified as single with no gender difference.

DISCUSSION

This study found a strong inverse association between consanguinity and age at onset of schizophrenia. These results independently confirm the findings reported in a study from Iran (Nafissi et al. 2011). The Iranian study examined this only in male patients. Both male and female participants whose parents were first cousins had a lower age at onset in the researchers' data. Many studies have examined the association between rate of schizophrenia and consanguinity, and apart from one study, all reported an increased risk (Chaleby and Tuma 1987; Dobrusin et al. 2009; Mansour et al. 2010; Bener et al. 2012a,b). No association was observed in a study from Sudan (Ahmed 1979), and in the PubMed search, the researchers could identify only one study which examined the association between consanguinity and age at onset of schizophrenia. The study by Nafissi et al. (2011) attempted to include double first cousins, first cousins, first cousin one removed and second cousins as well in their data, but finally, only compared offspring of first cousins and unrelated parents. In Pakistan, the consanguineous marriages are common (www.consang.net). The researchers preferred to limit their comparison to only the offspring of first cousins with other patients. There were two reasons behind this approach; they believed that it would be more reliable to identify the first cousin bonds through an interview with the patients and other informants, and secondly, with high prevalence of consanguinity in the population, the background sharing of any genetic factors will be similar in both the groups.

The patients with younger age of onset of disease were less likely to be married. This is most likely an understandable consequence of the disease. People get married early in Pakistan and it is possible that many people who developed this disease relatively later had already been married.

In Mendelian diseases consanguinity increases the risk of recessive disorders. The role of consanguinity in complex disorders is less clear (Bittles and Black 2010). Common variants with low penetrance, and rare variants with high penetrance have been implicated in the causation of schizophrenia (Owen et al. 2016; Torres et al. 2016). However, most of the molecular genetic studies of schizophrenia have been based on samples from non-consanguineous populations, and they have not examined recessive inheritance apart from comparing Runs of Homozygosity in case control collections. As argued by Johnson et al. (2016), this approach has its limi-

tations and is less reliable when socio-economic variables are not included in the analysis. In the absence of robust evidence for involvement of recessive inheritance in etiology of schizophrenia through molecular genetic studies, clinical investigations like this one provide clues to involvement of recessive genetic factors either by contributing to etiology or increasing the severity and as a result, affecting the prognosis of this disorder.

LIMITATIONS OF THE STUDY

Limitations of this study include small sample size and limiting the comparison to parents who are first cousins with all the other marriages. Small number of variables studied was the other limitation. There are multiple environmental causes associated with schizophrenia that the researchers were not able to study. These factors include obstetric complications, cannabis use and advanced paternal age (Matheson et al. 2011), and birth during winter or spring (Davies et al. 2003). Some of these factors affect the age at onset as well (Scherr et al. 2012); maternal infections with influenza during pregnancy (Landreau et al. 2012), exposure to measles during childhood (Yolken 2004), and behavioral deviances or delayed motor and speech development, exposure to adverse life events and exposure to substance use.

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