

IMPACT OF FAMILIAL AND ENVIRONMENTAL RISK FACTORS ON AGE OF ONSET OF SCHIZOPHRENIA

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ABSTRACT

Objectives: To determine impact of familial risk factor i.e. positive family history of schizophrenia on age of onset of schizophrenia. 2. To determine impact of environmental risk factor i.e. substance misuse on age of onset of schizophrenia.

Materials and Methods: In this cross sectional analytical study, 430 patients were enrolled from Sarhad Hospital for Psychiatric Diseases Peshawar through convenience non probability sampling technique. First Data was dichotomized on the basis of positive and negative family history of schizophrenia and later on the basis of positive and negative history of substance misuse. Frequency and percentage were calculated for categorical variable while mean and standard deviation for continuous variables. Independent-samples T test was used to compare means of two independent variables.

Results: The mean age of onset of schizophrenia is 22.28 years with early onset in males than females. In those with familial schizophrenia, the mean ages of onset of schizophrenia in males and females are 22.35 and 22.05 years while in those with sporadic cases, the mean age of onset of schizophrenia in males and females are 21.83 and 25.43 years respectively. Moreover non-tobacco substances and cannabinoids are having statistically significant impact on age of onset of schizophrenia.

Conclusion: There is significant gender difference in age at onset of schizophrenia and substance misuse. Family history of schizophrenia eliminates the gender difference in age at onset of schizophrenia. Moreover non-tobacco substances and cannabinoids misuse can cause early onset of schizophrenia.

Keywords: Familial risk factor, Environmental risk factor, substance misuse, mean age of onset of schizophrenia.

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INTRODUCTION

Schizophrenia is a lifelong major psychiatric illness with heterogeneous etiology characterized by positive and negative symptoms as well as behavioral disorganization and cognitive symptoms. About 0.3% to 0.7% of people are affected by schizophrenia worldwide during their life time¹. The peak for age of onset of schizophrenia is between 20 to 35 years, with early onset in males by 3 to 4 years as compare to females. The incidence estimates among Male and females are 4.15 and 1.71 per 10,000 persons per year respectively^{2,3}. The mean age of onset of schizophrenia is 21.44 years; 20.55 years for males and 22.67 years for females while mean age of onset of tobacco misuse is 17.2 years^{4,5}. According to a systematic review the pooled estimate of the gender difference is of 1.07 years with males having earlier onset as compare to females⁶. The peak in age is equal for both genders at

age of 22 with a difference in the mean age at onset being later for females⁷. Difference between males and female about age of onset of schizophrenia is only in sporadic cases and does not exist between those with familial schizophrenia or when there is comorbid cannabinoids misuse. Positive family history of schizophrenia, comorbid cannabinoids misuse and poor premorbid adjustment are associated with early onset of schizophrenia. Early onset schizophrenia is associated with poor clinical and social outcomes, larger cognitive deficit and less suicide rates as compare to late onset schizophrenia². According to another study Genetic risk factors causes early onset of schizophrenia more in females than males, poor course of illness and increased risk of illness in siblings⁷. Late onset schizophrenia is associated with weaker family history of schizophrenia, decrease rates of comorbid substance misuse, higher educational attainment and better premorbid adjustment⁸. In short when genetic load is high the sex difference in age of onset of schizophrenia is smaller or abolished at all. Type of onset and core symptoms doesn't differ between , males and females^{3,5}.

Comorbid substance misuse is quiet common in patients with schizophrenia. Substance misuse causes poor prognosis, is an established fact. But its role in etiology is controversial⁹. In different studies the prevalence of substance misuse in schizophrenic patients varies from

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10% to 70% depending upon the type of population under study and different criteria and definitions used¹⁰. Positive family history of psychiatric disorders and lifetime cannabis use are significantly associated with earlier onset of schizophrenia in both males and females¹¹. According to a meta-analysis, cannabis abuse can cause early onset of schizophrenia by at least 2.7 years. And this is even more significant when only female gender is considered^{12,13}. According to a study, Substance misuse is more common in schizophrenia as compare to bipolar affective disorder. Cannabis misuse can cause early onset of schizophrenia and vice versa. Among cannabis user, mean ages of onset of schizophrenia and bipolar affective disorder were comparable. However among non-user, bipolar patients were older than schizophrenic patients regarding their age of onset of illness. Cannabis misuse unmasks pre-existing genetic liability that is partially shared between bipolar disorder and schizophrenia¹⁴. However tobacco smoking doesn't affect mean age of onset of schizophrenia¹⁵. Similar studies have been conducted at national and international level but no such study has been conducted in our set up i.e. that is Khyber pakhtunkhwa in near past. This study will highlight the role of substance misuse and family history of schizophrenia in age of onset of schizophrenia.

MATERIAL AND METHODS

In this cross sectional analytical study 430 patients were enrolled through nonprobability convenience method of sampling from Sarhad Hospital for Psychiatric Diseases Peshawar from October 2020 to march 2021. Any patient who met criteria of International Classification of Disease Research version 10 (ICD-10) for schizophrenia and gave a valid consent was included. Information was collected from patients, accompanied attendants and record and hospital record if any through questionnaire after confirming diagnosis by consultant. If there was any ambiguity regarding dates, circumstantial evidence was taken. Misuse (of substances) was defined per ICD10 criteria as maladaptive patterns of substance use that impair health in broad sense (physically, psychologically and or socially). And the pattern of use has persisted for at least one month or has occurred repeatedly within a twelve-month period.

In first step frequency and percentage were calculated for all categorical variables. In second step, mean for ages of onset of schizophrenia and substance misuse was calculated. In third step, patients were segregated into two groups based on positive and negative family history of schizophrenia. Later on each group was further dichotomized on the basis of gender. In fourth step, patients were segregated into two groups with positive and negative history of substances misuse. Similar groups were also formed for tobacco, non-tobacco substances and cannabinoids misuse. Independent-samples T test was used to compare means of two independent variables using SPSS version 24 for statistical analysis.

RESULTS

Out of 430 patients, 85.1% are males and 14.90% are females. The frequency and percentage of various categorical variables are given in table 1. The mean ages of onset of schizophrenia and substance misuse are given in table 2. There was statistically no significant difference (p= 0.983) in mean ages of onset of schizophrenia between those with positive and negative family history of schizophrenia. But when each group was further dichotomized into males and females then there was statistically significant difference (p= 0.002) in mean ages of onset of schizophrenia between males and females in those with negative family history of schizophrenia. Further detail is given in table 3. As shown in table 4, there was statistically significant difference in mean age of onset of schizophrenia only in between those, who were having positive or negative history of non-tobacco or cannabinoids misuse.

Table 1: Frequency and percent of different categorical variables

		Frequency	Percent
Gender	Male	366	85.10
	Female	64	14.90
Education	No education	222	51.60
	Primary education	26	06.00
	Middle education	56	13.00
	High education	67	15.60
	Higher education	59	13.70
Marital status	Unmarried	191	44.40
	Married	212	49.30
	Divorced	17	04.00
	Separated	10	02.30
Any family history of schizophrenia	Yes	132	34.60
	No	252	65.60
Substance misuse	Yes	300	69.80
	No	130	30.20
Tobacco misuse	Yes	294	68.40
	No	136	31.60
Non-Tobacco substances misuse	Yes	179	41.60
	No	251	58.40
Cannabinoids misuse	Yes	176	40.90
	No	254	59.10

Table 2: Mean of current age, age of onset of schizophrenia and substance misuse

Gender	Current/ Present age N=430	Age of onset of schizophrenia N=428	Age of onset of substance misuse N= 290
Male	33.82 ± 10.74	21.96 ± 5.97	17.96 ± 7.03
Female	34.12 ± 11.03	24.12 ± 8.07	19.45 ± 4.42
Total	33.86 ± 10.77	22.28 ± 6.36	18.01 ± 6.96

Table 3: Impact of family history of schizophrenia on mean age of onset of Schizophrenia

Any family History of schizophrenia N= 382	Gender	Mean age of onset of schizophrenia	Sig. (2-tailed)	95% Confidence Interval of the Difference
Yes		22.30 ± 6.35	0.983	-1.33 ± 1.36
No		22.32 ± 6.40		
Yes	Male	22.35 ± 5.98	0.849	-2.82 ± 3.43
	Female	22.05 ± 8.39		
No	Male	21.83 ± 5.96	0.002	-5.88 ± -1.30
	Female	25.43 ± 8.13		

Table 4: Impact of substance misuse on mean age of onset of schizophrenia

History of substance misuse N=428		Mean age of onset of schizophrenia	Sig. (2-tailed)	95% Confidence interval of the difference
Substance misuse	Yes	22.23 ± 5.99	0.777	-1.50 ± 1.12
	No	22.42 ± 7.17		
Tobacco misuse	Yes	22.23 ± 6.03	0.788	-1.47 ± 1.12
	No	22.41 ± 7.05		
Non-Tobacco substances misuse	Yes	21.50 ± 5.43	0.032	-2.56 ± -0.117
	No	22.84 ± 6.91		
Cannabinoids Misuse	Yes	21.55 ± 5.45	0.047	-2.47 ± -0.015
	No	22.79 ± 6.89		

DISCUSSION

Age of onset of schizophrenia: In this study the mean age of onset of schizophrenia is 22.28 ± 6.36 years: 21.96 ± 5.97 years for males and 24.12 ± 8.07 years for females. So onset of schizophrenia is almost 2.1 years later in females as compare to males. These findings supported the findings of Miettunen et al². The late onset in females may be due to protective role of female sex hormones. Frequency and age of onset of substance misuse: In our study the frequency of any substance misuse is 69.80%: 68.40% for tobacco, 41.60% for non-tobacco substances and 40.90% for cannabinoids. This is according to the work of Winklbaur and Mallet.J^{4,10}. The increase frequency of substance misuse among schizophrenic patients is due to their shared genetic vulnerability, negative symptoms of schizophrenia and side effects of medications^{16,17}. The mean age of onset of substance misuse is 18.01 ± 6.96 years: 17.96 ± 7.03 years for males and 19.45 ± 4.42 years for females. So onset of substance misuse precedes onset of schizophrenia in our study. Moreover onset of substance misuse is almost 1.49 years earlier in males as compare to females. This is contradictory to the study of Naqvi et al¹⁸.

Impact of familial risk factor i.e. positive family history of schizophrenia on age of onset of schizophrenia: In our study the mean ages of onset of schizophrenia in those with positive and negative family history of schizophrenia are 22.30 ± 6.35 years and 22.32 ± 6.40 years respectively. So there was no statistically significance difference (p=0.98) between the two groups when gender is ignored. However when each group is further dichotomized on the basis of gender then statistically significant difference arises (p= 0.002) between males and females with in group of negative family history of schizo-

phrenia: 21.83 ± 5.96 years for males and 25.43 ± 8.13 years for females (age of onset of schizophrenia). These findings support our hypothesis that Positive family history of schizophrenia or more genetic load minimizes or eliminates the gender difference in mean age of onset of schizophrenia. These findings are consistent also with work of Hare and Dassori, in which they looked at the heritability of age of onset of psychosis in schizophrenia in 2010⁵. In their study too when genetic load is high the difference in mean age of onset of schizophrenia between males and females is abolished.

Impact of environmental risk factor i.e. substance misuse on age of onset of schizophrenia: Substance misuse can affect mean age of onset of schizophrenia and the evidence is more in favor of cannabinoids as compare to other substances¹¹. Keeping in view table No.4, there is statistically no significant difference in mean age of onset of schizophrenia when tobacco (p=0.788) and any substance misuse (p=0.777) are dichotomized into “Yes” and “No” groups. These findings are also consistent with work of Hickling and Ayesha¹⁵. Statistically significant difference in mean age of onset of schizophrenia is produced when non-tobacco misuse (p=0.032) and cannabinoids misuse (p=0.047) are dichotomized into “Yes” and “No” groups. For non-tobacco substance misuse, the mean ages of onset of schizophrenia are 21.50 ± 5.43 years for “Yes” group and 22.84 ± 6.91 years for “No” group. The onset is 1.3 years earlier in those who are misusing non-tobacco substances. For cannabinoids misuse, the mean ages of onset of schizophrenia are 21.55 ± 5.45 years for “Yes” group and 22.79 ± 6.89 year for “No” group. So the onset of schizophrenia is 1.24 years earlier in those who are misusing cannabinoids. Compton and Kelly also concluded similarly in their study in 2009¹³. Even though much work

has been done in this regard but still there arises need to look at other contributory factors in mean age of onset of schizophrenia for example: 1. Quantification of genetic load regarding their impact on mean age of onset of schizophrenia; 2. Impact of other substances individually e.g. stimulants, opioids, alcohol, sedative hypnotics, volatile solvents and hallucinogens etc. on mean age of onset of schizophrenia.

Patients and attendants were asked retrospectively regarding age of onset of schizophrenia and substance misuse. So recall bias may be there. 2. No biochemical (urine/blood screening for illicit drugs) test was done to confirm or exclude presently/currently misuse of any substance.

Mostly patients with chronic and severe schizophrenia or those who are very poor to get free medicines are visiting Sarhad Hospital for Psychiatric Diseases Peshawar. So findings of these patients can't be generalized to all schizophrenic patients within community.

CONCLUSION

There is significant gender difference in age at onset of schizophrenia and substance misuse. Family history of schizophrenia eliminates the gender difference in age at onset of schizophrenia. Moreover non-tobacco substance and cannabinoids misuse can cause early onset of schizophrenia.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

- Shakeel M:** Concept, study design, Confirming Diagnosis, Data collection and analysis, manuscript writing
- Adeela:** Data collection, entry and analysis
- Ali A:** Data collection
- Khan T:** Establishing provisional diagnosis

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.