Schizophrenia and its Correlation with Parental Age

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ABSTRACT

Background and aim - Schizophrenia is considered to be a Neuro developmental disorder with its pathogenesis going back to gestation and early childhood. New mutations secondary to advanced paternal age may operate to increase the risk of this disorder by adversely affecting the brain development.

Methods - The study was conducted in the department of psychiatry at Kasturba Hospital, Manipal, India during the period of five years (2004 June to 2009 June). Retrospective study of the hospital based records of the patients diagnosed with Schizophrenia (N=290) was carried out and compared with equal number of patients with non-psychotic illness (excluding organic mental illness & substance abuse) in relation to the maternal and paternal age and duration of marriage of the parents at delivery.

Results - Logistic regression study among the patients with Schizophrenia and Non-schizophrenic illness in relation to paternal and maternal age above 40 years and duration of marriage of parents above 15 years at delivery of the patient revealed the odd's ratio (95% CI) as 1.37 (0.81, 2.33), 1.3 (0.47, 3.5), 2.08 (1.4, 3.79) respectively. The analysis showed statistical significance in relation to duration of marriage of the parents ($p < 0.05$). The patients with Paranoid Schizophrenia showed late age of onset in comparison to non-paranoid type, which was statistically significant ($p < 0.05$).

Conclusion - A higher risk of developing schizophrenia was found with a paternal age of above 40 years. Further studies are necessary to establish association between Schizophrenic illnesses and parental age.

INTRODUCTION

Schizophrenia is considered to be a Neurodevelopmental disorder with its pathogenesis going back to gestation and early childhood. It is hypothesized that disruption of fetal development plays a role in the pathogenesis.[1] New mutations secondary to advanced paternal age may operate to increase the risk of this disorder by adversely affecting the brain development. Advancing paternal age is known to be associated with several other disorders, including Cancer and Achondroplasia, and is thought to be due to the age associated increase in sporadic de novo mutations in male germ cells.[1]

Advances in genomics have refocused attention on the vulnerability of sperm from older fathers (above 40 years) to carrying de novo mutations. Recent evidences show that a man's age does affect both fertility and the child's health. "Advanced paternal age" has been linked to miscarriages, birth deformities, cancer, and specific behavioral problems such as autism or schizophrenia.[2]

There were several reports illustrating the association between later paternal age and schizophrenia in earlier studies.[3-5] A study done using a large Israeli birth cohort demonstrated a robust and "dose-related" effect of paternal age on risk of schizophrenia and related disorders, a finding that was unaltered after adjusting for maternal age.[6, 7] Using data from the birth cohort of the Prenatal Determinants of Schizophrenia Study[8] to address the relation of paternal age to

schizophrenia, researchers explained the relationship between the advanced paternal age at conception and the risk for future development of Schizophrenia. It was later concluded that, identification of candidate genes for schizophrenia may be possible if the de novo mutation hypothesis can be confirmed by future studies.[9]

Using a large Swedish record linkage database (754 330 of cohort born between 1973-1980 and alive at the age of 16 years), researchers found a strong positive association between paternal age and schizophrenia that was neither due to demographic or socioeconomic factors nor related to perinatal factors, family history or early parental death. Hence, it was hypothesized that accumulating de novo mutations in the germ lines of older fathers could play an important part in the etiology of schizophrenia.[10]

Reanalyzing data on 33,437 children from the US Collaborative Perinatal Project (CPP), which had used a variety of tests given to children at ages 8 months, 4 years, and 7 years, to measure cognitive ability and to assess "motor skills", researchers found that

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children with older fathers had lower scores on all of the measures except one measure of motor skills. In contrast, children with older mothers had higher scores. They found that the older the father, the more likely was this result found.[2]

Considering the above conclusions from more recent studies, we tried to undertake this study, in order to look for the association between the parental ages of the patients diagnosed with schizophrenia.

METHODS

This was a Retrospective study of the hospital based records of the patients. The study was conducted in the department of psychiatry at Kasturba Hospital, Manipal, India during the period of five years (2004 June to 2009 June). The sample comprised of 580 patients, divided into two groups, as per their diagnosis of Schizophrenia (N1=290) vs. Non- Schizophrenic illness (N2=290).

All samples were collected by using retrospective study of the hospital records of the patients admitted in Psychiatry ward or evaluated in Psychiatric outpatient clinic in the Hospital. The hospital records were analyzed retrospectively till we obtained the desired number of patients with Schizophrenia and equal number of patients with

Non-Schizophrenic illness (290 in each group).

The Institutional Ethics Committee (IEC) of Kasturba Hospital, Manipal approved to undertake the study in the hospital utilizing hospital records of the patients. The protocol of the Study was presented to the IEC before getting formal approval from the Committee. SPSS software package (Version 13.0, SPSS Inc., Chicago, USA) was used to analyze the data. Logistic regression analysis was done to compare the variables between patients with Schizophrenia and Non-Schizophrenic illness. Appropriate parametric tests were administered to compare between paranoid and non-paranoid types of Schizophrenia.

Procedure

Data of 290 patients diagnosed with Schizophrenia as per ICD-10 criteria[11] were obtained from the hospital records. Equal number of patient sample with non-Schizophrenic illnesses (excluding Organic mental illness, Substance Abuse, Psychosis/ Delusional disorders) was taken as control population. Detailed evaluation proforma of all the sample population belonging to both the groups was retrieved from the department record section and studied to record ages of both the parents and duration of their marriage at birth of the patient, age of onset of schizophrenia, order of birth, type of Schizophrenia and socioeconomic status. All the variables so obtained were analyzed using statistical measures as explained above.

RESULTS

Table 1. illustrates the comparison between the two groups of the patients in relation to age of both the parents and duration of their marriage at birth of the patient. Fourty patients with Schizophrenia had incomplete data, hence excluded from the analysis. All the patients with Non- Schizophrenic illness were having complete data. Logistic regression analysis was done to compare between the two groups in order to establish the association of parental age in Schizophrenia. In relation to paternal age, patients having father more than 40 years were found to have more risk of Schizophrenia (OR=1.37). Similar finding was seen with patients having mother above 40 years (OR=1.3), though no statistical significance was seen. In relation to duration of marriage of parents, however, statistically significant association was found when duration of marriage was above 15 years (p<0.05).The patients with Schizophrenia were similarly reviewed in relation to their parental age and duration of marriage of the parents at their birth and compared among their different types as per the ICD-10 criteria.

As maximum number of patients were found to be diagnosed with Paranoid Schizophrenia (N=151) and other types of Schizophrenia (Undifferentiated, Catatonic, Hebephrenic, Residual, Simple etc) were found to be small in number, all of these types were grouped as Non-paranoid type. Mean age of both

Table 1. Distribution of Paternal age, Maternal age, Duration of marriage of the parents at birth of the patient among the two groups of patients

S No	Varaibles (in years)	Non-schizophrenic Illness N=290 (%)	Schizophrenia N=250 (%)	Odd's Ratio (95% CI)	p-value (*p<0.05)
1	**Paternal Age**				
	<=30	118 (40.7)	101 (40.6)	1	
	31-40	138 (47.6)	108 (43.4)	0.91 (0.63, 1.32)	0.63
	>40	34 (11.7)	40 (16.1)	1.37 (0.81, 2.33)	0.24
2	**Maternal Age**				
	<=20	57 (19.7)	56 (22.4)	1	
	21-30	182 (62.8)	138 (55.2)	0.77 (0.5, 1.2)	0.24
	31-40	43 (14.8)	46 (18.4)	1.09 (0.62, 1.9)	0.76
	>40	8 (2.8)	10 (4.0)	1.3 (0.47, 3.5)	0.64
3	**Duration of marriage of the parents**				
	<=1	79 (27.2)	65 (25.9)	1	
	2-4	81 (27.9)	58 (23.1)	0.87 (0.54, 1.34)	0.56
	5-9	71 (24.5)	53 (21.1)	0.9 (0.56, 1.47)	0.69
	10-14	35 (12.1)	34 (13.5)	1.18(0.66, 2.09)	0.57
	>=15	24 (8.3)	41 (16.3)	2.08 (1.14, 3.79)	0.017*

parents and mean duration of marriage of the parents at birth of the patient was calculated among both the groups and analyzed using t-test. No statistically significant association was found. The patients with Schizophrenia were similarly reviewed in relation to their

parental age and duration of marriage of the parents at their birth and compared among their different types as per the ICD-10 criteria. As maximum number of patients were found to be diagnosed with Paranoid Schizophrenia (N=151) and other types of Schizophrenia (Undifferentiated, Catatonic, Hebephrenic, Residual, Simple etc) were found to be small in number, all of these types were grouped as Non-paranoid type. Mean age of both parents and mean duration of marriage of the parents at birth of the patient was calculated among both the groups and analyzed using t-test. No statistically significant association was found. Similarly, both the groups of Schizophrenia were compared in relation to the age of onset of Schizophrenia, order of birth and socio-economic status using appropriate statistical measures.

The two groups of patients with Schizophrenia were found to be differing in the age of onset with paranoid type having late age of onset in comparison to non-paranoid type, which was statistically significant (p<0.05) on applying Chi-square test. There was no statistically significant association in relation to the order of birth. However, in relation to socio-economic status, statistically significant association was seen (p<0.005) with paranoid type having maximum patients from middle socio-economic status (55.4%) and maximum patients of non-paranoid type from lower socio-economic status (64.3%). (Table 3).

DISCUSSION

An attempt was made in this study to explore the possible association between the paternal age at birth and development of Schizophrenia among the patients being treated at general hospital psychiatry encouraged by findings in recent studies and researches done utilizing various birth cohorts and hospital registries. A Study[7] using proportional hazards regression analysis among 658 patients diagnosed with schizophrenia and related Non-affective psychoses among 1337 offspring admitted to psychiatric units before 1998, showed paternal age to be a strong and significant predictor of Schizophrenia after controlling for maternal age and other confounding factors (sex, ethnicity, education and duration of marriage). Our study, done by using retrospective review of psychiatry files, showed increase in relative risk of Schizophrenia in patients with paternal age above 40 years in comparison to the patients with various Non –Schizophrenic illness. A birth cohort study9 showed a marginally significant, monotonic association between advancing paternal age and risk of adult schizophrenia and schizophrenia spectrum disorders. We, in our study, attempted to analyze the association of parental age in paranoid and non-paranoid type of Schizophrenia. No statistically significant association could be established. Small sample size of

Table 2. Distribution of Paternal age, Maternal age, Duration of marriage of the parents at birth of the patient among the two groups of patients with Schizophrenia

S No	Type of Schizophrenia / Variables	Paranoid (N=151)	Non-paranoid (N=98)	Statistics tdf p-value
1	Paternal Age Mean +/- SD	33.19 (+/-7.02)	33.05 (+/-7.92)	0.147 247 0.205
2	Maternal Age Mean +/- SD	26.22 (+/-6.46)	26.51 (+/-7.58)	-0.327 248 0.07
3	Duration of marriage of the parents Mean +/- SD	6.29 (+/-5.58)	7.08 (+/-6.30)	-1.036 249 0.344

Table 3. Distribution of Paternal age, Maternal age, Duration of marriage of the parents at birth of the patient among the two groups of patients with Schizophrenia

S No	Type of Schizophrenia / Variables	Paranoid (N=177)	Non-paranoid (N=113)	Total (N=283)	Statistics tdf p-value
1	Age of onset of Schizophrenia Mean +/- SD	28.25 (+/-10.44)	24.38 (+/-7.93)	-	3.37 288 0.04*
2	Birth order [Number (%)]				
	Order 1 or Single child	50 (28.9)	23 (20.9)	73 (25.8)	2.268
	Miidle order (2 or 3)	72 (41.6)	50 (45.4)	122 (43.1)	2
	>3	51 (29.5)	37 (33.6)	88 (31.1)	0.322
	Missing data	4	3	7	
3	Socioeconomic Status				
	LSES	79 (44.6)	72 (64.3)	151 (52.2)	10.61
	MSES	98 (55.4)	40 (35.7)	138 (47.8)	1
	Missing data	0	1	1	0.001**

*p-value<0.05, ** p-value<0.005

different types of Schizophrenia may be the possible limitation in our study.

In a population based cohort study[10] using 754 330 Swedish Subjects people born between 1973 and 1980 found the overall hazard ratio for each 10 year increase in paternal age to be 1.47 for schizophrenia and 1.12 for non-schizophrenic non-affective psychosis after adjustment for birth related exposures, socioeconomic factors,

family history of psychosis and early parental death.

Rasmussen et al (2006)12 utilized the Medical Birth Register, the Military Service Conscription Register and the Inpatient Hospital Discharge Register for their study and concluded that the risk of schizophrenia was 4.62 times higher in subjects whose fathers were 50 years old at the time of conception than in subjects whose fathers were 21–24 years old. We looked into hospital records of five years duration with sample size of Schizophrenia and Non-Schizophrenic illness of 290 each and found both maternal and paternal age above 40 years having high relative risk for Schizophrenia though significant statistical significance could not be established. Duration of marriage of parents at birth above 15 years, however, showed statistically significant risk for Schizophrenia in the child. Variables such as infertility treatment in mother may be a limitation in interpreting this finding.

Our study is different from these recent studies and has many limitations. As we looked into hospital records of the patients and data regarding the age of parents at birth may not be the exact figure and only the approximate in some cases, though we tried to get exact data as far as possible. We had to omit many cases due to unavailability of all the required data. Our sample size was smaller. All the above mentioned studies were done using large Birth cohorts and well maintained Hospital Admission and Discharge Registry Systems using variety of statistical procedures. We could not apply all the statistical procedures due to methodological limitations.

CONCLUSION

In future, we will try to explore these issues further utilizing large pool of sample and variety of statistical tools. In conclusion, our study tried to broaden the possible association between the paternal age and Schizophrenia and also looked into possible differences between paranoid and non-paranoid types of Schizophrenia and obtained mixed results.

REFERENCES

1. Crow JF. The origins, patterns and implications of human spontaneous mutation. *Nat Rev Genet.* 2000; 1:40-47.

2. Saha S., Barnett A. G., Foldi C., et. al. Advanced Paternal Age Is Associated with Impaired Neurocognitive Outcomes during Infancy and Childhood. *PLoS Medicine* 2009; 6 (3): e1000040, 001-009, www.plosmedicine.org.

3. Bojanovsky J, Gerylovova A. The relation of schizophrenia to the age of parents of the patient. *Nervenarzt.* 1967;38:40-42.

4. Hare EH, Moran PA. Raised parental age in psychiatric patients: evidence for the constitutional hypothesis. *Br J Psychiatry.* 1979;134:169-177.

5. Kinnell HG. Parental age in schizophrenia. *Br J Psychiatry*. 1983;142:204.

6. Malaspina D., Harlap S., Fennig S., et. al. Advancing Paternal Age and the Risk of Schizophrenia. *Arch Gen Psychiatry.* 2001; 58: 361-67.

7. Malaspina D. Paternal factors and schizophrenia risk: de novo mutations and imprinting. *Schizophr Bull.*2001; 27:379–93.

8. Susser ES, Schaefer CA, Brown AS,et al.The Design of the Prenatal Determinants of Schizophrenia Study. *Schizophrenia Bulletin* 2000; 26(2):257-73.

9. Brown AS, Schaefer CA, Wyatt RJ. Paternal Age and Risk of Schizophrenia in Adult Offspring. *Am J Psychiatry* 2002; 159:1528–33.

10. Attila S., Rasmussen F., Harrison G. Paternal age and schizophrenia: a population based cohort study. *BMJ* 2004; 329: 1070-75.

11. World Health Organization (1992). The ICD-10 classification of mental and behavioural disorders—clinical descriptions and diagnostic guidelines. World Health Organization, Geneva.

11. Rasmussen F. Paternal age, size at birth, and size in young adulthood – risk factors for schizophrenia. *European Journal of Endocrinology.* 2006; 155: S65–S69.