ORIGINAL RESEARCH PAPER

Psychiatry

A STUDY ON MINOR PHYSICAL ANOMALIES IN PATIENTS WITH SCHIZOPHRENIA AND MOOD DISORDER AND ITS ASSOCIATION WITH FIRST DEGREE RELATIVES - A COMPARATIVE STUDY

KEY WORDS: Mood disorders, schizophrenia, and minor physical anomalies.

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ABSTRACT

Background: The presence of minor physical anomalies has been considered as a sensitive physical indicator of embryonic development. The neurodevelopmental hypothesis of schizophrenia which is well established in many controlled studies is partly based on the higher prevalence of minor physical anomalies (MPAs). **Aims And Objective:** The prevalence of minor physical anomalies (MPAs) was evaluated in patients with schizophrenia, mood disorders and their first-degree relatives. **Methods And Materials:** A modified form of the Waldrop-scale was used to detect the presence or absence of MPAs in 50 patients with schizophrenia, 50 with mood disorder, and in 50 first degree relatives of patients. **Results:** The rate and severity of minor physical anomalies was significantly higher in patients with schizophrenia as compared to their first-degree relatives and mood disorder patients. The cumulative number of MPAs was 105, while among their 50 First Degree Relatives the cumulative number of MPAs was 52. The mean of cumulative number of MPAs in schizophrenia group was 2.10 (SD 1.51) while the mean of cumulative MPAs in their FDRs was 1.04 (SD 0.94) and the mean cumulative MPAs in patient with diagnosis of mood disorder and their FDR were 1.40 (SD .92) and 0.56 (SD 0.78) respectively. **Conclusion:** Findings are consistent with the idea that Minor Physical Anomalies which may be a taken as indicator of neurodevelopmental etiology of both schizophrenia and mood disorder and in favor of MPAs as risk markers for both. Although the magnitude of effects tends to be greater with schizophrenia.

INTRODUCTION

Schizophrenia and mood disorder are two complex brain disorders with poorly defined etiology and pathophysiology. For more than two decades, the 'neurodevelopmental' model has been the prevailing explanatory theory especially for schizophrenia [1]. In its simplest form, schizophrenia results from an early (most likely perinatal) abnormality in neural development. This abnormality is latent (or partially latent in the case of patients with a poor premorbid history) until the affected region matures and is required to function optimally [1].

The neurodevelopmental hypothesis is supported by several pieces of evidence, including increased incidence of obstetric complications, season of birth, presence of minor physical anomalies (MPAs); presence of neurological, cognitive and behavioral dysfunction much before the disease onset. Further more recent structural and functional imaging studies of schizophrenia patients indicate that the brain derangement is already present in the patients when they experience the first episode of the disease [2]. An alternative approach to studying neurodevelopmental factors has been to look for markers of abnormalities in neurodevelopment in adult psychiatric patients. These markers are usually physical characteristics that are measurable in adults and reveal abnormal neuro developmental processes that occurred before or shortly after birth. Such markers include atypical handedness [3] dermatoglyphic signs [4] and Minor Physical Anomalies (MPAs).

Minor Physical Anomalies are minor abnormalities of the head, feet, hands, and face (e.g., high-steeped palate, large or small distance between tear ducts). MPAs and the central nervous system (CNS) both derive from the ectodermal layer. In addition, high rates of MPAs are associated with disorders that have known prenatal CNS involvement, such as Down's syndrome. Hence, MPAs are believed to reflect indirectly CNS development. The use of MPAs as a marker of abnormal neurodevelopment has clear advantages because it involves a brief examination, the assessments can be conducted reliably and the examination requires minimal supplies, only a tape measure and a ruler. MPAs have major informational value for diagnostic, prognostic, and epidemiologic purposes. They provide an important clue to specific malformation diagnosis, brain pathology, and timing of the adversity [5]. The studies comparing MPAs in schizophrenia patients, normal controls, their first-degree relatives and mood disorder have shown an excess of MPAs in schizophrenia patients [6], providing considerable support for a neurodevelopmental model in this disorder. Beyond this general conclusion, little else is known about the significance of MPAs in schizophrenia. The increase in MPAs does not appear to be an artifact of demographic or clinical profile. The symptomatic and neurobiologic overlaps between schizophrenia and mood disorders, as well as the presence of premorbid alterations in many bipolar patients, have led to the speculation that similar neurodevelopmental alterations may underlie mood disorders as well. However, the evidence for neurodevelopmental factors in the pathophysiology of bipolar disorders (BPD) remains to be clarified.

The evidence in favour of a neurodevelopmental basis for mood disorder remains less conclusive and controversial than is the case for schizophrenia [7]. Considering the persisting degree of uncertainty about the neuro developmental basis of mood disorder, there is a striking paucity of studies of Minor physical Anomalies in mood disorder patients. Unlike schizophrenia only few studies that

deal with the prevalence of MPAs specifically in patients with mood disorders [8] had relatively small sample sizes and focused on total anomaly scores of MPA. Although the study of MPAs, which has a rich history over the past 40 years but few fundamental questions still remain about the nature of MPAs. It is not clear if MPAs are specific to schizophrenia among the major psychiatric illnesses like mood disorder. The reports on the prevalence of MPAs in affective disorders are also controversial, and are based on highly different number of patients [9]. The current study is designed to compare the presence of minor physical anomalies in the mood disorder and schizophrenic patient including their first-degree relatives to address the question of neurodevelopmental etiology, specificity, severity and genetic vulnerability to schizophrenia and mood disorders.

MATERIAL AND METHODS:

Study Design

The study was a cross-sectional comparative hospital-based study. The subjects were recruited and the study was carried out at Madhubani Medical College, Madhubani, Bihar from December 2019 to August 2020 (9 months). Approval from the ethical committee and written informed consent was obtained from all.

Study subjects

The study sample consisted of total 200 subjects, 50 subjects with schizophrenia, 50 normal first-degree relatives of schizophrenia patients, 50 mood disorder patients and 50 normal first degree relatives of mood disorder patients fulfilling the following inclusion and exclusion criteria.

Inclusion criteria:

1. Patients of both sexes meeting the diagnostic criteria of ICD-10-DCR (WHO, 1992) for schizophrenia and mood disorders
2. First degree relatives of patients with schizophrenia who are free from any history of significant head injury, psychiatric illness, neurological disorders, epilepsy, major physical illness.
3. First degree relatives of patients with mood disorders who are free from any history of significant head injury, psychiatric illness, neurological disorders, epilepsy, major physical illness.
4. Patients and first-degree relatives in the age range of 18 years to 60 years.

Exclusion criteria:

1. Serious medical disorder, neurological condition, head injury, epilepsy as assessed by history and examination.
2. Mini Mental Status Examination score of less than < 24.
3. Past history of any other psychiatric disorder.
4. Substance use disorder.
5. Not given consent for study.

Study measures

Adult male and female patients and their first-degree relatives meeting the inclusion criteria were taken up for the study. Semi-structured pro-forma was used for recording demographic details like age, sex, marital status, religion, education, occupation socioeconomic status, and habitat, as well as clinical data such as duration of illness, age of onset, family history of psychiatric illness and substance use disorder. All patients and their FDRs were assessed for minor physical anomalies with the modified Waldrop scale. This is a modified version of the Waldrop scale developed by Mehes 1988. In addition, those included a large number of minor physical anomalies have been included in the scale. All the items were used in this study except for measuring the mandible size which needs specialized occipito-mental view in X-ray mandible, short sternum, and wide set nipple. The scale is appropriate for use in both adult and pediatric patients. All items were scored as present or absent only. The examination of minor physical anomalies was done qualitatively (present or absent) without score being used. A total MPA score derived by summing all items and mean of it was used to compare the prevalence of MPAs between the groups. In addition to examining mean scores, we also examined the prevalence by establishing three categories to determine the severity of MPAs among each of the four groups. The subjects were categorized into 3 categories; those having no minor physical anomaly as category 1 individual with 1 or 2 minor physical anomalies as category 2 (Mild to Moderate) and those having more than 2 anomalies as category 3(Severe). The cutoff score of more than two was chosen. This categorization was also helpful to identify the number of subjects in each group with prominent MPAs. In addition, they were also assessed using the Mini Mental State Examination (MMSE) and Family Interview of Genetics Studies (FIGS). It was developed by NIMH for systematically collecting information about relatives in family and genetics studies of the disorders. The FIGS becomes particularly important when reliance on direct information from a subject becomes impossible. Here subjects are asked to provide information about their relatives. Three steps -

1. Pedigree is drawn and reviewed with informant.
2. General screening questions are asked in reference to all known relatives.
3. Based on these, a face sheet and five symptoms checklist are completed for each first degree relative, spouse or other relatives.

It also included details of physical examination of all organ systems and mental status examination.

Statistical Analysis

The observed findings were analyzed by relevant standard statistical tests using Statistical Program for Social Science (SPSS, v.21) in consultation with a statistician and anova and Pearson correlation were used.

RESULTS:

Table-1: Group difference of socio-demographic variables (discrete)

Variable		Groups				2 (df)	P
		Schizophrenia (N=50) n (%)	FDR of Schizophrenia (N=50) n (%)	Mood Disorder (N=50) n (%)	FDR of Mood Disorder (N=50) n (%)		
Gender	Male	40 80.0%	37 74.0%	38 76.0%	43 86.0%	2.533	0.47
	Female	10 20.0%	13 26.0%	12 24.0%	7 14.0%		
Marital status	Married	22 44.0%	38 76.0%	34 68.0%	29 58.0%	14.276	0.02
	Unmarried	27 54.0%	12 24.0%	16 32.0%	21 42.0%		
	Others	0 0.00%	0 0.00%	0 0.00%	0 0.00%		
Education	Literate	34 68.0%	37 74.0%	34 68.0%	42 84.0%	4.393	0.22
	Illiterate	16 32.0%	13 26.0%	16 32.0%	8 16.0%		
Religion	Hindu	36 72.0%	37 74.0%	26 52.0%	26 53.1%	70.746	0.00
	Muslim	10 20.0%	9 18.0%	23 46.0%	22 44.9%		
	Christen	4 8.0%	4 8.0%	1 2.0%	1 2.0%		
Employment	Employed	7 14.0%	21 42.0%	16 32.0%	19 38.8%	10.823	0.01
	Unemployed	43 86.0%	29 58.0%	34 68.0%	30 61.2%		

Socioeconomic Status	Low	49 98.0%	49 98.0%	49 98.0%	48 96.0%	0.613	0.89
	Middle	1 2.0%	1 2.0%	1 2.0%	2 4.0%		
	Upper	0	0	0	0		
Residence	Rural	41 82.0%	42 84.0%	45 90.0%	45 90.0%	2.183	0.53
	Urban	9 18.0%	8 16.0%	5 10.0%	5 10.0%		

Depending on the socio-demographic profile of the data collected it was observed that in all four groups males were in majority most of the respondents in all four groups were unemployed, literate, hailing from rural areas, and belonging to lower socioeconomic status majority of the respondents are married except schizophrenia group in which 54% of respondent were unmarried whereas 44% are married (Table-1).

The mean age at the time of interview of schizophrenia patients was 32.26 years (SD=10.05) and of their first degree relative was 41.64 years (SD=12.26.). The mean age during interview of bipolar patient and their first degree relative were 35.44 years (SD=13.34) and 36.44 years (SD=13.07) respectively. The mean age of onset of schizophrenia patients was 24.22 (SD=7.96) years and mood disorder patients was 28.8 (SD=14.10) years. Mean duration of illness of schizophrenia and mood disorder patients were 7.62 (SD=6.42) and 7.24 (SD=7.24) years, respectively (Table-2).

Table-2: Group difference of sociodemographic and clinical variables (Continuous)

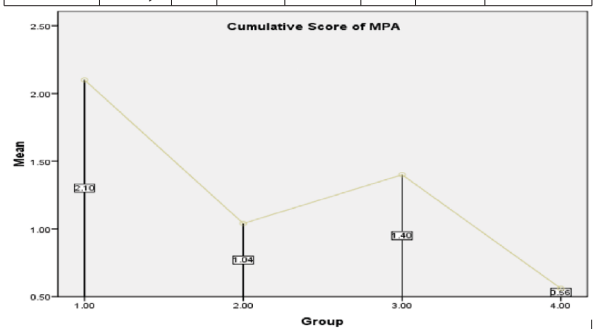
Variables	Schizophrenia M+SD	FDR Schizophrenia M+SD	Mood disorder M+SD	FDR Mood M+SD
Age (in Years)	32.26 + 10.05	41.64 + 12.26	35.44+13.34	36.44+ 13.07
Age of onset (in years)	24.22+7.96	-	28.12 + 14.10	-
Duration of illness (in years)	7.62+6.42	-	7.24 + 7.24	-

Comparison of minor physical anomalies (MPAs) in patients with schizophrenia and mood disorders and their first degree relatives (FDR)

The cumulative number of MPAs in all groups, among the 50 patients with a diagnosis of schizophrenia, the cumulative number of MPAs was 105, while among their 50 FDR the cumulative number of MPAs was 52 the cumulative number of MPA among 50 patients with diagnosis was 70 while in their 50 FDR the cumulative number of MPA was 28. The mean of cumulative number of MPAs in schizophrenia group was 2.10 (SD 1.51) while the mean of cumulative MPAs in their FDRs was 1.04 (SD 0.94) and the mean cumulative MPAs in patient with diagnosis of mood disorder and their FDR were 1.40 (SD .92) and 0.56 (SD 0.78) respectively. The maximum cumulative number of MPAs in an individual with the diagnosis of schizophrenia was eight while in their FDRs was four and the maximum cumulative number of MPAs in an individual with diagnosis of mood disorder and their FDR was three (Table-3 fig-1)

Table-3 Cumulative Mean score of Minor physical anomalies in all four groups

Group		N	Minimum	Maximum	Sum	Mean	Std. Deviation
Schizophrenia	Cumulative mpa	50	.00	8.00	105.00	2.10	1.51
	Valid N (list wise)	50					
Schizophrenia FDR	Cumulative mpa	50	.00	4.00	52.00	1.04	0.94
	Valid N (list wise)	50					
Mood disorder	Cumulative mpa	50	.00	3.00	70.00	1.40	0.92
	Valid N (list wise)	50					
Mood FDR	Cumulative mpa	50	.00	3.00	28.00	0.56	0.78
	Valid N (list wise)	50					



Cumulative Mean score of Minor physical anomalies in all four groups (fig:1)

No statistically significant correlation could be observed between with total Minor physical anomalies score and sociodemographic and clinical variables in any group across four groups. Although age of the patients was found to have a trend towards negative correlation with total MPAs score.

Statistically highly significant difference (p<.001) of mean of total MPA score could be observed between patients with schizophrenia and their FDR similar result were observed while comparing the mean of total MPA score between Mood disorder patients and their FDR. The comparison of mean of total MPA score between patients with Schizophrenia and Mood disorder showed statistically highly significant difference (p<.001) between two groups (Table-4).

Table-4 Comparison of mean of total MPA score between patients with Schizophrenia and Mood disorder

Group	N	Mean	Std. Deviation	t	df	p
Schizophrenia	50	2.10	1.51	2.78	98	0.006*
Mood disorder	50	1.40	0.92			
Schizophrenia	50	2.10	1.51	4.19	98	0.000**
Schizophrenia fdr	50	1.04	0.94			
Mood disorder	50	1.40	0.92	4.88	98	0.000**
Mood disorder fdr	50	0.56	0.78			

Category wise comparison of severity of minor physical anomalies across all groups revealed, in schizophrenia group, six patients (12.0%) had no MPAs twenty-nine patients (58%) had one or two MPAs and fifteen patients (30%) had more than two MPAs. in mood disorder group ten patient (20.0%) had no MPAs thirty-five patient (70%) had one or two MPAs and five patient (10%) had more than two MPAs.

Chi-square test revealed statistically significant (p<.03) difference in severity of minor physical anomalies between person with schizophrenia and mood disorder person with

schizophrenia had more numbers of subjects more than two MPAs (Table-5, Figure-2).

Table-5 Comparison of severity of minor physical anomalies between person with schizophrenia mood disorder and their First-degree relatives (fdr)

Groups	(Without MPA)	MPA = 1 or 2)	(MPA > 2)	2 (df)	p
Schizophrenia (N=50) n (%)	6 12.0%	29 58.0%	15 30.0%	6.56 2	0.038 *
Mood disorder (N=50)n (%)	10 20.0%	35 70.0%	5 10.0%		
Schizophrenia (N=50) n (%)	6 12.0%	29 58.0%	15 30.0%	10.26 2	0.006 *
FDR Schizophrenia (N=50) n (%)	15 30.0%	31 62.0%	4 8.0%		
Mood disorder (N=50) n (%)	10 20.0%	35 70.0%	5 10.0%	15.28 2	0.000 **
FDR Mood (N=50) n (%)	29 58.0%	19 38.0%	2 4.0%		

p<.05, p<.001 (2-tailed).

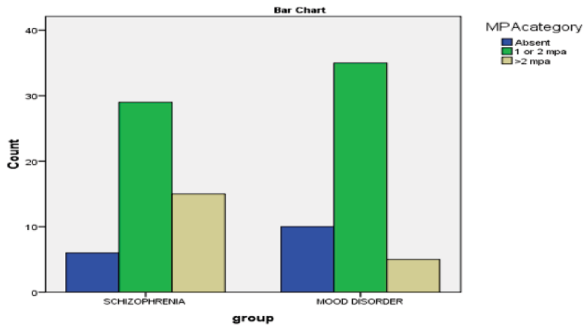


Fig:2

In First degree relatives of schizophrenia patients fifteen relatives (30.0%) had no MPAs thirty-one relatives (62.0%) had one or two MPAs and four relatives (8%) had more than two MPAs while severity score of FDR of mood disorder patients revealed patients twenty-nine (58.0%) had no MPAs nineteen (38.0%) had one or two MPAs and two (4%) had more than two MPAs. Statistically significant difference in severity of minor physical anomalies was observed in patient groups as compared to their first degree relatives (Table-5).

DISCUSSION

Majority of the subjects in the study sample were males in all four categories because most of the patients are accompanied by their male first-degree relatives and reluctance of giving consent by female participants. Similar to our study earlier study those having unmatched sample reported to have male as predominant population [19]. No significant difference was found in relation to gender and cumulative numbers of MPAs in our study. Although sex hormones may play a role in the timing of onset between males and females, the effect of MPA development due to some prenatal disturbances in brain structure would have an equal effect on males and females. More number of studies reported no sex differences in MPA frequency [6, 20] reported excessive MPAs in male schizophrenia patients.

The mean age at the time of interview of schizophrenia patients was 32.26 years (SD=10.05) and the mean age of mood disorder patient were 35.44 years (SD=13.34) respectively which is similar to most of the earlier studies. The slightly higher mean age of mood disorder patients can be understood by the fact that our study includes the patients of unipolar depression also which has mean age of onset of illness higher than the patients of schizophrenia. The extremes of age were excluded because an excess of MPAs were observed in the normative samples in earlier studies. Pearson correlation coefficients with cumulative MPAs found to be negatively correlated with age but the correlation was not statistically significant (r= -0.07, p=0.06) [19] reported similar finding but with original Waldrop scale. Trixler et al. (2001) and Tenyi et al. (2004) while used same scale as used in our study but they did not report any positive or negative correlation with age of the patients and total MPAs. In our study the mean age of onset of schizophrenia patients was 24.22 (SD=7.96) years and mood disorder patients was 28.8 (SD=14.10) years, which is supported by most of the literature for both the patient population. No Statistically significant positive or negative correlation was found with total MPAs. Lal et al. (1998) reported a positive correlation with early onset schizophrenia and total MPAs but that was not statistically significant. Other study Trixler et al. (2001) reported no such association. Overall, no significant association was found between minor physical anomalies and sociodemographic (education, marital status, religion, residence, employment) and clinical (age of onset, duration of illness) correlates across all the four groups. There is also no report of any such association previously in available literature using same scale.

We have found higher mean MPA score in schizophrenia group across all the four groups, and there was statistically significant (p= 0.00) difference of mean score between patients with schizophrenia and their FDR which was in accordance with previous studies. Similar to our study most of the earlier studies (Green et al., 1994; Ismail et al., 1998; Compton et al., 2011; Bozta et al., 2012) found the schizophrenia patients had significantly higher mean of total MPA scores than their unaffected first-degree relatives indicating that among biologically related individuals MPAs and schizophrenia tend to be associated phenotypes. In contrast Gourion et al. (2003) found familiarity for neurological soft signs but not for MPAs suggest that MPAs could be more dependent on epigenetic influences. In a metaanalysis by xu et al. (2011) studies involving relatives of individuals with schizophrenia showed a medium effect size of total minor physical anomaly score.

We also compared the prevalence of MPAs by establishing the three categories among each of the two groups (schizophrenia and schizophrenia FDR) to determine the severity of MPAs. Patient group had more numbers of subjects with one or two (Mild to Moderate) and more than 2 MPAs (Severe) than their FDR. Green et al. (1994) reported similar finding (p= 0.002), while comparing the patients with schizophrenia with their FDR. These findings and the findings in our study are consistent with the idea that MPAs may be a putative indicator of neurodevelopmental etiology of schizophrenia and argue in favor of MPAs as risk markers for schizophrenia.

We have also found slightly more number (not statistically significant) of individual (schizophrenia FDR) to have 1 or 2 MPAs (category 2), which support genetic explanation of occurrence of minor physical anomalies as has been suggested by earlier studies (Rossi et al., 1990; Ismail et al., 1998; Gourion et al., 2004).

While comparing MPAs prevalence the mean score of MPAs of patients with mood disorder (1.40 ± 0.92) was more than the mean score of their FDRs (0.56 ± 0.73) the difference was statistically significant (p= 0.00) between the group.

In addition, categorical (severity) comparison revealed statistically significant (p=0.00) group difference of the three categories of MPAs among the 2 groups. Patient group had more numbers of subjects with one or two and more than 2 MPAs than their FDR.

These finding seems to support the neurodevelopmental

hypothesis to be true in mood disorder although very few studies have been conducted in this regard. Some like Lohr and Flynn, (1993) and Green et al. (1994) using similar methodology did not find any significant difference in the rate of MPAs in mood disorder/bipolar group from their first-degree relatives/normal control. However, an important difference in their methodology from the present study is that the present study uses a more extensive list of MPAs than they used. The major difficulty in generalizing the findings however is the few numbers of studies done including this study but we have taken relatively larger sample size.

The mean of total MPAs was more in schizophrenia (2.10 ± 1.51) as compared to mood disorder patients (1.40 ± 0.92). In addition, category (severity) wise comparison between two groups revealed significant group difference of the three categories of MPAs among these groups. Schizophrenia group had a greater number of subjects with more than 2 MPAs and a smaller number of subjects without MPAs as compared to mood disorder.

Similar to our study green et al. (1994) found schizophrenia patients had significantly more total MPA score than bipolar patients (p=0.01) while using Waldrop scale with less numbers of item as compared to our study in contrast Trixler et al. (2001) using same scale that we have used and similar methodology did not find any significant difference of total MPAs between schizophrenia and bipolar patients. Also [19] found MPAs in the mood disorder group did not differ significantly from those in the schizophrenia group but they used original waldrop scale with a smaller number of items though the method of assessment of MPAs was similar to our study.

CONCLUSION:

There has been very limited research on MPAs in the context of these disorders. Some findings indicate that patients with schizophrenia have significantly more MPAs than patients with bipolar disorder, suggesting that MPAs may have some degrees of specificity to schizophrenia, despite the fact that some conceptualizations place schizophrenia and bipolar disorder on a common disease continuum with shared etiological antecedents. Comparing these two groups, over all our results suggest some degree of specificity for MPAs to schizophrenia perhaps indicating that neurodevelopmental factors are more relevant to the etiology of schizophrenia as compared to mood disorder.

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