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Minor Physical Anomalies in Schizophrenia : A Clinical Study

KEYWORDS: Schizophrenia, minor physical anomalies, first degree relatives, PANSS.

Rakesh Kumar
Senior Resident Doctor, Department of Psychiatry, Indira Gandhi Institute of Medical Sciences, Patna.

Bianca Honnekeri
M.B.B.S. Student, Grant Medical College and Sir J.J. Group of Hospitals, Mumbai.

Sagar Karia
Speciality Medical Officer, Department of Psychiatry, Lokmanya Tilak Municipal Medical College, Mumbai.

Avinash Desousa
Research Associate, Department of Psychiatry, Lokmanya Tilak Municipal Medical College, Mumbai.

ABSTRACT *Background: Minor physical anomalies (MPA) have been noted in patients with schizophrenia and their first degree relatives (FDR). The prevalence of MPA has ranged from 8-16% across studies depending on which criteria was used. MPA has infact been considered by researchers as fixed trait biomarker for schizophrenia. The aim of the present study was to compare the prevalence of MPA in patients with schizophrenia, their FDR and general population.*

Methodology: 50 cases of schizophrenia diagnosed as per the ICD-10 diagnostic criteria along with 50 of their first degree relatives were subjects of the study. This was matched to age appropriate controls from the general population that made up another 50 subjects. All the patients chosen with schizophrenia were drug naïve and off medical treatment for at least 4 weeks prior to the study. The Modified Waldrob scale was used to measure MPA and the Positive and Negative Symptom Scale for Schizophrenia (PANSS) was used to measure the severity of schizophrenia symptoms. The data was analyzed using appropriate statistical measures and computerized software.

Results: All three groups were well matched socio demographically. MPAs were significantly greater in the schizophrenia group than in FDRs and age matched controls ($p<0.01$). The MPA scores for head anomalies correlated with positive ($p = 0.002$), negative ($p = 0.001$) and general psychopathology scores on PANSS ($p = 0.009$). The scores for MPAs elsewhere however only correlated with PANSS positive ($p=0.01$) and negative scores ($p=0.03$).

Conclusions: The reasons for the results could be the correlation between fixed trait markers and fluctuating markers which are symptom domains. The findings of the study cannot be generalized by the presence of MPAs supports the neurodevelopmental hypothesis of schizophrenia and must be looked at as a fixed trait biomarker in schizophrenia in larger community and hospital based studies.

INTRODUCTION

A minor physical anomaly (MPA) is an insignificant physical defect, a deviation in appearance from essential physical characteristics [1]. The different terms used in literature to describe them include- minor congenital anomalies, minor malformations, Informative morphogenetic variant, etc. [2, 3]. MPA comprises a range of minor alterations in the development of various physical structures, having little functional or cosmetic significance and are known to be usually associated with developmental disorders, particularly when multiple [4, 5]. Since both the skin and the central nervous system originate from the same ectodermal tissue in utero, MPAs are recognized as external markers of abnormal brain development. Hence it is suggested that they can be used as biological markers in tracking down developmental disturbances timed according to the chronological order of the normal embryonic development [6]. Commonly included MPAs are electric hair, abnormal-sized head, epicanthus, hypertelorism, low-seated ear, adherent ear lobes, malformed or asymmetrical ears, furrowed tongue, single transverse palmar crease, syndactyly of the toes, gap between first and second toes etc. Most of which are the constituents of the Waldrop scale for assessing minor physical anomalies [2].

MPAs have been found to be more prevalent in a range of neurodevelopmental disorders such as mental retardation, attention deficit disorder, autism, foetal alcohol syndrome, and cerebral palsy [7]. Investigation of MPAs in psychosis dates back to the last century itself. Scottish psychiatrist Thomas Clouston in 1891 published evidence that palatal abnormalities (steep, narrow roofed palates) were more common in those patients he regarded as having 'adolescent insanity', a severe psychosis that he noted had a strong familial tendency [8].

A study comparing schizophrenia population (n=64) with other psychiatric illness population (n=127) and normal controls (n=171) found highest scores in schizophrenia group on subset of Waldrop Scale [9]. Another study in male schizophrenics (n=40) found that the patient group had higher rates of MPAs than published norms [10]. A study with the help of 13 items of the Waldrop scale assessed minor physical anomalies in the 80 inpatient schizophrenic populations at the Central institute of psychiatry, Ranchi and compared with the patient's first degree relative. Schizophrenic group had mean MPAs= 6.8± 2.00SD significantly higher than the first degree Controls measured 2.9± 1.76SD [11].

A study with a modified version of Waldrop scale compared number of minor physical anomalies in schizophrenics (n=67) with normal controls (n=88) found that schizophrenics had significantly more abnormalities, particularly around the oral area [12]. A family study was conducted study to compare the minor physical anomalies in familial

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and sporadic schizophrenia [13]. Assessments were carried out on 214 subjects in five groups by the 1st author, over a period of two years. The groups comprised (1) patients with schizophrenia from multiple affected families, (2) their first degree relatives, (3) patients with schizophrenia without a family history (sporadic patients), (4) first degree relatives of sporadic schizophrenic patients, and (5) a group of normal controls. A narrow definition of abnormality was used (Waldrop score of 4 or more) which defined 4.3% of the control group as abnormal. A broad definition of abnormality was also used (Waldrop score of 3 or more) which defined 10.6% of the control group as abnormal. Percentage of subjects with abnormal minor physical anomaly scores from the total schizophrenic population in the study was 9.4% ($p<0.10$) for the narrow criterion and 18.8% ($p<0.05$) for the broad criterion. The total schizophrenic group did not have a significant increase in minor physical anomalies using a narrow criterion of abnormality, but did when a broader criterion was used. A significant increase in the proportion of subjects with an abnormally high number of minor physical abnormalities was shown in the group of sporadic schizophrenic patients (uncorrected $p<0.01$). Separate analyses for males and females showed a significant increase in the male sporadic group (uncorrected $p<0.05$), and a smaller non-significant increase in the female sporadic group. Neither the familial schizophrenic group nor either group of first degree relatives showed any significant increases in the proportion of patients with high abnormality scores. This study concluded that prenatal developmental abnormality is a mechanism for sporadic, but not familial, schizophrenia.

Thus various studies have found higher prevalence of MPAs in schizophrenia patients and its probable use as a biomarker. So we conducted this study with aims to find the prevalence and type of minor physical anomalies in patients of schizophrenia and to compare it with first degree relative and general population in OPD and inpatients.

METHODOLOGY

50 patients, age group 14- 65 years, diagnosed of schizophrenia as per ICD-10 DCR criteria along with 50 unaffected first degree relative and 50 age matched normal control will be taken for study from the hospital locality, belonging to same ethnic background. Patients were taken mostly from in patient. From outpatient only those patients were taken whose diagnosis of schizophrenia was confirmed. Only drug naive or drug free patients (drug free duration to be 4 weeks for oral and 12 weeks for depot medications) were chosen for the study to minimize the effect of medicine on the expression of illness. Patients from extreme of age have been excluded. So that structural changes due to old age can be excluded. Available first degree relatives of patient were taken who did not have major psychiatric illness. Controls were taken from general population. Controls were matched with the patient as per age, sex, education status, religion, locality and other socio-demographic profiles as much as possible. Those having history of any neurological illness, significant head or body injury in early life, and childhood metabolic disorders were excluded.

Individuals were interviewed according to a semi-structured proforma where socio-demographic data and illness related data were collected. Modified Waldrob Scale was used to screen for minor physical anomalies and Positive and negative syndrome scale (PANSS) score was applied for calculating severity of schizophrenia [2, 14].

TOOLS USED IN THE STUDY

Modified Waldrob scale: This is a modified version of the Waldrop scale developed by Mehes in 1988 incorporating all the items in the Waldrop scale except for head circumference and longer third toe. In addition to those included, a large number of minor physical anomalies recently described in pediatric literature were also included in the scale. All of the items were used in this study except for measuring the mandible size which needs specialized occipito-mental view in X-ray mandible. Total number of MPAs assessed is 52. All items were scored as present or absent only. In a major publication its interrater reliability was found to be high with kappa coefficient of > 75% [15].

Positive and negative syndrome scale (PANSS): The PANSS is a 30 item 7 point (1-7) rating scale which amalgamated the 18 item BPRS and 12 items from the Psychopathology Rating Schedule. The PANSS was divided into positive, negative and general psychopathology sub scales. Sub-scale scores were shown to be normally distributed and independent of each other; they were robust to the effects of mood, chronicity, medication side effects and cognition. The PANSS was furthermore sensitive and specific regarding pharmacological manipulation of the levels of both positive and negative symptoms in patients with schizophrenia. A potentially confusing feature of the PANSS, however, is that even those without any mental ill health will score 30. In effect, this means that 30 must be subtracted from the patient's score in order to gain a meaningful understanding. Several studies have sought correlations between PANSS total and sub- scale scores, and other aspects of the illness, to demonstrate concurrent validity. Cronbach's Alpha ranged from 0.70 to 0.85 suggesting an acceptable internal consistency.

Statistical analysis of the data was done by applying appropriate tests and $p < 0.05$ was considered to be significant for all the tests applied.

RESULTS

Total of 150 subjects were included in the study, 50 each in 3 groups. The mean ages were 39.42yrs, 47.18 yrs and 39.42yrs in schizophrenia, first degree relative and normal groups respectively. There were equal number of males (68%) and females (34%) in all 3 groups. 70% of them were single in patient group whereas 80% and 72% of them were married in FDR and control group. Birth and developmental anomalies were present in 44%, 20% and 8% in patient, FDR and control groups respectively (χ^2= 18.421, p=0.0001). Table 1 shows prevalence of MPAs among different groups. When all the mean values were compared with each other it was found that there was high incidence of MPA (Head) in patient group compared to FDR & normal population group. Table 2 shows correlation between MPA and PANSS. It shows very significant correlation between minor physical anomalies of head MPA (Head) with PANSS Positive, Negative and General psychopathology score. Similarly there is significant correlation between MPA (elsewhere) and PANSS Positive and Negative score but not with General psychopathology score.

DISCUSSION

Mean age of FDR is higher compared to other two groups as subjects of FDR group were siblings or parents of patients. Birth and developmental anomalies were found more in patients of schizophrenia compared with FDR and normal population. This particular finding is important because there is a suggested possible association between obstetric complications and number of minor physical

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anomalies [16]. O'Callaghan et al. in 1991 had similar findings in their studies [17].

The mean values of minor physical anomalies total score in patient, FDR & normal population were 5.8, 2.82, and 1.22 respectively. Among different studies as mentioned in Table 3 mean MPA total among schizophrenia patients varies from 1.95 to 7.82. This strengthens the neurodevelopment hypothesis of schizophrenia and as unaffected FDR also share the endophenotype of patients so there is significantly high prevalence of MPA (Total).

The mean values of minor physical anomalies of head in patient, FDR & normal population group were 4.08, 1.66 & 0.56 respectively. Mean value of MPA of head was found 3.3 in study conducted by O'Callaghan et al. in 1995 [18]. Earlier studies also show similar findings. Minor physical anomalies were assessed as total score as well as two sub scores- MPAs in the craniofacial region and MPAs in other body regions. All the three scores were significantly higher in the schizophrenia patients than healthy controls. This finding supports the finding that total and regional MPA scores, assessed using the Extended Waldrop Scale (EWS), are significantly higher in schizophrenia patients compared to healthy controls. This study confirms the stability and reproducibility of MPA as a construct specifically assessed with EWS in schizophrenia.

More specific increases in craniofacial MPAs than MPAs elsewhere in the body among schizophrenia patients compared to controls has been found in previous studies [7, 19, 20]. These findings constitute direct evidence for disturbed craniofacial development in schizophrenia and indicate origins in the fetal period during which the characteristic human facial pattern evolves in close association with brain differentiation.

The mean values of minor physical anomalies of elsewhere in patient, FDR & normal population were 1.72, 1.16, and 0.66 respectively. Study conducted by O'Callaghan et al. found it 0.9 for patient group which was little less compared to our study [18]. Patients had significantly more minor physical anomalies than comparison subjects in all body areas tested and also more minor physical anomalies in total than their siblings. Siblings had significantly more minor physical anomalies than normal comparison subjects. Higher levels of minor physical anomalies (especially in the eye, mouth, and hand/foot regions) characterize both schizophrenic patients and their normal siblings, but there is little similarity in these anomalies between patients and siblings in the same family. Thus, one or more genetic or shared environmental factors may increase the risk for development of both minor physical anomalies and schizophrenia in these families at large. Minor physical anomalies associated with schizophrenia are frequently found in, but are clearly not limited to, the head or facial region. The Waldrop scale identifies minor physical anomalies strongly associated with schizophrenia. Nevertheless, assessment of the new items clearly indicates that many additional minor physical anomalies are found in schizophrenic patients [4].

When minor physical anomalies were correlated to PANSS score then it showed significant correlation between minor physical anomalies of head MPA (Head) with PANSS Negative score in current study. Similarly there was significant correlation between s MPA (Total) and PANSS Negative score. There is significant correlation between MPA (Head) and PANSS positive score. Similarly there is significant correlation between MPA (total) and PANSS Positive. It explains that there is association of PANSS positive score with minor physical anomalies but it is not as strong as PANSS negative score. This study has shown MPAs (regional and other) have significant correlation with schizophrenia psychopathology (PANSS scores). Several studies in the past found no significant correlation between MPA and PANSS [21- 24]. This may in part be due to heterogeneity in the cluster of MPAs studied as well as symptom profiles of schizophrenia patients. Further, this lack of association might also be explained by obvious difficulties in attempting to correlate fixed, trait markers (MPAs) with fluctuating state markers (symptom domains) [25]. This issue is more true to our study as all the patients were acutely symptomatic and over that they all were un-medicated. So comparing the findings with previous studies we can say that findings in our study may be incidental and we cannot generalize this finding.

These findings support the neurodevelopment hypothesis of schizophrenia. As in neurodevelopment disorder there would be high prevalence of birth and developmental defects.

Our study had limitations in form that electrophysiological studies like EEG or ERP and structural and functional imaging were not done to correlate it with minor physical anomaly.

Table 1: Prevalence of Minor physical anomalies among different groups:

	Patient	FDR	Normal Population	p value
MPA(Head)	4.08 ±1.839	1.66 ± 1.081	0.56 ± 0.733	<0.01
MPA(Elsewhere)	1.72 ± 0.858	1.16 ± 0.766	0.66 ± 0.658	<0.01
MPA(Total)	5.8 ± 2.483	2.82 ± 1.561	1.22 ± 1.183	<0.01

Table 2: Correlation between MPA and PANSS:

MPA	PANSS (Positive)	PANSS (Negative)	PANSS (General)	PANSS (Total)
MPA (Head)	-0.429** p= 0.002	0.637** p<0.01	0.366** p= 0.009	0.252 p= 0.077
MPA (Elsewhere)	-.508** p<0.01	0.406** p=0.003	0.174 p= 0.228	0.002 p= 0.989
MPA (Total)	-0.493** p<0.01	0.612** p<0.01	0.331* p=0.019	0.187 p=0.192

Table-3 List of studies in comparing the frequency of MPAs in patients with schizophrenia and control population with number of items (i.e. MPAs) assessed

Serial no	Studies	Number of items assessed	Schizophrenia	Control (Normal unless specified)
1	Gualtieri et al. (1982) [9]	12	4.00 ± 0.90	2.60 ± 0.90
2	Guy et al. (1983) [10]		6.875 ± 2.884	No control
3	Lal& Sharma (1987) [11]	13	6.8 ± 2.00	2.9 ± 1.76
5	Green et al.(1989) [12]	18	1.95 ± 1.44	0.95 ± 1.06

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6	O'Callaghan et al. (1995) [18]	17	Total- 4.2 ± 4.0, Head 3.3 ± 3.2, Peripheral body regions 0.9 ± 1.1	No control
7	Lane et al. (1997) [19]	18	7.30 ± 2.30	4.20 ± 2.10
8	Ismail et al. (1998) [4]	41	6.37 ± 2.62	2.73 ± 1.68
9	McGrath et al. (2002) [26]	24	Schiz(n=130) 7.82 ± 3.05	7.26 ± 2.85
10	Gourion et al. (2003) [27]	41	5.9 ± 4.1	4.5 ± 2.1(parents)
11	Hata et al. (2003) [28]	15	3.32 ± 1.98	2.19 ± 1.18
12	Gourion et al. (2004) [29]	41	5.80 ± 4.00	2.20 ± 1.20
13	Joo et al.(2005) [30]	15	4.59 ± 1.86	4.06 ± 1.61

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