Research Article

Regional Analysis of Minor Physical Anomalies in Schizophrenia

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Abstract

Aims and objectives: Morphological evidence of the developmental insults has been consistently documented in schizophrenia patients in the form of minor physical anomalies (MPAs). Schizophrenia patients with higher number of MPAs are considered as a subgroup of Schizophrenia having clear developmental basis. But so far no study has found any specific MPA that is consistently or exclusively present in this subgroup of schizophrenia. We analyzed regional MPAs in schizophrenia patients having higher and lower number of MPAs and healthy controls. **Methodology:** 105 schizophrenia patients and 50, agematched, right-handed healthy controls were assessed for MPAs on the Extended Waldrop Scale (EWS). Patients were median-split into high- (H) and low-MPA (L) groups based on EWS scores and were assessed for psychopathology on positive and negative syndrome scale (PANSS). Group differences for the continuous and categorical variables were computed using oneway ANOVA and Fisher's exact test, respectively. Comparison of clinical variables between the H and L groups was done using Independent t-test and Fisher's exact test. Individual and region-wise comparison of MPAs among groups was done using one-way ANOVA. Pearson correlation was then conducted. **Results:** The MPA scores ranged from 0 to 8 with a median of 2.5. H group had significantly higher total ($p<.01$), and regional – head and face ($p<.01$); elsewhere ($p<.01$) number of MPAs than lowMPA and healthy groups. Although nineMPAs were found exclusively in the H group, only prominent forehead ($p<.001$) and lack of ear lobe ($p<.01$) reached statistical significance. In the H group, significant positive correlation ($r= .52$, $p=.012$) between asymmetric size

of ears and PANSS general scores. **Conclusions:** Regional specificity of MPAs in schizophrenia is significant from a neurodevelopmental point of view. Prominent forehead and lack of ear lobe are the specific MPAs which would be found in the developmentally buttressed schizophrenia group.

Key Words : Mona Physcial Anamolies (MPA), Schicophronica.

Introduction

Central nervous system and superficial connective tissue develop from ectoderm in utero, hence the early or the prenatal brain damage described in neurodevelopmental models are associated with a range of minor alterations in the development of various physical structures as well. Among these alterations are minor physical anomalies (MPAs).An MPA is an insignificant physical defect, a deviation in appearance from essential physical characteristics [1]. Because of their relation to development of central nervous system, MPAs can be used as biological markers in tracking down developmental disturbances timed according to the chronological order of the normal embryonic development (Tarrant and Jones, 1999). Though the pathogenesis of these anomalies could not be clearly specified, they appear to be the result of a combined interaction between inherited genetic defects, chromosomal aberrations, early pregnancy complications and environmental teratogenic agents through some unknown mechanisms[2]. Schizophrenia, on the otherhand is conceptualized as a neurodevelopmental disorder with increasing evidence from genetics, environmental factors, and brain pathology research to support this view[3]. The developmental insults may start as early as the first trimester in-utero leading to abnormal development of neural networks that manifest as schizophrenia symptoms later in life [4]. Numerous studies comparing the incidence of MPAs in patients with schizophrenia and healthy population postulate that MPAs are found in relatively high numbers in schizophrenia patients than the control population.

Studies (Griffiths et al., 1998; Ismail et al., 2000; McGrath et al., 1995; Mittal and Walker, 2011;Schiffman et al., 2002; Trixler et al., 1997; 2001) show that within the schizophrenic population MPAs occur in significantly varying frequencies[5,6,7,8,9,10]. Schiffman et al. (2002) and Mittal and Walker (2011) studied population at high-risk for developing psychosis[9,8]. These two studies divided the population on median number of MPAs and compared the groups. Mittal and Walker (2011) found that individuals at high-risk for developing psychosis showing elevated MPAs were distinguished by elevated cortisol, deûcit immediate and delayed visual memory, and higher levels of disorganized prodromal symptoms when compared with those participants exhibiting

a lower incidence of MPAs[8]. Both MPAs and schizophrenia have been associated with inherited as well as acquired genetic risk factor[11,12]. The 22q11 micro-deletion syndrome, associated with specific cranio-facial malformations and an elevated risk for psychosis, is being considered as a genetic subgroup of schizophrenia[13]. Common pathophysiological mechanisms involving the retinoid system have been proposed for schizophrenia as well as MPAs [14,15]. These findings support the idea that schizophrenia patients with high number of MPAs represent a distinct subgroup of schizophrenia having a neurodevelopmental basis.

In a meta-analysis of 13 studies, Weinberg et al. (2007) shows significantly more overall and regional MPAs, without any regional specificity, in schizophrenia patients compared to controls[16]. However, MPAs in craniofacial region may be more specifically linked to neurodevelopmental insults considering their concurrent in-utero development with neural structural changes associated with schizophrenia. Consistent with this, a higher discriminant value of MPAs in craniofacial region in classifying schizophrenia patients and controls has been found (Akabaliev et al., 2001; Compton and Walker, 2009; Compton et al., 2011; Lane et al., 1997)[17,11,12,18]

Aim of this study was to analyze minor physical anomalies regionally as well as individually and compare such regional specificity between schizophrenia patients with higher number of MPAs and schizophrenia patients with lower number of MPAs and normal controls. We also aimed at correlating MPAs specific to schizophrenia group with higher number of MPAs, if any with psychopathology domains.

2. Methods

The data presented is a synthesis of MPA and psychopathology rating scores from 3 studies (conducted by the lead author) that were approved by the Institute Ethics Committee of Central Institute of Psychiatry (CIP), Ranchi, India. Written informed consent was taken from all the participants (and their legally qualified representatives in case of patients) before enrolling them.

2.1. Participants

Patients were recruited by purposive sampling from the out-patient services of CIP. 105 patients (95 males) in the age group of 18 - 50 years, having a diagnosis of schizophrenia as per ICD-10 DCR (World Health Organization, 1992), who were either drug naïve or drug free (for at least 4 weeks for oral and 12 weeks for depot medications) were taken up for the study. Patients having history of neurological illness, significant head injury, co-morbid substance dependence (excluding nicotine and caffeine), other psychiatric disorder, or history of electroconvulsive therapy within previous 6 months were excluded. The healthy control group included fifty right-handed males, age

matched to patients, recruited from the hospital staff and community living in the vicinity of CIP.

2.2. Clinical assessment

Relevant socio-demographic and clinical data was collected from all the participants. Handedness was assessed using the Sidedness Bias Schedule (SBS) - Hindi version[19]. Baseline severity of psychopathology in patients was evaluated by administering the Positive and Negative Syndrome Scale (PANSS) [20]. Healthy controls were screened with General Health Questionnaire (GHQ)-12 (Goldberg and William, 1998)[21]; only those with scores less than 3 were included. A modified version of the Waldrop scale- Extended Waldrop scale (EWS) (Mehes, 1988) was used for the assessment of MPAs in all the participants[22]. All the items (55) in EWS were assessed except for mandible size, due to logistic constraints in getting the required X-ray mandible (occipito-mental view) done. Items on the EWS were divided into those in the head and face region- 33 items and elsewhere in the body- 21 items, and were scored as absent or present.

2.5. Statistical analysis

Based on evaluation of MPAs in people having high-risk for psychosis (Mittal and Walker, 2011; Schiffman et al., 2002), we used the median split of the total MPA scores to divide our patient group into high-MPA and low-MPA groups[8,9]. Group differences for the continuous and categorical variables were computed using one-way ANOVA and Fisher s exact test, respectively. Comparison of clinical variables between the high-MPA and low-MPA groups was done using Independent t-test and Fisher s exact test. Individual and region-wise comparison of MPAs among groups was done using one-way ANOVA (post-hoc Tukey HSD).Spearman s correlation coefficients were computed between MPA scores and PANSS variables.

3. Results

3.1. Socio-demographic and clinical profile

The three groups were comparable in terms of socio-demographic characteristics, except occupation. The mean age in the High-MPA, Low-MPA and control groups were 30.75(7.65),29.35(7.39) and 27.93 (6.51) years respectively. 71.2%, 67.92% of the patients in High-MPA and Low-MPA groups were drug free; rest were drug naïve. Significantly higher number of healthy controls were employed as compared to patients in both the schizophrenia groups ($p<.01$). The duration of illness was 4.16(SD 4.57) years in the *high-MPA* group and 4.28 (SD 3.98) in the *low-MPA* group and the two groups were comparable on individual and composite PANSS scores.

3.2. Minor physical anomalies

The MPA scores ranged from 0 to 8 with a median of 2.5. Comparisons of MPAs

in the three groups are summarized in *Table 2*. *High-MPA* group had significantly higher regional – head and face, 4.4 (SD 1.05; p<.01); elsewhere, 0.7 (SD 0.8, p<.01) number of MPAs than *low-MPA* (total – 0.6, SD 0.82; head and face – 0.55, SD 0.76; elsewhere – 0.05, SD 0.22), and healthy control (total – 1.0, SD 1.45; head and face – 0.85, SD 1.18; elsewhere – 0.15, SD 0.37) groups. Among the MPAs in the head and face region - prominent forehead, double posterior hair whorl, furrowed tongue, frontal up swap, lack of earlobe, confluent eyebrows, mongoloid slant,asymmetrical size of ears, and in the elsewhere regions - pigmented naevi, were significantly higher in the high-MPA group compared to other groups. Among MPAs that were found exclusively in the high-MPA group, only prominent forehead and lack of ear lobe reached statistical significance. Seventeen MPAs, including pre-auricular pits, lip pit, flat forehead, partial syndactyly of toes 2-3, hemangiomas, café-au-lait spots and Sydney line, were not found in any of the groups studied.

3.4 Correlations among MPAsand PANSS

In the *high-MPA* group, no significant correlations were found between regional MPA scores with PANSS values, except for a significant positive correlation (rs= .55, p=.012) between *asymmetric size of ears* and PANSS general scores.

4. Discussion

4.1 MPAs and Schizophrenia

This study supports the finding that regional MPA scores, assessed using the EWS, are significantly higher in schizophrenia patients compared to healthy controls. More importantly, we show that there is a significant heterogeneity within the schizophrenia group, with a sub-group (*high-MPA*) having significantly higher MPAs, while the other group (*low-MPA*) is essentially similar to healthy controls in terms of MPA scores, which is consistent with significant quantitative and qualitative heterogeneity reported in MPAs in schizophrenia (Compton and Walker, 2009; Tikka et al., 2013; Weinberg et al., 2007)[11,23,16].

4.2 Regional specificity

The topographical distribution of MPAs in schizophrenia can unravel the temporal course and nature of abnormal neurodevelopment. Regional analysis in our study showed that MPAs in cranio-facial and elsewhere regions were both significantly higher in the high-MPA group. Though there are studies that show specific cranio-facial MPAs may be associated with schizophrenia (Compton et al., 2007), but meta-analysis by Weinberg et al (2007) failed to show any regional specificity[24,16].

4.3 Individual specificity

Although, we conceptualized that schizophrenia subjects with high number of

MPAs represent a distinct group, given a total of 54 anomalies or even 33 of MPAs in head and face region, concerns arise whether this group is truly a homogenous group. In the present study, we found that two MPAs- prominent forehead and lack of earlobe were found exclusively in the H group and also reached statistically significant levels in comparison to the other two groups. In addition to these two MPAs, furrowed tongue, confluent eyebrows, mongoloid slant and asymmetrical size of ears were also significantly higher in the H group. Of all six MPAs, two belonged to the ear and eye region and one each to head and mouth regions. This finding is unlike results of a meta-analysis by Weinberg et al. (2007), which showed that regional MPAs were in the order- mouth> head> eyes> feet> hands> ears (according to pooled effect size)[16]. This inconsistency can be attributed to the heterogeneity shown by these MPAs as well as the small sample size (n=7; for regional MPA analysis) in the meta- analysis.

4.4 MPAs and Psychopathology

There is inconsistent evidence regarding the association of MPAs with specific symptoms of schizophrenia. John et al (2008) reported higher positive and negative symptoms in schizophrenia patients with higher MPAs[25]. Several other studies have failed to show any association between MPAs and symptoms (McGrath et al., 1995; Compton et al., 2007)[7,24]. Apart from the significant correlation between asymmetric size of ears and PANSS general scores, we did not find any significant association in the high-MPA group. This inconsistency may in part be due to heterogeneity in the cluster of MPAs studied as well as symptom profiles schizophrenia patients. Pertinently, it has been suggested that MPAs may be associated with neurodevelopmental disorders in general (Compton and Walker, 2009)[11].

4.5 Limitations

Our study had only a few female participants, which could limit the generalizability of these findings. There have been reports of quantitative or qualitative gender differences in MPAs in schizophrenia, though meta-analysis revealed no significant gender differences (Weinberg et al., 2007)[16]. Future studies with evenly divided gender groups should clarify this issue. Specificity of prominent forehead and lack of ear lobe in the developmentally buttressed schizophrenia group having higher MPAs found in this study needs more studies with significant sample size for generalization.

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Table 1: Comparison of total, regional and individual Minor Physical Anomalies across *high-MPA*, *low-MPA*, and healthy control groups

Minor physical anomalies		*High-MPA* (N=52) mean±SD	*Low-MPA* (N=53), mean±SD	Control (N=50) mean±SD	F(dF=2, 102)	p
Head and face	Prominent forehead[1, 2]	**0.35±0.49**	0	0	10.23	**<.001****
	Double posterior hair whorl[2]	0.3±0.47	0	0.10±0.31	4.43	**.016***
	Furrowed tongue[1, 2]	**0.35±0.49**	0	0.05±0.22	7.43	**.001****
	Frontal up swap[1]	0.25±0.44	0.10±0.31	0	3.25	**.046***
	Lack of earlobe[1, 2]	**0.20±0.41**	0	0	4.75	**.012***
	Confluent eyebrows[1, 2]	**0.60±0.50**	0.10±0.31	0.25±0.44	7.25	**.002****
	Mongoloid slant[1, 2]	**0.60±0.50**	0.15±0.37	0.05±022	11.79	**<.001****
	Asymmetrical size of ears[1, 2]	**0.50±0.51**	0.15±0.37	0.05±0.22	7.49	**.001****
	Pre auricular tags	0.10±0.31	0	0.05±0.22	1.04	.361
	Bifid uvula	**0.05±0.22**	0	0	1.0	.374
	Prominent occiput	0.1±0.31	0	0.10±0.31	1.06	.355
	Flat occiput	0.20±0.41	0	0.05±0.22	2.98	.059
	Earlobe crease	**0.05±0.22**	0	0	1.0	.374
	Short palpebral fissure	**0.05±0.22**	0	0	1.0	.374
	Antimongoloid slant	0.10±0.31	0	0.05±0.22	1.04	.361
	Protruding auricle	0.15±0.37	0	0.05±0.22	1.90	.159
	Low set ears	0.20±0.41	0.05±0.22	0	2.98	.059
	Large oral opening	0.05±0.22	0.05±0.22	0	1.0	.374
	High arched palate	0.20±0.41	0	0.05±0.22	2.98	.059
	Large tongue	**0.05±0.22**	0	0	1.0	.374
	Total[1, 2]	**4.40±1.05**	**0.55 ± 0.76**	**0.85± 1.18**	**89.67**	**<.01****
Else where	Pigmented naevi[1]	0.25±0.44	0.05±0.22	0	4.25	**.019***
	Super numeric nipples	0.15±0.37	0	0.1±0.31	1.53	.226
	Simian crease	0.05±0.22	0	0.05±0.24	0.5	.609
	Sole crease	0.05±0.22	0.15±0.37	0	1.0	.374
	Wide set nipples	**0.10±0.31**	0	0	2.11	.130
	Wide distance between 1st and 2nd toes	**0.05±0.22**	0	0	1.0	.374
	Unusual length of fingers	**0.05±0.22**	0	0	1.0	.374
	Total[1, 2]	**0.70±0.80**	**0.05±0.22**	**0.15±0.37**	**8.89**	**<.01****

*p<.05, **p<.01; Post-hoc tests showed significant difference between *high-MPA* and healthy controls[1], and *high-MPA* and *low-MPA*[2].

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