

Minor Physical Anomalies Among Schizophrenic Patients as a Biomarker of Its Developmental Origin in Northwest Ethiopia

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Purpose: Although there are highly precise and advanced diagnostic methods, the etiology and pathophysiology of schizophrenia remain poorly understood. There are several theories about schizophrenia origin, among which the neurodevelopmental theory is widely accepted. Our study aimed to assess minor physical anomalies among schizophrenic patients as putative indices of its developmental origin in North West Ethiopia 2018–2019.

Patients and Methods: Institutional-based comparative cross-sectional study design was conducted in Debre Markos comprehensive, specialized hospitals in 190 schizophrenic patients, 190 healthy controls, and 190 1st-degree relatives. Data were collected using standard methods, entered into EpiData version 3.1, and exported to SPSS version 24 for analysis. Descriptive data were analyzed using descriptive statistics, and discriminant function analysis was conducted and a value of 0.03 was taken as the cutoff point for prediction of group status of the study samples.

Results: Five hundred seventy study samples, male 375 (65.8%), and female 195 (34.2%), were included in this study. The discriminate function 1 and 2 revealed a significant association between groups and all predictors, accounting for 83.5% and 16.5% of between-group variability, respectively. However, closer analysis of the structure matrix revealed longitudinally furrowed tongue, \geq Five palate ridges, high steeples palate, transversely and randomly furrowed tongue, protruding supraorbital ridge as significant predictors.

Conclusion: Depending on predictor variables in this study, minor physical anomalies can serve as a biomarker for early screening of schizophrenic patients and clue for its developmental origin.

Keywords: minor physical anomalies, schizophrenia, neurodevelopment, Ethiopia

Introduction

Although there are highly precise and advanced diagnostic methods, the etiology and pathophysiology of schizophrenia remain poorly understood. There are several theories about schizophrenia origin, among which the neurodevelopmental theory is widely accepted.^{1–3}

According to the neurodevelopmental approach to schizophrenia developmental insults, both genetic and environmental, during early life underlies the structural and functional changes in the brain and the face. These neurodevelopmental disorders are often concentrated in the craniofacial region of schizophrenics but are clinically dormant until after puberty.^{4,5}

Though the period of insult was difficult to assess directly, there are various sets of evidence that emphasize early life exposure to schizophrenia. One approach to

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studying neurodevelopmental disturbances among schizophrenic patients is somatic physical evidence or neurodevelopmental markers. These markers are measurable in adults and reflect abnormal neurodevelopmental processes that occurred before or shortly after birth.^{6,7} Minor physical anomalies and dermatoglyphic features are somatic physical markers of prenatal disruptions.

Minor physical anomalies (MPAs), are subtle abnormal features of the head, eyes, ears, mouth, hands, and feet.^{8,9} MPAs are of no serious medical significance, but they indicate the possible presence of associated major anomalies.^{10,11} As the brain and skin are derived from the neuroectodermal layer of an embryo, the presence of multiple MPAs could suggest the possibility of an underlying genetic and/or environmental insult affecting organogenesis.¹² Furthermore, since the way and the timing of the disturbance(s) during early life is not clear, the distribution of MPAs could provide clues to the pathophysiology of schizophrenia as they reflect adverse events during critical periods of development,¹³ usually within the first or early second trimester.¹¹

So, an early assessment of the minor physical anomalies may indicate potential clues of neurodevelopmental disorders like schizophrenia.^{14–16} Numerous studies report an increased frequency of minor physical anomalies (MPAs) in schizophrenic individuals compared with controls. A meta-analysis was carried out on the existing MPA literature to better understand the relationship between MPAs and schizophrenia. The regional MPA analysis revealed significantly increased MPAs in all six anatomical regions.¹⁷ The findings of other meta-analysis indicated that MPAs have been demonstrated in patients with schizophrenia as compared to healthy controls, and a lesser extent in unaffected relatives. These findings supported the idea that MPAs may represent a putative endophenotype for schizophrenia. However, it recommended more research including first-degree family members is warranted.¹⁸ Minor physical anomalies can be measured using the Waldrop Scale.⁸ This research assessed the potential value of exploring minor physical anomalies among schizophrenic patients for early screening of disease among patients and controls objectively and as part of studying its etiology in the northwest, Ethiopia.

Patients and Methods

Study Design and Setting

The institutional-based comparative cross-sectional study design was conducted. This study was undertaken from October 2018 to September 2019 in the psychiatry unit of Debre Markos Referral Hospital. Debre Markos has

located 300 km from Addis Ababa, the capital of Ethiopia, and 256 km from Bahir-Dar, the capital of Amhara Regional State. Debre Markos Referral Hospital is the only referral hospital found in East Gojjam Zone and serves >3.5 million people in its catchment area.

Population

The Study populations were all schizophrenic patients, 1st-degree relatives, and healthy controls in the psychiatry outpatient department who fulfill the definition criteria for this particular study. Schizophrenic patients were those schizophrenic patients diagnosed using the DSM-III-R whereas controls were those patients without mental disorders.

Eligibility Criteria

Inclusion Criteria

All samples who met the case/1st degree relative/control definition; and who volunteered to participate.

Exclusion Criteria

Any history of head injury, epilepsy, significant alcohol or drug abuse, oral-maxillofacial surgery, and those seriously ill patients

Sample Size and Sampling Procedure

The sample size was calculated using Fleiss with CC Formula on epi info version 7.0 software; by setting a significance level of 95%, power of 80%, and a case-control ratio of 1:1. The final sample size was 570, (190 schizophrenic patients, 190 1st degree relatives), and 190 Controls. A purposive sampling technique was used to select the study samples.

Variables of the Study

Independent Variables

Socio-demographic characteristics and minor physical anomalies

Dependent Variable

Patient control status of schizophrenia

Operational Definitions

Schizophrenia

Schizophrenia is a severe mental disorder, diagnosed subjectively using DSM-III-R, patient.

Minor Physical Anomalies

Are cosmetically insignificant subtle defects of the craniofacial region, hands, and feet which are not detrimental to health.

First Degree Relatives (FDR)

Mother or father or sister or brother or children of the case.

Data Collection Procedure

Socio-demographic and psychiatric characteristics of the study sample were collected using a structured interviewer-administered questionnaire. Diagnose of the patient was conducted based on the structured clinical interview for DSM-III-R, patient version (SCID-P, version 1.0). The presence and absence of MPAs were assessed in 6 regions (head, eye, ear, mouth, hand, and feet) using a modified Waldrop scale,⁸ incorporating 25 elements.

Data Quality Assurance

Data were collected by trained data collectors with strict supervision. Data collection tools were pretested. Two days of training were given for data collectors about the objectives of the study, the contents of the Waldrop scale and questionnaire, data collection techniques, and ethical issues. The principal investigator and supervisors supervised the overall data collection procedure on daily basis. Data were collected by two trained midwives.

Data Analysis

Data were entered via Epi data version 3.1 and analyzed using SPSS version 24. Chi-square tests were used to select variables to be entered into a multivariate discriminant analysis. Independent variables that had a significant relationship with schizophrenia at a $p < 0.05$ level were retained for inclusion in the analysis. Discriminant Function Analysis undertakes the same task as multiple linear regression by predicting an outcome. Discriminant function analysis assumes that the sample is normally distributed for the trait. Just like factor loadings, 0.30 was seen as the cut-off between important and less important predictor variables.

Results

Socio-Demographic Characteristics of the Study Samples

A total of 570 study samples, male 375 (65.8%), and female 195 (34.2%) were included in this study. The mean ages of schizophrenics, their 1st-degree relatives, and healthy controls were 35.62 years, 39.97 years, and 33.56 years respectively with no significant difference between patients and control. All study populations were aged between 16 to 74 years with a mean age of 36.38

years and 318 (55.8%) were married. Most of the study population were from Amhara with an annual income of 25,000–50,000 (Table 1). 93.2% of schizophrenic patients experienced early-onset schizophrenia.

Minor Physical Anomalies (MPAs)

The presence and absence of MPAs were assessed qualitatively in 6 regions (head, eye, ear, mouth, hand, and feet) using a modified Waldrop scale, incorporating 25 elements. For continuous variables, (head circumference and intercanthal distance), we had categorized as normal and

Table 1 Socio-Demographic Characteristics of Schizophrenic Patients, Their First-Degree Relatives and Healthy Control (N=570)

Variables	Category	Number	Percent
Sex	Male	375	65.8
	Female	195	34.2
Age	<18	2	0.4
	≥18	568	99.6
Religious responsibility of the sample	Yes	26	4.6
	No	544	95.4
marital status of the study sample	Married	318	55.8
	Unmarried	179	31.4
	Divorced	64	11.2
	Widowed	9	1.6
Educational status	Below 8th	293	51.4
	9–12	89	15.6
	Diploma	161	28.2
	Degree	21	3.7
	Master and PhD	6	1.1
Ethnicity	Amhara	553	97.0
	Oromo	3	0.5
	Tigrie	8	1.4
	SNNPE*	3	0.5
	Others*	3	0.5
Occupation	Farmers	228	40.0
	private employee	140	24.6
	government employee	165	28.9
	Merchant	37	6.5
Annual income of the study sample/family (birr)	>250,000	2	0.4
	100,000–250,000	9	1.6
	75,000–100,000	24	4.2
	50,000–75,000	72	12.6
	25,000–50,000	312	54.7
	<25,000	151	26.5

Notes: *SNNP- southern nations nationalities and peoples of Ethiopia. *Others- Agaw, Benishangul-Gumuz

abnormal depending on the mean of the control group. If the mean value of patient and first-degree relatives lies within two standard deviations of the control, it was labeled as normal. If the mean value lies outside the two standard deviations of the control mean considered abnormal' ie subnormal or supernormal. The inter-rater reliability, evaluated using the intra-class correlation coefficient was 0.97.

After adjusting the above-mentioned procedures chi-square test was conducted. A higher frequency of some minor physical anomalies was observed in schizophrenic patients than healthy control and their 1st-degree relatives. The highest difference was found for the high steeped palate, \geq Five palate ridges, longitudinally furrowed, transversely, and randomly furrowed tongue which appeared in schizophrenic patients with high frequency ($p < 0.001$) (Table 2).

Discriminant Function Analysis

The multivariate discriminant analysis was performed in the field of minor physical anomalies. Two discriminant functions were obtained by multivariate discriminant analysis of variables with p -value < 0.05 in the chi-square test. These functions statistically significantly differentiated the

groups of subjects included in the analysis. While the log determinants were quite similar, Box's M indicated that the assumption of the equality of covariance matrices was violated. However, given the large sample, this problem is not regarded as serious. The discriminate function 1 and 2 revealed a significant association between groups and all predictors, accounting for 83.5% and 16.5% of between-group variability respectively (Table 3).

This structure matrix table shows the correlations of each variable with each discriminate function. These Pearson coefficients are structure coefficients or discriminant loadings. They serve like factor loadings in factor analysis. Longitudinally furrowed tongue, \geq Five palate ridges, high steeped palate, abnormal intercanthal distance, abnormal head circumference, the anticlockwise direction of hair whorls, coverage of epicanthus, the curvature of the fifth finger, slanted eye fissure, displayed the highest correlations with the first discriminant function. Generally, just like factor loadings, 0.30 is seen as the cut-off between important and less important variables. Based on this, longitudinally furrowed tongue ($r=0.587$), \geq Five palate ridges ($r=0.354$), high steeped palate ($r=0.331$) strongly predict allocation to the schizophrenic patients, their 1st-degree relatives, and healthy

Table 2 Topographical Distribution and Frequencies of Minor Physical Anomalies Between Schizophrenic Patients, 1st-Degree Relatives, and Healthy Controls

	Minor Anomaly	Schizophrenic Patients (N=190) N (%)	1st Degree Relatives (N=190) N (%)	Healthy Control (N=190) N (%)	Chi-Square (χ^2 Test)
Head	Anticlockwise hair whorl direction	39 (20.5%)	58 (30.5%)	64 (33.7%)	$\chi^2=8.847$ $p=0.012^*$
	\geq Two number of hair whorls	16(8.4%)	11(5.8%)	12(6.3%)	$\chi^2=1.156$ $p=0.561$
	Abnormal head circumference	40(21.1%)	18(9.5%)	25(13.2%)	$\chi^2=10.689$ $p=0.005^*$
Eyes	Protruding supraorbital ridge	33(17.4%)	31(16.3%)	17(8.9%)	$\chi^2=6.562$ $p=0.038^*$
	Coverage of Epicanthus	18(9.5%)	7(3.7%)	7(3.7%)	$\chi^2=8.012$ $p=0.018^*$
	Slanted eye fissure	43 (22.6%)	29 (15.3%)	25 (13.2%)	$\chi^2=6.659$ $p=0.036^*$
	Abnormal intercanthal distance	34(17.9%)	17(8.9%)	12(6.3%)	$\chi^2=14.241$ $p=0.001^{**}$
Ear	Low seated ears	23(12.1%)	7(3.7%)	15 (7.9%)	$\chi^2=9.265$ $p=0.010^*$
	Adherence of ear lobes	131(68.9%)	116(61.1%)	103(54.2%)	$\chi^2=8.720$ $p=0.013^*$
	Hypoplastic	19(41.3%)	14(30.4%)	13 (28.3%)	$\chi^2=1.466$ $p=0.480$
Mouth	High steeped palate	34(17.9%)	9(4.7%)	17(8.9%)	$\chi^2=18.218$ $p<0.001^{**}$
	\geq Five palate ridges	48 (25.3%)	19 (10.0%)	23 (12.1%)	$\chi^2=19.554$ $p<0.001$
	Longitudinally furrowed	77(40.5%)	22(11.6%)	32(16.8%)	$\chi^2=51.044$ $p<0.000^{**}$
	Transversely and randomly furrowed tongue	132(69.5%)	134(70.5%)	98(51.6%)	$\chi^2=18.670$ $p<0.000^{**}$
Hound	Inward curvature of fifth finger	60(31.6%)	42(22.1%)	39(20.5%)	$\chi^2= 7.294$ $p= 0.026^*$

Notes: ** The highest significant differences between groups. *Shows significant differences between groups.

Table 3 Canonical Discriminative Functions for the Group of Schizophrenic Patients, 1st-Degree Relatives, and Healthy Control

Discriminant Functions	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation	After Discriminant Function	Wilks' Lambda	Chi-Square	df	Sig.
1.	0.283	83.5	83.5	0.469	1 through 2	0.738	169.989	28	0.000
2.	0.056	16.5	100.0	0.230	2	0.947	30.507	13	0.004

controls. Abnormal intercanthal distance ($r=0.290$) marginally predicts group status (Table 4).

The second discriminant function was mainly defined by four minor physical anomalies (Transversely and randomly furrowed tongue, protruding supraorbital ridge, adherence of ear lobes, low seated ears). From this transversely and randomly furrowed tongue ($r=0.713$), and protruding supraorbital ridge ($r=0.382$) had the highest correlations with this function and strongly predict group status (Table 4).

Generally, the regional minor physical anomalies (MPAs) scores that distinguished between schizophrenia patients and controls belonged mainly to the craniofacial region. All five significant minor physical anomalies included in the discriminant model were localized in the head and face.

Discussion

This study revealed that patients with schizophrenia showed five multiple minor physical anomalies in the

craniofacial region, that readily distinguish them from control subjects.

Closer analysis of the structure matrix in our study revealed that longitudinally furrowed tongue, presence of \geq Five palate ridges, high steeped palate; transversely and randomly furrowed tongue, and protruding supraorbital ridge were significant predictors of schizophrenia.

Generally, the regional minor physical anomalies (MPAs) scores that distinguished between schizophrenia patients and controls belonged mainly to the craniofacial region. All five significant minor physical anomalies included in the discriminant model were localized in the head and face.

This showed that MPAs associated with schizophrenia are commonly found in the craniofacial region. This is in line with previous studies on the topography of MPAs in schizophrenia,^{14,19-21} and is in support of the relation between early brain and craniofacial development. Minor physical anomalies in the craniofacial area can occur along with structural changes of the cerebrum in the intrauterine life of schizophrenics.^{8,22} These findings are consistent with a model of cerebro-craniofacial dysmorphogenesis.²

Many studies showed that the mouth region is highly susceptible to MPAs in schizophrenic patients,^{14,21,23} with the highest prevalence of the palate and tongue anomalies²³⁻²⁶ which is consistent with our study. Facial-cerebral morphogenesis postulated as dysmorphology in schizophrenia patients' face affects principally the midfacial region.²⁷ During embryogenesis the midfacial region is populated with cranial neural crest cells, which could explain the coincidence of midfacial minor anomalies and schizophrenic disorder.

High/steeped palate represents a microform of cleft palate, which is itself frequently associated with midline brain anomalies as in fetal alcohol syndrome. Further, midline brain anomalies such as enlarged cavum septum pellucidum and corpus callosum abnormalities have been found with increased incidence in patients with schizophrenia.^{28,29}

In this study longitudinal fissure of tongue and presence of tongue, furrow was found as significant predictors of schizophrenia. Most studies showed a furrowed tongue to

Table 4 Function-Variable Correlations for the Group of Schizophrenic Patients, 1st-Degree Relatives, and Healthy Controls

Variables	Function	
	1	2
Longitudinally furrowed tongue	0.587***	0.146
\geq Five palate ridges	0.354**	0.053
High steeped palate	0.331**	0.196
Abnormal intercanthal distance	0.290*	-.187
Abnormal head circumference	0.252*	0.148
The anticlockwise direction of hair whorls	-.227*	0.153
Coverage of epicanthus	-.225*	0.031
The curvature of the fifth finger	-.211*	0.093
Slanted eye fissure	-.197*	0.125
Transversely and randomly furrowed tongue	-.139	0.713**
Protruding supraorbital ridge	-.111	0.382**
Adherence of ear lobes	-.201	0.273*
Low seated ears	-.217	-.243*

Notes: *Largest absolute correlation between each variable and any discriminant function. **Strong predictors of group status

be a significant marker of schizophrenia without respect to the type of furrows.³⁰ While other studies reported randomly furrowed tongue, transversely furrowed tongue³¹ or longitudinal fissure of the tongue and few fissures diffusely distributed across the dorsal tongue surface.³⁰

Conclusion

In our study closer analysis of the structure matrix revealed longitudinally furrowed tongue, \geq Five palate ridges, high steeped palate; transversely and randomly furrowed tongue, protruding supraorbital ridge as a significant predictor. Depending on this study, minor physical anomalies can serve as a biomarker for early screening of schizophrenic patients and clue for its developmental origin as part of studying its etiology.

Abbreviations

DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders; MPAs, minor physical anomalies; SCID-P, Structured Clinical Interview for DSM-III-R patient; ICD, intercanthal distance.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the participants, and the study was conducted per the Declaration of Helsinki. The ethical clearance was taken from Debre Markos University, school of medicine Ethical review committee. The letter was formally submitted for Debre Markos' referral hospital and got permission.

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Author Contributions

Both authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article was submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declared that they have no competing interests in this work.

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