Minor Physical Anomalies in Patients with Schizophrenia and Healthy Controls - A Comparative Analysis in Odisha

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ABSTRACT

BACKGROUND

Schizophrenia being one of the most debilitating and chronic psychiatric illnesses still puzzles researchers due to its complex aetiology. Currently, neurodevelopmental hypothesis of schizophrenia is widely accepted explaining aetiology of schizophrenia. As per this hypothesis abnormal neurological development during gestation and childhood due to various factors make the individual susceptible for development of schizophrenia later in life. Presence of minor physical anomalies (MPA) points towards abnormal neurodevelopment during gestation which increases the risk of developing schizophrenia in later life. Purpose of our study was to evaluate the presence of minor physical anomalies in patients of schizophrenia and compare them with healthy controls.

METHODS

This was a cross-sectional comparative study. 50 schizophrenic patients were selected from OPD (outpatient department) and the presence of minor physical anomaly in those patients was compared with 50 normal healthy control subjects using Waldrop's minor congenital anomaly scale. Schizophrenic groups were also categorised into the early-onset group and late-onset group and mean score of Waldrop's minor physical anomalies in both the groups were compared. Patients with family history of schizophrenia were compared with those without any family history of schizophrenia.

RESULTS

Minor physical anomalies were significantly higher in the schizophrenic group (mean = 2.4) as compared to healthy controls (mean = 0.87). Incidence of minor physical anomalies in the early onset group (mean = 3.91) was higher than the late-onset group (mean = 1.53) but the difference was not statistically significant.

CONCLUSIONS

As the incidence of minor physical anomalies is more in schizophrenia, presence of MPAs in asymptomatic patients can predict the risk of developing schizophrenia in later life.

KEYWORDS

Minor Physical Anomalies, Schizophrenia, Waldrop's Minor Congenital Anomaly Scale

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BACKGROUND

Among all the psychiatric disorders schizophrenia is the most debilitating and has a huge impact on the socio-economic functioning of the patient. It is characterised by positive symptoms (delusion and hallucination) negative symptoms (asociality, avolition, affective blunting, etc.) and impairment of various cognitive functions like working memory, verbal memory, attention, facial recognition, emotional recognition, etc. Even with vast number of researches conducted on schizophrenia, its pathophysiology and aetiology still remain elusive and we still have insufficient knowledge regarding the cause and mechanism of this enigmatic disease but our knowledge about this illness has expanded, thanks to clinical genetics, post-mortem studies and structural and functional imaging studies.

Minor physical anomalies are minor congenital physical abnormalities with no cosmetic significance[1] and consist of features such as low-set ears, single transverse palmar crease, telecanthus, micrognathism, macrocephaly, hypotonia, hypertelorism and furrowed tongue.[2] Minor physical anomalies are considered as one of many candidate endophenotype in schizophrenia.

Since the dawn of psychiatry in early 20th century there has been tremendous research to establish the aetio-pathological basis of schizophrenia. After the discovery of effectiveness of chlorpromazine in schizophrenia, dopamine hypothesis became prominent to explain the symptomatology of this disease. But dopamine abnormalities in schizophrenic patients can only explain positive symptoms but not negative and cognitive symptoms. Subsequently, use of phencyclidine and its potency to cause schizophrenia like symptoms in normal persons gave way to glutamate hypothesis which can explain all symptoms domain in schizophrenia. Chemical imbalance of glutamate level in the brain of schizophrenic patients is thought to be due to abnormal neural circuitry due to neurodevelopmental anomaly.

Currently, the neurodevelopmental hypothesis is widely accepted to explain the aetiology of schizophrenia, as per this hypothesis abnormal neurodevelopment in patients of schizophrenia actually starts years before the onset of the symptoms. Neurodevelopmental hypothesis of schizophrenia suggests that well before the formal onset of symptom especially during gestation and early developmental period, exposure to pathogenic factors disrupts the normal course of neural development.[3] Development of brain (neurodevelopment) is a highly complex process involving expression of various genes in timely manner. Developing nervous system is highly dynamic and can undergo modifications in response to experience and when exposed to insults.[4] Any significant abnormalities in the process of neurodevelopment can give rise to many brain disorders. These not only include childhood neuropsychiatric disorders but also adult debilitating disorders like schizophrenia and bipolar disorder. Exposure to these pathogenic factors leads to subtle alteration in neurons, glia, circuits which makes the individual susceptible to the development of the illness later in life.

Neuro-Developmental Model of Schizophrenia

Schizophrenia is the behavioural outcome of subtle deviances in early brain development which does not manifest until adolescence or early childhood. Children who later develop schizophrenia have higher rates of minor physical anomalies indicative of a subtle disruption of ectoderm development e.g., craniofacial and dermatoglyphics anomalies and neurological soft sign.[5] Further absence of inflammatory reaction in the brain of people with a diagnosis of schizophrenia rules out neurodegenerative hypothesis of schizophrenia. Reduced neuronal size, dendritic arborization and spine density in the cortex and hippocampus appear to be consistent finding across studies.[6] Neuroimaging and pathological studies have revealed several abnormalities in schizophrenic patients such as smaller prefrontal cortex, small hippocampus with enlarged ventricles which suggests abnormal neural development. Out of all the neuropathological evidence most compelling is the finding of abnormally located clusters of neurons found in lamina ii of entorhinal cortex and within the white matter of pre frontal and temporal cortex.[7] These abnormalities suggest disrupted neural development especially during the process of neural migration. The products of various candidate genes implicated in schizophrenia like Neuregulin, Reelin and Disc1 gene is particularly implicated and its product regulates neural migration, neural cell growth and neural maturation.[8] All these evidences gathered from various neuroimaging, neuropathological[7] and genetic studies.[7] point towards some disruption during the process of neurodevelopment which supports the neurodevelopmental model of schizophrenia.

Minor physical anomalies are subtle developmental anomalies which are of no cosmetic or functional significance. Minor physical anomalies primarily involve the structures in the craniofacial region and the limbs which are derived from neural crest cells during the process of neural development.[9] The presence of minor physical anomalies can be regarded as the marker of disrupted neural development.[10]

The concept of MPAs has been derived from studies of morphological anomalies in new born, pre-school and school-aged children[11] having behavioural disturbances like impulsivity and hyperactivity. Subsequently MPAs became a construct to support neuro-developmental hypothesis in schizophrenia and other neuro developmental disorders like autism and attention deficit hyperactivity disorder (ADHD).[12]

MPAs can be assessed qualitatively or quantitatively. Qualitative assessment of MPAs include palatal abnormalities, furrowed tongues, low-set ear, curved fifth digit of the hands and increased gap between first and second toes to name a few. Qualitatively measured MPAs include reduced head circumference and elongation of lower facial region.

MPA as Endophenotype in Schizophrenia

Endophenotype in simple terms can be explained as manifestations which are internal and are not apparent to unaided eyes during routine clinical examinations. The

concept was burrowed from a study on insect biology by John and Lewis in 1966, in which they found that geographical distributions of grasshoppers was a function of some features not overtly apparent but are internal and microscopic. They suggested the term endophenotype for these internal and microscopic features.[13]

Gottessman and Shield in 1973 applied the term endophenotype in the field of psychiatry and suggested that to be useful in psychiatric classification as endophenotypes specific alteration in brain structures and functions can be identified by certain objective procedures like neuroanatomical, neurophysiological or cognitive approaches. Endophenotypes are considered by researchers as more promising than clinical syndrome to study the genetic study factors in psychiatry illnesses that provide direct clues to the genetic underpinnings of the illness.[14] It must fulfil certain criteria.[15]

- It must be associated with the illness in the population
- It is heritable, must be present in illness free first-degree relatives
- State dependent, must be present in diseased person, not depending on whether the person is symptomatic or not.
- It should co-segregate with the disease in the affected family

Endophenotypes lying on the way between genotype (genetic makeup of an individual) and phenotypes (overt symptomatology of an illness) and being objective and miserable biological entities are better representation of underlying genetic underpinnings of psychiatric diseases. There are considerable evidences that genetic abnormalities contribute to the aetiology of schizophrenia and aberrant genetic makeup should give rise to corresponding anatomical or functional abnormalities that can serve as endophenotypes for schizophrenia.[16]

Endophenotypes can be categorized into six groups such as anatomical, developmental, electrophysiological, metabolic, sensory, psychological or cognitive. Among all these endophenotypes MPAs fall under the developmental category of endophenotype along with identifiable abnormalities in neuroimaging and neuropathological studies, minor physical anomalies can be considered as an indirect evidence to support the neurodevelopmental hypothesis of schizophrenia.[17]

Akavaliev EH, Sivkov ST et al. evaluated the frequency and topographical distribution of minor physical anomalies in schizophrenic patients and the ability of the Waldrop scale to predict the patient control status. They found that compared with controls, schizophrenia patients showed a higher incidence of almost all studied minor physical anomalies.

The distribution frequencies of MPAs in schizophrenia tended to increase in cranial direction. The pattern of changes in the morphological characteristics suggests they maybe a random outcome of a general neurodevelopmental defect or may reflect different neurodevelopmental defects that allow better characterisation of schizophrenia patient sub-groups.[18] Michael T Compton and Peter F Buckley in 2011 reported that MPAs are more prevalent among individuals with schizophrenia than healthy controls. MPAs are more prevalent individuals with schizophrenia than unaffected relatives and MPAs are not consistently related to symptom domain.[19] Rakesh Lal and Shridhar Sharma in 1987 studied the prevalence of minor physical anomalies in schizophrenic patients. They investigated the presence of minor physical anomalies in schizophrenic patients and found a significantly higher incidence of minor physical anomalies in schizophrenic patients. They concluded that this raises the possibility of intrauterine developmental defects in schizophrenia.[20]

Punya Mulky, P Poornachandrika and Heber Anandan in 2017 studied the prevalence of minor physical anomalies in patients with schizophrenia, comparing it with their first-degree relatives and with the general population. They selected 50 schizophrenic patients, 50 unaffected first-degree relatives and 50 normal controls and used the Waldrop scale for assessment of MPAs. The Waldrop scores were higher for patients (48 %) followed by relatives (28 %) and controls (10 %), with more anomalies in the head, eyes, ears and feet. They pointed out that MPAs can be considered as an endophenotype for schizophrenia.[21] Purpose of the study was to evaluate the minor physical anomalies in patients of schizophrenia and compare them with healthy controls.

METHODS

This was a cross-sectional comparative study conducted in the Department of Psychiatry, VSSIMSAR, Burla, from December 2019 to December 2020.

Consent was taken from both study and control subjects. Waldrop minor physical anomaly scale was applied to evaluate the presence of minor physical anomalies both in study group and control group. The study group was also evaluated for presence or absence of a family history of schizophrenia and based on onset of illness, those with the onset of illness at or before 18 years were included in early-onset group and rest were included in late-onset group.

Selection of Study Group

Patients diagnosed with schizophrenia as per DSM-V attending psychiatric OPD, aged between 15 to 50 years were included in the study group. Patients with a history of epilepsy, mental retardation or having major medical illness were excluded from the study. Violent and uncooperative were also excluded from the study.

Selection of Control Group

Attendants accompanying various psychiatric patients to the Department of Psychiatry, VSSIMSAR, Burla, who were not biologically related to or without any family history of schizophrenia were included in the control group.

Tools Used

A semi-structured clinical proforma was used for data collection pertaining to age, gender, socio-economic status

location and background. Waldrop's minor congenital anomaly scale was used to assess the presence of minor physical anomalies in study and control groups. Waldrop minor congenital anomalies scale is a scale which standardizes the measurement of 18 different minor physical anomalies of the head, eyes, ears, mouth, hands and feet. In most studies, minor physical anomalies score 3 or more was considered positive.

Statistical Analysis

- For the study P-value of less than 0.005 was considered significant with confidence interval of 95 % prior to commencement of study. For comparative analysis of mean MPA score between study and control group, one-way analysis of variance (ANOVA) was used. Same statistical tool was also used for comparing the mean MPA score for groups categorised as per age of onset of illness and presence of family history within the study group. Every statistical analysis was done using SPSS software. Data was analysed by t-test.

		Anomaly	Score
Head	1.	Fine electric hair:	
		Does not come down	2
		Awry soon after combing	1
	2.	Hair whorls ≥ 2	0
	3.	Head circumference	
		1.5 - 2.0 S.D.	1
		> 2 S.D.	2
Eyes	4.	Epicanthus	
		Partly covered	1
		Deeply covered	2
	5.	Intercanthal distance	
		1.5 - 2.0 S.D.	1
		> 2 S.D.	2
Ears	6.	Low-seated ears	
		≤ 0.5 cm below the outer corner of eye	1
		> 0.5 cm below the outer corner of eye	2
	7.	Adherent ear lobes	
		Straight back towards the rear of neck	1
		Upward and back towards the crown of head	2
	8.	Malformed ears	1
	9.	Asymmetric ears	1
	10.	Soft and pliable ears	0
Mouth	11.	High / steepled palate	
		Flat and narrow at the top	1
		Definitely steepled	2
	12.	Furrowed tongue	1
	13.	Tongue with smooth / rough spots	0
Hands	14.	Curved 5th finger	
		Slightly curved	1
		Markedly curved	2
	15.	Single transverse palmar crease	1
Feet	16.	3rd Toe	
		= 2nd toe	1
		> 2nd toe	2
	17.	Partial syndactyly of 2nd and 3rd toe	1
	18.	Big gap between 1st and 2nd toe	1

Waldrop's Minor Congenital Anomaly Scale

RESULTS

The mean Waldrop's score was significantly higher in study subjects as compared to the control group and the difference was statistically significant at P < 0.005 (Table 1). The mean score in study group was 2.4 while it was 0.87 in control group. Assessment of significance using one-way ANOVA revealed significant difference in the mean between study and control groups.

Study Group	Total	Mean Score	Standard Deviation	T-Value [95 % CI]	P-Value
Schizophrenia (N = 50)	120	2.4	2.31		0.003
Control (N = 50)	43	0.87	1.04		

Table 1. Distribution of MPA Score in Study and Control Group.

Total MPA score for early-onset schizophrenic patients' group was compared with the late-onset group (Table 2). In our study 19 patients had the onset of schizophrenic symptoms before 18 years of age and categorised as early onset group and rest were categorised as late onset group. Although total MPA score in the early-onset group was higher than the late-onset group, the difference statistically was not significant as P-value > 0.005.

Age of Onset of Illness	Mean Score	Standard Deviation	T-Value [95 % CI]	P-Value
Early onset (≤ 18 years) (N = 19)	3.91	2.59	3.09	0.29
Late onset (> 18 years) (N = 31)	1.53	1.65		

Table 2. Distribution of Mean MPA Score in Study Group According to Age of Onset of Illness

Schizophrenic patient with a family history of schizophrenia was compared with patients without a family history of schizophrenia for the presence of MPA (Table 3). In our study, 35 patients had family history of schizophrenia while 15 patients did not have any family history of schizophrenia. Here also the total score of MPA in patients with family history was higher than those without family history but the difference was statistically not significant.

Family History of Schizophrenia	Mean Score	Standard Deviation	T-Value [95 % CI]	P-Value
Yes (N = 35)	3.22	2.81	1.29	0.26
No (N = 15)	2.04	2.03		

Table 3. Distribution of Mean MPA Score in Study Group According to Family History of Schizophrenia

DISCUSSION

Currently, the neurodevelopmental hypothesis of schizophrenia is the prevalent theory to explain the aetiology of this complex disease. In our study, we have found a higher minor physical anomaly score in the patient of schizophrenia as compared to normal control subject which points towards abnormal neurodevelopment in schizophrenia patient. Furthermore, incidence of minor physical anomalies in the craniofacial region is more in schizophrenia group as compared to extremities region. Presence of minor physical anomalies especially in the craniofacial region strongly indicates abnormal neurodevelopment during gestation or early childhood increasing the development of schizophrenic symptoms later in life. These findings are in keeping with the findings of an earlier study conducted in India by Rakesh Lal and Shridhar Sharma.[20]

When the onset of illness was taken into consideration the schizophrenia patients with early onset of the disease had more incidence of minor physical anomalies as compared to the late-onset group. So increased incidence of minor physical anomalies in the early-onset group maybe due to more abnormality in neurodevelopment which pushes

the onset of the disease to early years. But whether higher incidence of MPAs is associated with more severe schizophrenic symptoms was not evaluated in our study. Patients with a family history of schizophrenia have more incidence of minor physical anomalies than those without a family history. Making subjects with minor physical anomalies as one of the good candidates for endophenotype.

Presence of minor physical anomalies even before schizophrenic symptoms may indicate a higher risk of developing schizophrenia in later age.

CONCLUSIONS

Presence of minor physical anomalies in patients of schizophrenia is statistically higher than in normal controls and helps in early diagnosis. Schizophrenia patient with early onset of the disease has more incidence of minor physical anomalies as compared to the late-onset group. Presence of minor physical anomalies even in asymptomatic patients can predict the development of schizophrenia later in life.

Limitations

Sample size (N = 50) was comparatively small in our study. Only presence of MPAs as markers of neurodevelopment was considered in our study excluding other candidate endophenotypes. Association of incidence of MPAs with the severity of type of schizophrenia was not evaluated.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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