Acta Med. Nagasaki 47 : 133−137

Minor Physical Anomalies in Japanese Patients with Schizophrenia

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We assessed the prevalence of minor physical anomalies (MPAs) in Japanese patients with schizophrenia (n=313) and normal controls (n=128) using the Waldrop scale. There was a significant difference in the scale scores between the patients with schizophrenia and control subjects (U=17274.5, p=0.02). Patients had significantly more MPAs than controls on the individual scale items of malformed ears (p=0.039), furrowed tongue (p=0.006), high steepled palate (p=0.041) and head circumference which was 1.5 SDs below the average of normal controls (p=0.015). When we defined subjects at or above the median MPA score to be in the high anomaly group, significantly more patients than normal controls were represented in this group (p=0.033). Waldrop scores were not found to be related to age at onset of schizophrenia.

ACTA MEDICA NAGASAKIENSIA 47 : 133−137, 2002

Key Words: minor physical anomalies, schizophrenia, Waldrop scale, neurodevelopment, age of onset, high steepled palate

Introduction

Several researchers have suggested that some cases of schizophrenia are associated with abnormal prenatal development.[1−5)] For example, some data show an association between prenatal exposure to influenza virus or obstetric complications with the development of schizophrenia.[1,3)] Based on these data the neurodevelopmental hypothesis of schizophrenia has been promoted.[6,7)] According to this hypothesis, schizophrenia results from a neurodevelopmental abnormality during the prenatal period. Remarkable schizophrenic symptoms are latent until the affected region matures and is required for optimal functioning.[6)] In support of this hypothesis, several markers of abnormal neurodevelopment have been suggested. These include subtle neurological signs[8)], neuropathological findings[9)], dermatoglyphic signs[4)] and minor physical anomalies (MPAs).[5,10−12)]

MPAs are slight deviations in external physical characteristics (e.g., 'low-seated ears', 'high-steepled palate', 'curved fifth finger', 'partial syndactyl of the two middle toes'). Kraepelin, in his descriptions of dementia praecox, reported that "so-called signs of degeneracy were often observed: smallness or deformity of the skull, child-like habitus, missing teeth, deformed ears", and suggested a possible association between MPAs and mental illness.[19)] High rates of MPAs have indeed been reported in many neurodevelopmental disorders including Down's syndrome, hyperactivity, autism, epilepsy, learning disabilities, mental retardation, violent recidivistic criminal behavior, speech and hearing impairments, and poor motor coordination.[10,11,13−18)] Structures showing identified MPAs and the central nervous system (CNS) both derive from ectodermal tissue; thus, MPAs are believed to reflect abnormal development of the CNS.[11)]

In comparison studies between patients with schizophrenia and normal controls, more MPAs have consistently been found in patients with schizophrenia.[10,11,18,20,21)] The majority of studies that have examined the prevalence of MPAs in schizophrenia have used the Waldrop scale.[5,10−12)] The Waldrop scale is based on abnormalities found in Down's syndrome[14)] and is a standardized assessment tool that examines 18 anomalous features of the head, eyes, ears, mouth, hands, and feet that are believed to occur in the first and/or second trimester of gestation.[22)] In previous studies, more MPAs have consistently been found in patients with schizophrenia.[5,10−12,23−25)] Additionally, the association of MPAs and various factors such as family history, age of onset, and obstetric complications have been investigated.[24)] However, there are few studies which investigate the association between MPAs and mental illness in Japanese patients.

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Therefore, we examined whether there were higher rates of MPAs in Japanese schizophrenic samples compared to previous studies using other samples. In addition, we examined whether there was a difference in the prevalence of MPAs according to the age of onset of schizophrenia.

Materials and Methods

The subjects were 313 patients with schizophrenia (152 male and 161 female) and 128 normal controls (62 male, 66 female). All of the patients had been admitted to Michino-o Hospital and fulfilled DSM-III-R (American Psychiatric Association, 1987) criteria for schizophrenia. The mean age of patients was 47.2 years (SD: 12.0, range 15 - 92 years). Normal controls were drawn from hospital staff. The controls were screened to exclude those with a history of psychiatric illness and were well-matched with the patients for age and gender. The mean age of the controls was 44.9 years (SD: 12.9, range 19 - 70 years).

The MPA rating for the patients was performed by two examiners who were blind to the diagnosis and other clinical information. We used the Waldrop scale[11], a widely used, standardized scoring system for the assessment of MPAs (Table 1). The scale is a simple assessment of 18 anomalous features of the head, eyes, ears, mouth, hands, and feet.[17] All subjects received this approximately 5-minute examination for MPAs. The majority of the 18 items were rated as being present or absent, while weighted scores were calculated for a number of Waldrop items. Because mentally retarded patients sometimes have prominent MPAs, interrater reliability was assessed with 45 mentally retarded patients residing in the intellectual disabilities rehabilitation institution, Nijigaoka Gakuen. The intraclass correlation coefficient for the Waldrop scale total score was $r = 0.73$ ($p < 0.001$).

The Mann-Whitney U test was used to compare the Waldrop scale scores of schizophrenia patients and normal controls. We considered subjects at or above the median in the Waldrop scale score to be in the high anomaly group. The proportion of subjects in the high anomaly group in the patient and control groups was compared using Fisher's exact test. The association between MPA occurrence on each items of the Waldrop scale in the patients and controls was tested by Fisher's exact test.

Spearman correlations were used to assess the relationship between the Waldrop scale scores in the schizophrenia sample and the age of onset of illness. We compared the Waldrop scores in the early onset patients group (before age 18) with those in the other patients group by the Mann-Whitney U test.

Table 1. Waldrop list of MPAs with scoring weights (Guy et al., 1983)

Region	Item	Weight
Head		
	Fine, electric hair	
	Very fine hair that will not comb down	2
	Fine hair that is soon awry after combing	1
	Two or more hair whorls	0
	Head circumference outside normal range:	
	>1.5 SD	2
	>1.0 SD <1.5 SD	1
Eyes		
	Epicanthus	
	Where upper and lower lids join the nose, point of union is:	
	Deeply covered	2
	Partly covered	1
	Hypertelorism	
	Approximate distance between tear ducts:	
	>1.5 SD	2
	>1.0 SD <1.5 SD	1
Ears		
	Low-seated ears	
	Point where ear joins head, not in line with the corner of eye and nose bridge:	
	Lower by > 0.5 cm	2
	Lower by < 0.5 cm	1
	Adherent ear lobes	
	Lower edge of ears extend:	
	Upward and back toward crown of head	2
	Straight back toward rear of neck	1
	Malformed ears	1
	Asymmetrical ears	1
	Soft and pliable ears	0
Mouth		
	High-steepled palate	
	Roof of mouth:	
	Definitely steepled	2
	Flat and narrow at the top	1
	Furrowed tongue (one with deep groves)	1
	Tongue with smooth-rough spots	0
Hands		
	Curved fifth finger	
	Markedly curved inward toward other fingers	2
	Slightly curved inward toward other fingers	1
	Single transverse palmar crease	1
Feet		
	Third toe longer than second:	
	Definitely longer than second toe	2
	Appears equal in length to second toe	1
	Partial syndactylia of two middle toes	1
	Big gap between first and second toes	1

(SD : SD from mean based on age)

Results

Table 2 shows the distribution and the average of the Waldrop scale scores. The mean score for the patients (2.10, SD=1.69) was significantly higher than the mean score for the normal controls (1.67, SD=1.41) ($U=17{,}274.5$, $p=0.02$).

To determine if more patients than controls were represented in the high anomaly group, we defined

Table 2. Distribution and average of the Waldrop scale scores

Waldrop scale score	Schizophrenia patients N=313	Normal controls N=128
0	58 (18.5%)	31 (24.2%)
1	64 (20.4%)	33 (25.8%)
2	86 (27.5%)	32 (25.0%)
3	46 (14.7%)	16 (12.5%)
4	35 (11.2%)	13 (10.2%)
5	14 (4.5%)	2 (1.6%)
6	3 (1.0%)	0 (0.0%)
7	4 (1.3%)	1 (0.8%)
8	2 (0.6%)	
9	0 (0.0%)	
10	1 (0.3%)	
Average	2.10	1.67
SD	1.69	1.41

scores at or above the median of the Waldrop scale score, 2, in each group to be the high score. A significantly greater proportion of patients relative to controls were classified as high anomaly subjects (p=0.03). Patients had significantly more MPAs than controls on the following individual items of the Waldrop scale: malformed ears (p=0.039; odds ratio=1.04, 95%confidence interval 1.02 - 1.06), furrowed tongue (p=0.006; odds ratio=2.36, 95% confidence interval 1.25 - 4.46); small head circumference (> 1.5 SD from normal; p=0.015; odds ratio=2.89, 95%confidence interval 1.19 - 7.02); and high steepled palate p=0.04; odds ratio=2.93, 95% confidence interval 1.00 - 8.54).

Within the patients group, there was no significant correlation of the Waldrop score with age of onset (r =0.031). The average age of onset for patients with schizophrenia was 24.0 years (SD=8.8) excluding one patient whose age of onset was not able to be determined. Sixty-seven patients with schizophrenia had disease onset before age 18 and their average Waldrop score was 2.0 (SD=1.7). Two hundred and forty-five patients with schizophrenia had disease onset at or after age 18 and their average Waldrop score was 2.1 (SD=1.7). There was no significant difference in Waldrop scores between these two groups (U=7884.0, p=0.61).

Discussion

When the cutoff score was defined to be the median Waldrop score (2), the patients with schizophrenia had significantly higher scores than normal controls. In previous studies, when the cutoff score was defined to be 3, patients with schizophrenia also had significantly higher scores than normal controls.[23,26] However, when we employed the cutoff score of 3, although there was a trend for patients to have higher scores than normal controls, this difference was not statistically significant (p=0.078).

The patients had significantly higher scores than controls on the individual items of malformed ears, furrowed tongue, high-steepled palate and small head circumference. These findings support the previous report that MPAs in patients with schizophrenia are found predominantly in the head and facial regions.[27] In addition, higher scores on the comprehensive item of high-steepled palate have also been shown previously among patients with schizophrenia.[5,24,26,28]

High-steepled palate represents a microform of cleft palate, which is itself frequently associated with midline brain anomalies as in fetal alcohol syndrome. Midline brain anomalies such as enlarged cavum septi pellucidi and corpus callosum abnormalities have been found with increased incidence in patients with schizophrenia.[29,30] Therefore, the finding of a higher rate of high-steepled palate is especially interesting.

There has been some speculation as to whether patients with schizophrenia have smaller head sizes than normal controls.[31] Several investigators have measured head size in patients with schizophrenia and normal controls and reported no significant differences between the two groups.[6,32,33] In our study, the average head circumference of patients with schizophrenia was 554.3 mm (SD=21.3) and that of normal controls was 556.7 mm (SD=19.0). However, more patients with schizophrenia than controls had small head circumference, which was defined as head circumference 1.5 SDs below the average of normal controls (p=0.015). Smaller head size may be due to an abnormal prenatal development process, because brain size and cranial development are closely linked.

Green et al.[12] reported an association between the presence of MPAs and an earlier age of disease onset in patients with schizophrenia; however, other investigators have found no such association.[5,11,23] We could find no association between higher MPA scores and an earlier age of onset in patients with schizophrenia. The Waldrop scale has also been used to study MPAs in a variety of other psychiatric disorders. Generally, MPAs have been found uniformly across various other

psychiatric disorders and an excess of MPAs does not appear to be specific to schizophrenia. However, this issue concerning the lack of specificity should be addressed by comparing MPAs in schizophrenia with those in other disorders.

Several researchers have suggested an association between MPAs in patients with schizophrenia and various variables such as sex, family history, obstetric complications, premorbid function levels, number and length of admissions, structural neuroimaging and tardive dyskinesia.[5,11,12,23,24] However, the relationship between those variables and MPAs in patients with schizophrenia is still uncertain. Further studies are necessary to define these relationships.

To our knowledge, the current study is the first to examine MPAs in a large number of Japanese subjects. In this study, subjects were ethnically uniform, matched to controls on age and gender, and the number of cases was considerably large compared with previous research. Our data are consistent with those reported for Caucasian populations.[5,10-12,23-25]

Because we performed face-to-face examinations, we were not completely blind to diagnosis and thus some bias could have been introduced. We plan to score the Waldrop scale using photographs of subjects' body regions to exclude this potential bias. Recently, a prospective study to exclude bias reported that MPAs appeared to signal stressors relevant to schizophrenia spectrum disorders.[34]

The Waldrop scale is limited in that it has relatively few assessment items and the definition of the weighted points is vague.[27] There have been studies in which more inclusive, more quantitative original assessment scales were employed. And those assessments of the new items clearly indicated that many MPAs other than the Waldrop scale items were found in patients with psychosis.[28,35]

MPAs reflect some insult or maldevelopment in the prenatal period but determining more precisely when MPAs evolve is difficult. To study the impact of genetic and environmental factors on the formation of MPAs, it will be necessary to examine the association between MPAs and several variables such as the presence of influenza infection in the mother during pregnancy, obstetric complications, family history and the prevalence of MPAs in siblings.

References

1) Parnas J, Schulsinger F, Teasdale TW, *et al*: Perinatal complications and clinical outcome within the schizophrenia spectrum. *Brit J Psychiatry* 140:416-420, 1982

2) Gal P, Sharpless M.K: Fetal drug exposure - Behavioral teratogenesis. *Drug Intell Clin Pharm* 18:186-201, 1984

3) Mednick SA, Machon RA, Huttunen MO, *et al*: Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 45:189-192, 1988

4) Bracha HS, Torrey EF, Bigelow LB, *et al*: Subtle signs of prenatal maldevelopment of the hand ectoderm in schizophrenia: A preliminary monozygotic twin study. *Biol Psychiatry* 30:719-725, 1991

5) O'Callaghan E, Larkin C, Kinsella A, *et al*: Familial, obstetric, and other clinical correlates of minor physical anomalies in schizophrenia. Am *J Psychiatry* 148:479-483, 1991

6) Weinberger DR. Implications of normal brain develop-ment for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44:660-669, 1987

7) Murray RM, Lewis SW, Owen MJ, *et al*: The neurodevelopmental origins of dementia praecox. In *Schizophrenia*: The Major Issues, edited by Bebbington, P. and McGuffin, P. Heinemann, London, pp. 90-106, 1988

8) Fish B, Marcus J, Hans SL, *et al*: Infants at risk for schizophrenia: Sequelae of a genetic neurointegrative defect. A review and replication analysis of pandysmaturation in the Jerusalem infant devel-opment study. *Arch Gen Psychiatry* 49:221-235, 1992

9) Bogerts B. Recent advances in the neuropathology of schizophrenia. *Schizophr Bull* 19:431-445, 1993

10) Gualtieri CT, Adams A, Shen CD *et al*: Minor physical anomalies in alcoholic and schizophrenic adults and hyperactive and autistic children. *Am J Psychiatry* 139:640-643, 1982

11) Guy JD, Majorski LV, Wallace CJ, *et al*: The incidence of minor physical anomalies in adult male schizophrenics. *Schizophr Bull* 9:571-582, 1983

12) Green MF, Satz P, Gaier DJ, *et al*: Minor physical anomalies in schizophrenia. *Schizophr Bull* 15:91-99, 1989

13) Krouse JP, Kauffman JM. Minor physical anomalies in exceptional children: a review and critique of research. *J Ab Child Psychol* 10:247-264, 1982

14) Waldrop MF, Pedersen FA, Bell RQ: Minor physical anomalies and behavior in preschool children. *Child 0ev* 39:391-400, 1968

15) Rapoport JL, Quinn PO, Lamprecht F. Minor physical anomalies and plasma dopamine-beta-hydroxylase activity in hyper-active boys. *Am J Psychiatry* 131:386-390, 1974

16) Steg JP, Rapoport JL. Minor physical anomalies in normal, neurotic, learning disabled, and se-verely disturbed children. *J Autism Child Schizophr* 5:299-307, 1975

17) Paulhus DL, Martin CL. Predicting adult temperament from minor physical anomalies. *J Pers Soc Psychol* 50:1235-1239, 1986

18) GoldfarbW, Botstein A. *"Physical Stigmata in Schizophrenic Children."* Unpublished manuscript, Henry Ittleson Center for Child Research, Brooklyn, NY, 1967

19) Kraepelin F. Dementia praecox. *Psychiatrie* (5th edo). Leipzig: Barth, 1896

20) Campbell M, Geller B, Small AM, *et al*: Minor physical anomalies in young psychotic children. *Am J Psychiatry* 135:573-575, 1978

21) Green MF, Satz P, Soper HV, *et al*: Relationship between physical anomalies and age at onset of schizophrenia. *Am J Psychiatry* 144:666-667, 1987

22) Smith DW. *Recognizable Patterns of Human Malformation.* Philadelphia, WB Saunders, 1970

23) Lohr JB, Flynn K. Minor physical anomalies in schizophrenia and mood disorders. *Schizophr Bull* 19:551-556, 1993

24) McGrath JJ, van Os J, Hoyos C, *et al*: Minor physical anomalies in psychoses: associations with clinical and putative aetiological variables. *Schizophr Res* 18:9-20, 1995

25) Murphy KC, Owen MJ. Minor physical anomalies and their relationship to the aetiology of schizophrenia. *Br J Psychiatry* 168:139-142, 1996

26) Green MF, Satz P, Christenson C. Minor physical anomalies in schizophrenia patients, bipolar patients, and their siblings. *Schizophr Bull* 20:433-440, 1994

27) Lane A, Kinsella A, Murphy P, *et al*: The anthropometric assessment of dysmor-phic features in schizophrenia as an index of its developmental origins. *Psychol Med* 27:1155-1164, 1997

28) Ismall B, Cantor-Graae E, McNeil TF. Neurological abnormalities in schizophrenic patients and their siblings. *Am J Psychiatry* 155:84-89, 1998

29) DeLisi LE, Hoff AL, Kushner M, *et al* : Increased preva-lence of cavum septum pellucidum in schizophrenia. *Psychiatr Res Neuroimaging* 50:193-199, 1993
30) Swayze VW II, Andreasen NC, Ehrhardt JC, *et al* : Developmental abnormalities of the corpus callosum in schizophrenia. *Arch Neurol* 47:805-808, 1990
31) Andreasen NC, Nasrallah HA, Dunn V. *et al* : Structural abnormalities in the frontal system in schizophrenia. *Arch Gen Psychiatry* 43:136-144, 1986
32) Reveley MA, Reveley AM Hat size in schizophrenia. [Letter] *Arch Gen Psychiatry* 44:673-674, 1987
33) Stevens JR, Waldmon IN. Hat size in schizophrenia. [Letter] *Arch Gen Psychiatry* 44:673, 1987
34) Schiffman J. Ekstrom M. LaBrie J, *et al* : Minor physical anomalies and schizophrenia spectrum disorders: a prospective investigation. *Am J Psychiatry* 159:238-243, 2002
35) McGrath J. El-Saadi O. Grim V. *et al* : Minor physical anomalies and quantitative measures of the head and face in patients with psychosis. *Arch Gen Psychiatry* 59:458-464, 2002