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<td>Author(s)</td>
<td>Fujimaru, Kosuke; Imamura, Akira; Tsujita, Takahiro; Uraguchi, Mayuko; Hashida, Aoi; Mori, Takatoshi; Matsumoto, Sumitaka; Matsumoto, Shyunji; Okazaki, Yuji; Nakane, Yoshibumi</td>
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<tr>
<td>Citation</td>
<td>Acta medica Nagasakiensia. 2002, 47(3-4), p.133-137</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2002-12-17</td>
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<tr>
<td>URL</td>
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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.1,5 Based on these data the neurodevelopmental hypothesis of schizophrenia has been promoted.4,7 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 signs5, neuropathological findings5, dermatoglyphic signs4 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 syndactyly 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.10 High rates of MPAs have indeed been reported in many neurodevelopmental disorders including Down's syndrome5,11 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.12 The Waldrop scale is based on abnormalities found in Down's syndrome14 and is 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.12 The majority of studies that have examined the prevalence of MPAs in schizophrenia have used the Waldrop scale.5,10-12

In comparison studies between patients with schizophrenia and normal controls, more MPAs have consistently been found in patients with schizophrenia.5,10-12,23-25 The majority of studies that have examined the prevalence of MPAs in schizophrenia have used the Waldrop scale.5,10-12,23-25 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.26 However, there are few studies which investigate the association between MPAs and mental illness in Japanese patients.
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, 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. 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 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 item 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.

**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

<table>
<thead>
<tr>
<th>Waldrop scale score</th>
<th>Schizophrenia patients (N=313)</th>
<th>Normal controls (N=128)</th>
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<tbody>
<tr>
<td>0</td>
<td>58 (18.5%)</td>
<td>31 (24.2%)</td>
</tr>
<tr>
<td>1</td>
<td>64 (20.4%)</td>
<td>33 (25.8%)</td>
</tr>
<tr>
<td>2</td>
<td>86 (27.5%)</td>
<td>32 (25.0%)</td>
</tr>
<tr>
<td>3</td>
<td>46 (14.7%)</td>
<td>16 (12.6%)</td>
</tr>
<tr>
<td>4</td>
<td>35 (11.2%)</td>
<td>13 (10.2%)</td>
</tr>
<tr>
<td>5</td>
<td>14 (4.5%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>6</td>
<td>3 (1.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>7</td>
<td>4 (1.3%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>8</td>
<td>2 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>2.10</td>
<td>1.67</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>1.69</td>
<td>1.41</td>
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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. 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. In addition, higher scores on the comprehensive item of high-steepled palate have also been shown previously among patients with schizophrenia. 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. 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. Several investigators have measured head size in patients with schizophrenia and normal controls and reported no significant differences between the two groups. 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. 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. 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. 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.

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.

The Waldrop scale is limited in that it has relatively few assessment items and the definition of the weighted points is vague. 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.

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.

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