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RESEARCH ARTICLE

Investigation of second to fourth finger length ratio (2D:4D) in schizophrenia patients

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ABSTRACT

Objective: Schizophrenia is a significant burden for the patient and causes great costs for society. The etiology of schizophrenia, which is known to be a neurodevelopmental disorder, has not been fully elucidated. Differences in prenatal gonadal hormones have been suggested to play a role in the pathogenesis of schizophrenia. An easy way to evaluate a biomarker that gives insight about prenatal androgen is the second to fourth digit ratio (2D:4D) of the hand. In this study, we aimed to compare the 2D:4D ratio of schizophrenia patients to healthy controls and to investigate the relationship with positive and negative symptoms.

Method: Seventy-six patients with schizophrenia and 67 healthy controls were included in the study. Finger lengths were measured from the proximal finger crease to the tip using a digital vernier caliper with a precision of 0.01 mm. The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) were used to evaluate the symptoms of schizophrenia.

Results: While the left 2D:4D ratio of the patients with schizophrenia was not different from the controls', the right 2D:4D ratio was significantly lower. The correlation between finger lengths and the SAPS and SANS scores by gender showed a negative correlation of the left and right 2D:4D ratio with the SANS scores in female patients, while the SANS scores were found to be positively correlated with the right 2D:4D ratio in men.

Conclusion: The findings of our study support the view that the right 2D:4D ratio may be an indicator for schizophrenia.

Keywords: Digit ratio, estrogens, finger length ratio, schizophrenia, testosterone

INTRODUCTION

Schizophrenia constitutes a serious burden for the patient and significant expenses for society (1). Accordingly, studies seeking a better understanding of schizophrenia represent an important effort. While the neurodevelopmental nature of schizophrenia is known, its etiology is not fully understood. The pathophysiological mechanism of the disease has been shown to consist in an interaction between genetic and environmental factors, and a relation with an impairment of the central nervous system in the fetal period has been suggested (2,3). Sex hormones might be highly relevant for an understanding of individual differences in schizophrenia from a molecular perspective. A role of prenatal differences in gonadal hormones in the pathogenesis of schizophrenia has been proposed (4). Gonadal sex hormones such as testosterone and estrogen play a significant role in brain development (5). Gonadal androgens, especially testosterone, affect the migration of

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nervous cells, synaptogenesis, and the organization of dendritification (6). While it is still controversial, it is assumed that imbalanced exposure to sex steroids could be related to numerous diseases in adulthood, including certain cancers, fertility, heart diseases, and schizophrenia (7-10). As an approximate biological indicator for prenatal androgen, a simple measure is the evaluation of the 2D:4D ratio in the hand.

Determined in the 13th gestation week, the ratio between the lengths of the index finger (2D) and the ring finger (4D), expressed as 2D:4D, is a sexually dimorphic anatomical characteristic (11). This ratio, which remains relatively stable during adulthood, is considered as a marker for the intrauterine level of sex hormones (12-14). Correlations have been found between index finger length and estrogen levels in women and between ring finger length and testosterone level in men (15). These sexual differences in finger lengths are thought to be caused by different effects of sex steroids on the growth of the finger bones. In this framework, a low 2D:4D ratio can be considered to indicate high fetal testosterone and low estrogen levels, while a high 2D:4D ratio suggest higher fetal estrogen and lower testosterone levels (16). This effect is particularly prominent in the right hand, though the reason for this phenomenon is not yet clear (17). The ratio of 2nd to 4th finger is stable throughout life (18,19).

Until now, a number of studies examining the relation between the 2D:4D ratio and central nervous system diseases such as autism and schizophrenia have been carried out (10,15,20). Manning et al. (15) reported a significantly reduced 2D:4D ratio in children with autism spectrum disorder compared to healthy controls. Walder et al. (21) studied the 2D:4D ratio in adolescents with schizotypal personality disorder, where it was found to be increased in male patients compared with controls. Venkatasubramanian et al. (20) noted that in females with schizophrenia, the 2D:4D ratio was lower than in controls, while they found no difference in males. Most recently, Collinson et al. (10) compared the finger ratios between inpatients with a diagnosis of schizophrenia and outpatients, finding higher 2D:4D ratios in male schizophrenia patients. Furthermore, exposing pregnant rats experimentally to high testosterone levels led to low 2D:4D ratios and elongated 4Ds in the left and right front paws of their progeny (22).

It has been observed that sex steroid hormones can change the course and symptoms of schizophrenia (23). Especially high estrogen levels in female and high testosterone levels in male patients can have a positive effect on negative symptoms in schizophrenia (24-27). We hypothesize that the 2D:4D finger length ratio, which is assumed to be a likely indicator for intrauterine sex steroid hormone exposure, could be different in schizophrenia and might be related with illness symptoms. In Turkey, only a limited number of studies examine the relation between 2D:4D ratio and schizophrenia. Our aim was to compare the 2D:4D ratio in schizophrenic patients with healthy controls and to establish possible relations with positive and negative symptoms.

METHOD

In our study, we enrolled 76 patients with a diagnosis of schizophrenia according to DSM-IV followed at the psychiatric policlinic of Suleyman Demirel University Research and Training Hospital and 67 healthy controls. The control group was selected among hospital staff with similar sociodemographic characteristics coming in for periodic health checks. Individuals who were themselves affected by psychiatric disorders or who had first-degree relatives suffering from psychiatric conditions were not included in the study. All patients and controls were screened for fractures or other events that might affect the length and/or shape of their fingers. The participants were asked to place their hands palm upwards on a table and to extend their fingers as far as possible. Finger lengths were measured from the proximal finger crease to the tip, using a digital vernier caliper with a sensitivity of 0.01 mm, a common method of measurement for this kind of studies. Each finger was measured twice, and the arithmetic mean of the measurements was used for the statistical analysis. The 2D:4D ratio was calculated dividing the length of the index finger by the length of the ring finger.

Schizophrenia symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS). The study was approved by the local ethics committee, and written consent was received from all participants after providing detailed explanation of the study.

Measures

Scale for the Assessment of Positive Symptoms (SAPS): This instrument evaluates the level and spread of positive symptoms in schizophrenia, developed by Andreasen (28). Validity and reliability of the Turkish version were established by Erkoc et al. (29). It contains 34 items in 4 subscales: hallucinations, delusions, bizarre behavior, and positive formal thought.

Scale for the Assessment of Negative Symptoms (SANS): This instrument, also developed by Andreasen (28), measures the level and spread of negative symptoms in schizophrenia. Validity and reliability of the Turkish version were studied by Erkoc et al. (30). The scale includes 25 items in 5 subscales: affective blunting, alogia, avolition, anhedonia, and attention disorder.

Statistical Analysis

Data were evaluated using SPSS version 18. Normal distribution was controlled using Kolmogorov-Smirnov test. For the statistical analysis of normally distributed data, Student's t test was used; results were reported with mean and standard deviation. To measure the degree of difference in 2D:4D finger length ratio between patients and control group, Cohen's d effect size was calculated. For small, medium, and large effects, 0.2, 0.5, and >0.8 were used as standardized Cohen's d effect size. Covariance analysis (ANCOVA) was used to separate finger lengths according to sex. Relations between data within groups were examined using Pearson correlation analysis. Results were evaluated within a 95% confidence interval at a level of significance of $p<0.05$.

RESULTS

There was no significant difference between patient and control groups according to age (p=0.177) and sex (p=0.521) (Table 1). Finger lengths were evaluated as dependent variables by ANCOVA tests with diagnostic groups and sex covariance as independent variable. While left 2nd finger length and left 4th finger length showed no difference between schizophrenia patients and the control group ($F[1,140]=2.172$, $p=0.142$, $\eta_p^2=0.015$; $F[1,140]=1.100$, $p=0.296$, $\eta_p^2=0.008$, respectively), right 2nd and 4th fingers were significantly elongated compared with the controls ($F[1,140]=6.273$, $p=0.013$, $\eta_p^2=0.043$; $F[1,140]=15.850$, $p<0.001$, $\eta_p^2=0.102$, respectively). In groupwise comparison of the 2D:4D ratios, no difference was found for the left hand of schizophrenia patients ($F[1,140]=0.776$, $p=0.380$, $\eta_p^2=0.006$), while the ratio was significantly lower in the right hand ($F[1,140]=7.054$, $p=0.009$, $\eta_p^2=0.048$) (Table 2).

Table 1: Demographic characteristics and scale scores of the schizophrenia group and the control groups

	Schizophrenia (n=76)		Control (n=67)			
	Mean	SD	Mean	SD	t(df)/χ^2	p
Age	40.59	11.15	38.40	8.03	1.358 (135.8)	0.177[a]
Gender (%)						
Male	46	60.5%	37	55.2%	0.411	0.521[b]
Female	30	39.5%	30	44.8%		
SAPS	18.04	13.67				
SANS	25.88	9.58				

[a]Student's t test, [b]chi-square test, SAPS: Scale for the Assessment of Positive Symptoms, SANS: Scale for the Assessment of Negative Symptoms, n: number of participants, mean: mean value, SD: standard deviation, 2D: length of second finger, 4D: length of fourth finger.

Table 2: Finger lengths in the schizophrenia group and the control group

	Schizophrenia (n=76)		Control (n=67)		ANCOVA[a]		
	Mean	SD	Mean	SD	F(1.140)	p	η_p^2
Left 2D	69.48	5.45	68.26	3.40	2.172	0.143	0.015
Left 4D	70.08	5.62	69.12	3.24	1.100	0.296	0.008
Right 2D	69.05	4.50	67.43	3.52	6.273	0.013	0.043
Right 4D	71.65	5.51	68.99	3.22	15.850	<0.001	0.102
Left 2D:4D	0.992	0.040	0.987	0.025	0.776	0.380	0.006
Right 2D:4D	0.965	0.031	0.977	0.020	7.054	0.009	0.048

n: number of participants, mean: mean value, SD: standard deviation, 2D: length of second finger, 4D: length of fourth finger, η_p^2: partial eta squared, [a]Covariance analysis (ANCOVA) carried out after separation by sex.

Table 3: Mean 2D:4D ratio in the schizophrenia group and the control group by sex

	Schizophrenia		Control				
	Mean	SD	Mean	SD	t(df)	p[a]	Cohen's d
Female	(n=30)		(n=30)				
Left 2D:4D	1.001	0.049	0.985	0.028	1.456 (58)	0.151	0.376
Right 2D:4D	0.985	0.027	0.968	0.014	2.930 (44.3)	0.005	0.757
Male	(n=46)		(n=37)				
Left 2D:4D	0.986	0.032	0.989	0.022	-0.370 (81)	0.712	-0.082
Right 2D:4D	0.951	0.025	0.984	0.022	-5.966 (81)	<0.001	-1.317

[a]Student's t test, n: number of participants, mean: mean value, SD: standard deviation, 2D: length of second finger, 4D: length of fourth finger.

Table 4: Correlation between patients' SAPS and SANS scores and finger lengths

		Left 2D	Left 4D	Right 2D	Right 4D	Left 2D:4D	Right 2D:4D
Females							
SAPS	r	-0.114	0.071	-0.121	-0.013	-0.260	-0.231
SANS	r	0.024	0.480*	0.024	0.374	-0.589**	-0.759**
Males							
SAPS	r	0.083	0.076	-0.022	0.025	0.004	-0.099
SANS	r	0.088	0.003	0.160	-0.086	0.155	0.436*

*p<0.05, **p<0.01, r: Pearson correlation coefficient, SAPS: Scale for the Assessment of Positive Symptoms, SANS: Scale for the Assessment of Negative Symptoms, 2D: length of second finger, 4D: length of fourth finger.

Analysis by sex established that the right-hand 2D:4D ratio in female patients was significantly greater than in female controls (p=0.005), while in male schizophrenia patients, the right-hand 2D:4D ratio was significantly lower than in controls (p<0.001) (Table 3).

In the correlation between finger lengths and SAPS and SANS scores by sex, a positive correlation was found in female patients between SANS scores and left 4th finger lengths (r=0.480 p=0.020) and a negative correlation with left and right 2D:4D ratios (r=-0.589 p=0.003, r=-0.759 p<0.001). In male patients, a positive correlation was found between SANS scores and right-hand 2D:4D ratio (r=0.436 p=0.023). No significant difference was found between SAPS scores and finger lengths in either women or men (Table 4).

DISCUSSION

It is believed that intrauterine testosterone and estrogen levels are responsible for changes in the ratio of the 2nd to 4th finger lengths (14). It is also known that gonadal androgens, especially testosterone, play an important role in the migration of nerve cells, synaptogenesis, and the organization of dendritification. Furthermore, there is evidence for testosterone affecting neural factors responsible for communicative and social behavior (31). Thus testosterone can be related to the likely outcome of behavioral problems preceding the development of schizophrenia. In our study, we found a significantly lower 2D:4D ratio in the right hand of schizophrenia patients compared to the controls. In previous schizophrenia research, findings regarding the 2D:4D ratio and its asymmetry were not always consistent (10,32-34). In line with our study, Divakaran et al. (34) found a lower right-hand 2D:4D ratio in schizophrenia patients compared to healthy controls. In contrast to our results, though, they observed no difference between male patients with a diagnosis of schizophrenia and healthy controls in their 2D:4D ratios, while in patients with a family history of schizophrenia, the left-hand 2D:4D ratio was lower than in healthy controls. They emphasized that this difference might be related with the pathogenesis of schizophrenia, possibly indicating a genetic base only in male patients diagnosed with schizophrenia. In another study comparing 160 patients diagnosed with schizophrenia and 80 healthy controls, Arato et al. (32) observed a higher 2D:4D ratio both in male and in female patients with schizophrenia. Their results might indicate that schizophrenia patients could have been exposed to lower testosterone and higher estrogen concentrations in utero. The researchers assumed that there might be a relation between a low fetal androgen/estrogen ratio and premorbid personality in

schizophrenia. In a study comparing male schizophrenia patients and healthy controls in Turkey, Bolu et al. (33) found the right-hand 2D:4D ratio elevated and the left 2D:4D ratio lowered. By contrast, our study found a lower right 2D:4D ratio in male patients. It has been reported that exposure to testosterone affects the brain areas related with finger development and cerebral lateralization, inhibiting the growth of certain brain areas in the left hemisphere and facilitating it in the right hemisphere (5). The reason for our study and others in the literature finding different 2D:4D ratios right and left may lie in the different ways in which testosterone affects the left and right hemispheres of the brain. Interestingly, one meta-analysis concluded that the right-hand 2D:4D ratio was a more specific indicator of the prenatal testosterone exposure than the left-hand ratio (17), which might explain why in our study the right-hand 2D:4D ratios could be correlated with schizophrenia. It is accepted in the literature that the 2D:4D ratio may be a potential indicator for prenatal androgen exposure (35,36). This study suggests, in view of the different 2D:4D ratios, that schizophrenic male patients could have been exposed to elevated prenatal testosterone and female patients with schizophrenia to elevated prenatal estrogen concentrations. Although results for the 2D:4D finger length ratios in our study and others varied, we believe that this ratio could play a role in the pathogenesis of schizophrenia. It is possible that fetal exposures in early stages of development set off neurodegenerative changes triggering the development of schizophrenia.

Some studies have been done examining sex steroid levels and clinical symptoms in patients with schizophrenia. Studies on estrogen levels in female patients suggest a protective role regarding the clinical symptoms of the disease. It has been shown that high estrogen levels are correlated with a reduction in negative symptoms of schizophrenia (24,37). Adding estrogen to the therapy of females with schizophrenia also showed positive effects on negative and other psychotic symptoms (25,38-40). At the same time, testosterone may also show a protective effect against symptoms of schizophrenia. A number of studies reported an inverse relation between testosterone plasma concentration and negative symptoms in male patients (26,27,40). Furthermore, an addition of testosterone to the treatment of schizophrenic patients was found to improve negative symptoms significantly (41). In schizophrenia, even when the development of secondary sexual characteristics appeared normal, some studies reported that concentrations of luteinizing hormone (LH) and serum testosterone were reduced especially in patients with negative symptoms (42-44). In line with the literature, our study found a negative correlation between the increased 2D:4D ratio indicating high estrogen exposure and negative symptoms in female patients. With a higher 2D:4D ratio, we determined a reduction in negative symptoms. Similarly, in male patients we found a positive correlation between 2D:4D ratio and negative symptoms, suggesting that an elevated prenatal testosterone exposure could be related with a reduction in negative symptoms of schizophrenia.

It has been reported that in the developing brain, prenatal sex hormones can affect cortico-limbic networks that play a role in the management of stress, including structures like the amygdala and the hippocampus (45). It is also assumed that prenatal testosterone and prenatal estrogen modulate the expression of Hox genes playing a vital role in brain formation as well as in finger development (46,47). A defect in hormone levels may cause an abnormal expression of a Hox gene, which may in turn lead to anomalies in brain development and finger ratios. From this perspective, it is suggested that exposure to elevated prenatal estrogen or reduced prenatal testosterone levels during fetal development could cause an increase in the 2D:4D ratio as well as the risk of developing schizophrenia in adulthood. Vertebrate Hox genes, especially the posterior HoxA and HoxD genes expressed in urogenital and digit development, are of critical importance for the development of the axial skeleton and the limbs (46). In mice, the elimination of these genes leads to the absence of external genital organs and digit agenesis (48). Testosterone and estrogen modulate Hox gene expression in utero. Therefore, hormonal defects occurring cause abnormal Hox gene expression (47). Accordingly, prenatal disturbances in testosterone altering Hox complex expression may cause subsequent developmental anomalies reflected in the axial skeleton.

Our study has certain limitations. Firstly, finger lengths measurements were made using a digital caliper. Applying additional methods like the evaluation of electronically scanned photographs might strengthen the analyses. On the other hand, we measured each finger of the participants twice and used the arithmetic mean for our analysis, which strengthened our results. Secondly, the small sample size of our study limits the generalizability of the results.

Aim of our study was to investigate if the 2D:4D ratio was distinctive for schizophrenia patients. We found the right-hand 2D:4D ratios in schizophrenic

patients to be statistically significantly lower than in the control group. While the 2D:4D ratios are an indicator for prenatal androgen/estrogen levels, there is not enough evidence to assess them as a risk indicator for schizophrenia. Therefore, more confirmatory studies with larger samples are needed. The results of our study have showed that schizophrenia patients compared to controls had a lower 2D:4D ratio, which indicates higher prenatal testosterone or lower prenatal estrogen exposure during their fetal development.

Contribution Categories		Author Initials
Category 1	Concept/Design	F.K.
	Data acquisition	A.D., F.A.
	Data analysis/Interpretation	F.K., U.I.
Category 2	Drafting manuscript	F.K., U.I.
	Critical revision of manuscript	A.D.
Category 3	Final approval and accountability	F.K., U.I., A.D., F.A.
Other	Technical or material support	F.K., F.A.
	Supervision	A.D.

Ethics Committee Approval: This study was approved by Suleyman Demirel University Ethical Committee. (Date: 13.12.2018, Number: 251)

Informed Consent: Written informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declared no conflict of interest.

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