The Ratio of 2nd and 4th Digit Length in Autistic Children

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Objective: *To compare 2D:4D ratios of autistic to non-autistic children as a risk factor of autism.*
Material and Method: *A hospital based case-control study was conducted from March 2007 to July2008. Demographic data and general risk factors of autism had been collected using questionnaires from case and age matched control subjects aged 18 months to 15 years. Length of 2nd and 4th digits was measured by an electronic digital caliper.*
Results: *The ratio of right hand 2D:4D of autistic children was 0.99 ± 0.06 compared with 1.02 ± 0.04 of non-autistic children (p = 0.01). On the other hand, 2D:4D ratio of left hand of autistic children was 0.99 ± 0.07 while the ratio of non-autistic children was 1.01 ± 0.03 (p = 0.04). The 2D:4D ratio of both hands between 0.96 and 1.01 were risk factors of autism with odds ratio between 3.22 and 5.35 (p < 0.05).*
Conclusion: *The ratios of 2D:4D of both hands of autistic children were higher than non-autistic children. The ratios of 2D:4D between 0.96 and 1.01 of both hands associated with an increased risk of autism in children aged 18 months to 15 years.*

Keywords: *Autistic disorder, Fingers, Testosterone*

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Autism is a developmental and behavioral disorder characterized by communication and social deficits and behavioral problems. The worldwide prevalence is 4-58.7 per 10,000[1,2]. Diagnosis can be made by clinical criterions according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[3]. Measures of therapeutic result relied on the IQ of patients, severity of symptoms and age at enrollment to therapy[4-6]. Nowadays, causes of autism remain unclear even though there are a few theories mentioned, and a high level of intrauterine testosterone is the one among those described. A study in Cambridge, the United Kingdom (UK), found that the high level of intrauterine testosterone inversely related to social development but directly related to repetitive interest, which is a symptom of autism[7]. Another study in the UK also reported that children who had a high level of intrauterine testosterone from congenital adrenal hyperplasia had higher autistic spectrum scores from autistic spectrum quotient than normal children[8]. The high level of intrauterine testosterone also influences a ratio of the 2nd and the 4th digits (2D:4D ratio). Many studies found that the high level of intra-uterine testosterone was inversely related to 2D:4D ratio and it was also associated with autism and some studies reported that autistic children had lower 2D:4D ratio than non- autistic children[9-12]. However, the normal ratios were different between ethnics, *i.e.*, black ethnic had the lowest 2D:4D ratio and Asian ethnic had the highest ratio[13]. No study reported this ratio of Asian autistic children.

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Objective

The objective of the present study was to compare the 2D:4D ratio of autistic children to non-autistic children as a risk factor of autism. Results of the present study may lead to early detection for further measure of prevention, and early intervention for better quality of life and prognosis of autistic children.

Material and Method

A case-control study was conducted from March 2550 to July 2551 at Bangkok Metropolitan Administration Medical College and Vajira Hospital. There were 46 autistic children diagnosed by

developmental and behavioral pediatrician based on DSM IV criteria. Participants aged between 18 months and 15 years were recruited. The control group was an equal number of the same sex non-autistic children with age-matched within 6 month differences who visited an out-patient department in the same period. The present study excluded children who had any deformity of their digits, autistic spectrum disorder children who did not fulfill criterions following DSM IV such as PDD-NOS and Asperger syndrome, and children in whom their pivotal data for statistical analysis were not completed. Demographic data was collected by questionnaire; research assistants plotted the highest point of the 2nd and 4th digits and the lowest point at the same reference of both hands of all participants on pieces of white paper. A researcher was blinded to measure the length of digits twice from the unknown coded plotted white paper, using an electronic digital caliper (DP®) in millimeters with two decimals. The average numbers of the length of digits were used for statistical analysis.

Statistical analysis

Statistical analysis was performed by using SPSS (version 16). Demographic data was analyzed by descriptive analysis. Pearson's Chi-square or Fisher's Exact test was used to explore relations of categorical variables where appropriate. Independent t-test or Mann Whitney U-test was used to analyze continuous variables depending on data distribution. Mantel-Haenzel was performed to calculate odds ratios with 95% confidence interval (95% CI). Correlation coefficients between the length of right and left hand's indexes were performed by regression analysis. ROC curve was generated to evaluate a property of the ratios to predict autism. Statistical significance was declared if p-value was less than 0.05.

Results

Of 92 subjects, there were 46 participants from the case and control groups, which were 39 males (84.8%) and seven females (15.2%) equally. Mean of age was 63.00 $\pm$ 26.32 months in the autistic group and 62.96 $\pm$ 32.02 months in the control group. There were no differences of parental education and their household income between case and control groups as shown in Table 1. The lengths of digits were not different between case and control (Table 2) but the ratios of 2D/4D were statistically significant between the two groups (p = 0.01 of right hand, and p = 0.04 of left hand). The 2D:4D ratio of right hand of autistic children was 0.99 $\pm$ 0.06 while the control group was

Table 1. Demographic data

Factors	Case (%) n = 46	Control (%) n = 46	p-value
Mean of age (month $\pm$ SD)	63.00 $\pm$ 26.32	62.96 $\pm$ 32.02	0.99*
Sex			
Male	39 (84.8)	39 (84.8)	
Female	7 (15.2)	7 (15.2)	1.00**
Paternal education			
Primary school or lower	8 (17.4)	12 (26.1)	
Secondary school	25 (54.3)	21 (45.7)	
Vocational school	9 (19.6)	9 (19.6)	
Graduate	0 (0)	1 (2.2)	
Post-graduate or higher	4 (8.7)	3 (6.5)	0.68**
Maternal education			
Primary school or lower	15 (32.6)	13 (28.3)	
Secondary school	7 (15.2)	16 (34.8)	
Vocational school	7 (15.2)	6(13.0)	
Graduate	13 (28.3)	10 (21.7)	
Post-graduate or higher	4 (8.7)	5 (5.4)	
Paternal age (years), mean $\pm$ SD	38.67 $\pm$ 7.84	41.33 $\pm$ 12.46	0.23*
Maternal age (years), mean $\pm$ SD	34.67 $\pm$ 6.67	35.28 $\pm$ 7.89	0.69*
Household income (baht/month), mean $\pm$ SD	21,478.74 $\pm$ 16,542.19	18,277.89 $\pm$ 14,293.46	0.32*

* Independent t-test, ** Pearson Chi-square test

Table 2. Length of 2D and 4D of autistic children and control

Factor	Case (mean; mm ± SD)	Control (mean; mm ± SD)	p-value*
2nd digit; Rt	56.57 ± 9.18	54.92 ± 10.45	0.42
4th digit; Rt	57.14 ± 9.44	53.75 ± 10.58	0.11
2nd digit; Lt	55.58 ± 9.08	54.74 ± 10.81	0.69
4th digit; Lt	56.33 ± 9.79	54.32 ± 10.90	0.36

* Independent t-test

Table 3. Odds ratios of 2D:4D of autistic children and control

Ratio of right 2D:4D	Odds ratio (95% CI)	p-value*	Ratio of left 2D:4D	Odds ratio (95% CI)	p-value*
0.95	5.35 (1.09 to 26.33)	0.55	0.95	6.75 (0.78 to 58.50)	0.18
0.96	6.16 (1.87 to 20.18)	<0.01	0.96	9.63 (2.97 to 31.25)	<0.01
0.98	8.08 (2.48 to 26.28)	<0.01	0.98	13.65 (4.20 to 44.41)	<0.01
1.00	7.44 (2.93 to 18.92)	<0.01	1.00	16.90 (6.03 to 47.35)	<0.01
1.01	3.22 (1.37 to 7.56)	0.01	1.01	7.39 (2.81 to 19.40)	<0.01
1.02	2.78 (1.06 to 7.3)	0.06	1.02	1.47 (0.62 to 3.48)	0.51

* Mantel-Haenzel test

1.02 ± 0.04. Left hand 2D:4D ratio of autistic was 0.99 ± 0.07, and the control was 1.01 ± 0.03 as shown in Fig. 1 and 2. In respect to Mantel-Hanszel, 2D:4D ratios between 0.96 and 1.01 were risks of autism statistically significant with odds ratio between 3.22 to 8.08 for ratio of right hand and 7.39 to 16.90 for the left hand respectively as presented in Table 3. Area under ROC curve of the 2D:4D ratio of right hand was 0.69 (Fig. 3) and left hand was 0.78 (Fig. 4). There was a correlation between the 2D:4D ratios of right hand and those of the left hand statistically significant with correlation coefficient 0.48 ($p < 0.01$) as shown in (Fig. 5).

Discussion

The present study revealed that 2D:4D ratios between 0.96 and 1.01 were able to predict risks

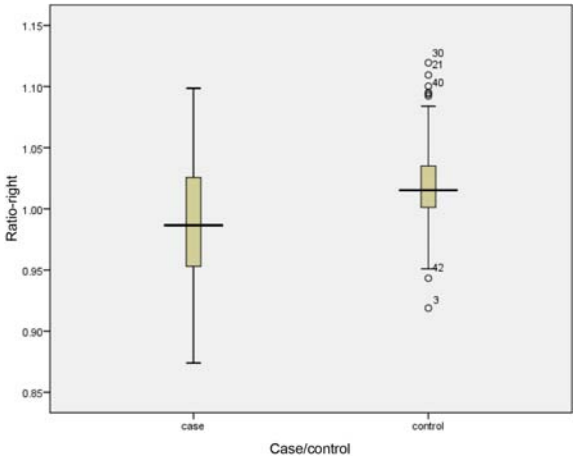

Fig. 1 Box plot 2D:4D ratio of right hand of autistic and control subjects

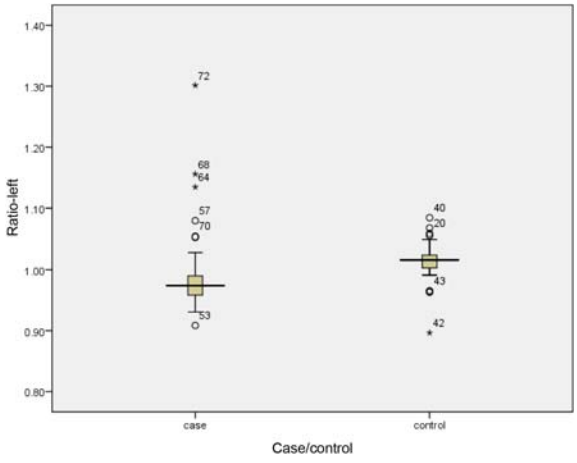

Fig. 2 Box plot of 2D:4D ratio of left hand of autistic and control subjects

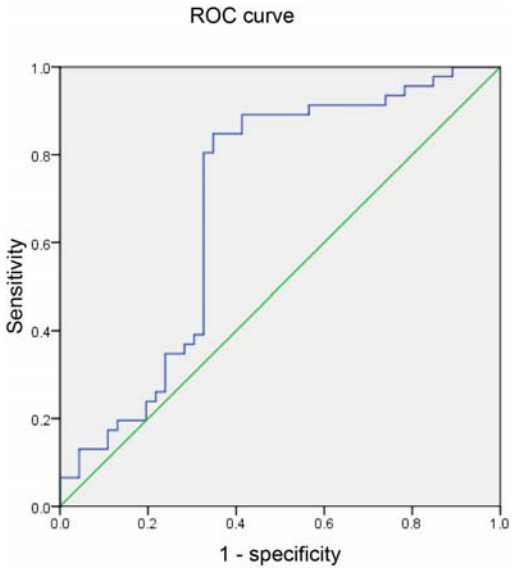

Fig. 3 ROC Curve of 2D:4D of right hand

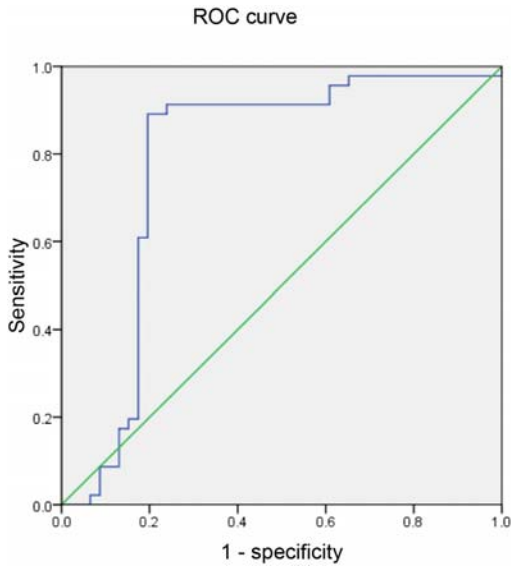

Fig. 4 ROC Curve of 2D:4D ratio of left hand

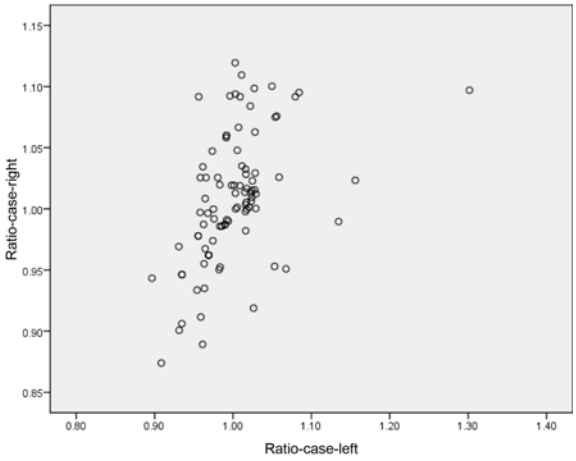

Fig. 5 Relationship between 2D:4D of right hand and left hand

of autism as reported in other studies[9,11,12]. We have evidence that autism is difficult to diagnose before 18 months, even though there are some clinical symptoms in the first year of life[14-16]. This method may be helpful for this purpose if there is more evidence from research into children younger than 18-month-old. The results of the present study may not be able to generalize to the general population beyond the age range in the present study. However, ratios that can predict risks of autism differ from those found in European studies[11,12]. This may be caused by ethnics as a report showed that Asian ethnic had the highest 2D:4D ratios[13]. As a result, clinical implementation should be based on data from the same origin. Although the 2D:4D ratios may be able to predict the risks of autism, it is an indirect cause. The direct cause should be evaluated by measuring a level of intrauterine testosterone, which is one of the suspected causes of autism[7,8,17]. If we can do so, it will help us to diagnose autism earlier since intra-uterine life. Apart from that, most subjects in several studies on autism were males, which is similar to the present study[18]. This may be a limitation for generalization to female subjects. The other limitation of the present study is accuracy of the measurement from the electronic digital caliper that was able to measure only two decimals. Rounding up the number may affect accuracy to the measurement, and measurement in young children may not be reliable because of their cooperation. Roentgenogram of hands and direct measure from pharangeal bones may be a remedy to improve accuracy for further study and clinical implementation in a clinical setting. In addition, the small samples of the present study is also one of limitations, and this leads to low precision and small effect size, which is shown by wide ranges of confidence interval; increasing subjects in replicated study or a meta-analysis will eliminate this limitation. Thus, prospective studies with a larger population are also suggested to support this theory.

Conclusion

The ratios of 2D:4D of both hands between 0.96 and 1.01 associated with an increase risk of autism in children aged 18 months to 15 years. In addition, there was no difference of predictive abilities between both hands.

Acknowledgements

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สัดส่วนความยาวของนิ้วชี้และนิ้วนางในเด็กออทิสติก

พงษ์ศักดิ์ น้อยพยัคฆ์

วัตถุประสงค์*: เพื่อเปรียบเทียบสัดส่วนความยาวนิ้วชี้ต่อนิ้วนางของเด็กออทิสติกและเด็กที่ไม่ได้เป็นออทิสติก และความสามารถในการใช้สัดส่วนของนิ้วชี้และนิ้วนางในการทำนายความเสี่ยงต่อการเกิดออทิสซึม*

วัสดุและวิธีการ*: เป็นการเก็บข้อมูลพื้นฐานและข้อมูลทางคลินิกด้วยแบบสอบถามในผู้ป่วยเด็กออทิสติก และเด็กที่ไม่ได้เป็นออทิสติกอายุระหว่าง 18 เดือน ถึง 15 ปี ซึ่งเข้ารับบริการที่หน่วยพัฒนาการเด็ก ภาควิชากุมารเวชศาสตร์ วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล ระหว่างเดือนมีนาคม พ.ศ. 2550 ถึง เดือนกรกฎาคม พ.ศ. 2551 และทำการวัดความยาวนิ้วชี้และนิ้วนางของมือทั้งสองข้างด้วยเครื่องวัดชนิดดิจิตอล นำมาคำนวณสัดส่วนและความเสี่ยงในการเกิดออทิสซึม*

ผลการศึกษา*: สัดส่วนของนิ้วชี้ต่อนิ้วนางของมือข้างขวาของเด็กออทิสติกมีค่าเท่ากับ 0.99 $\pm$ 0.06 ขณะที่เด็กที่ไม่เป็นออทิสติกมีค่าเท่ากับ 1.02 $\pm$ 0.04 มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p = 0.01$) สัดส่วนนิ้วชี้และนิ้วนางของมือข้างซ้ายในเด็กออทิสติกเท่ากับ 0.99 $\pm$ 0.07 ส่วนเด็กที่ไม่เป็นออทิสติกเท่ากับ 1.01 $\pm$ 0.03 และมีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p = 0.04$) ค่าสัดส่วนของนิ้วระหว่าง 0.96 และ 1.01 สามารถทำนายความเสี่ยงต่อการเกิดออทิสซึมได้อย่างมีนัยสำคัญทางสถิติ ($p < 0.05$) โดยมี odds ratio อยู่ระหว่าง 3.22 และ 5.35*

สรุป*: สัดส่วนของนิ้วชี้ต่อนิ้วนางระหว่าง 0.96 และ 1.01 ของมือทั้งสองข้างมีความสัมพันธ์กับความเสี่ยงของการเกิดออทิสซึมในเด็กอายุระหว่าง 18 เดือนและ 15 ปี*