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Finger bone immaturity and 2D:4D ratio measurement error in the assessment of the hyperandrogenic hypothesis for the etiology of autism spectrum disorders

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Abstract

Emerging hypotheses suggest a causal role for prenatal androgen exposure in some cases of autism spectrum disorders (ASD). The ratios of the lengths of the bones of the 2nd to the 4th digit (2D:4D) are purported to be markers for prenatal androgen exposure and to be established early in gestation. Elongation of the 4th digit in response to testosterone is said to reduce 2D:4D in males versus females. We examined the ratios of bones from the left hand radiographs of 75 boys and 6 girls 4–8 years of age, diagnosed with ASD, to evaluate digit ratio as a marker for gestational androgen exposure. Contrary to our expectations, girls had reduced 2D:4D compared to boys but the difference was not significant (Cohen's D 0.51–0.66, P>0.05). The limited sample size for this study and the absence of a referent group precluded providing robust estimates for girls and identifying possible statistical differences between the sexes. Tanner-Whitehouse 3 (TW3) rating of finger bone growth suggested relative immaturity of the 4th relative to the 2nd digits. Positive correlations were detected for 2D:4D ratios, body mass index (r=0.23, P=0.039), chronologic age (r=0.35, P=0.001), and skeletal age (r=0.42, P<0.0001). The TW3 ratings and associations between 2D:4D ratios and indicators of growth suggest that digits develop at different rates. This asynchronous development may produce differences in 2D:4D over time which could lead to erroneous interpretation of androgen exposure *in utero* among young ASD children.

Keywords

Autism spectrum disorder; digit ratio; hyperandrogenic hypothesis; measurement error

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1. Introduction

Autism spectrum disorders (ASD) are a subset of the Pervasive Developmental Disorders that include autistic disorder (autism), Asperger's syndrome, and atypical autism (Pervasive Developmental Disorder - Not Otherwise Specified) [1]. A comprehensive understanding of the etiology of ASD remains elusive [2]; however reports of excess ASD diagnoses among males, approximately 4:1 compared with females [3], suggest an important role for X-linked risk factors [4], such as prenatal androgen exposure. This suggests that ASDs may comprise 'hyper-male' phenotypes [5] and motivates the so-called 'hyper-androgenic' etiologic hypothesis.

Digit ratio, defined as the length of the 2nd digit divided by the length of the 4th digit (2D:4D), is purported to be a marker for androgen exposure *in utero* [6]. During gestation, development of the bones of the hands, the metacarpals and phalanges, are governed by the Hox/Homeobox genes, which also orchestrate development of the male reproductive tract, and respond to circulating androgens [7]. Excess androgen exposure secondary to fetal testis synthesis at approximately seven weeks of gestation [8] elicits elongation of the 4th digit relative to the 2nd digit, and thus lower 2D:4D ratios are generally indicative of higher *in utero* androgen exposure [9].

Investigators have previously employed the 2D:4D ratio as a marker of exposure to test hypotheses concerning androgen exposure *in utero* as an etiologic factor for ASD. One report found children with autism or Asperger's syndrome, along with their 1st-degree relatives (unaffected siblings, mothers, and fathers), to have significantly lower 2D:4D ratios than sex-matched controls [10]. More recently, lower 2D:4D ratios from the right and left hands of boys with autism, as well as other disorders of the autism spectrum, were reported in comparison to a reference group [11]. A contemporary review of the literature underscores the consistency of these reports describing inverse associations between 2D:4D ratio, indicating a more masculine pattern among subjects receiving ASD diagnoses [12]. However, the magnitude of these reported associations demonstrates substantial variability.

The aim of this study was to further consider the tenability of left hand 2D:4D as a marker of *in utero* androgen exposure among children with ASD for investigation of the hyper-androgenic etiologic hypothesis. We employed several markers of bone maturity and growth to evaluate the dynamic nature, if any, of 2D:4D ratios and thereby characterize variability within-subject which might confuse assessment of prenatal androgen exposure using this approach. A secondary data analysis was conducted in which the left hand radiographs of 81 children diagnosed with autism or non-autism ASD were measured for digit length, 2D:4D ratios, bone maturity and growth indicators.

2. Methods

This study is part of an exploratory study designed to investigate the growth, maturation, and hormonal profiles of pre-pubertal children with ASD [13]. Briefly, 81 four to eight year olds, including 75 boys and six girls, with a clinical diagnosis of idiopathic autism, Asperger's Syndrome, or PDD-NOS were recruited between March, 2002 and February, 2004. Classification of all participants was confirmed by the Autistic Diagnostic Observation Schedule-Western Psychological Services Edition (ADOS) [14]. In addition, the parent study included a sample of same-aged children (59 boys and 21 girls) recruited from other clinics as controls. All participants received a physical examination, and parents completed a brief structured interview regarding demographic factors and medical history. The parent identified the race of the study participant as Caucasian, African American, Asian, or Other, and ethnicity as Hispanic or non-Hispanic. A left hand-wrist ventral surface radiograph was taken for each

of the 81 ASD participants, although not for the control children because of risk/benefit safety concerns raised by our institutional review boards. The study protocol was approved by the institutional review boards of both the Cincinnati Children's Hospital Medical Center, Cincinnati, OH, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD.

Bone lengths for the metacarpals and phalanges of the 2nd and 4th digits were measured to the nearest 0.10 mm using a digital caliper by a single observer. Measures were taken in duplicate from the proximal end of the bone epiphysis to the mid-point of the distal end of the bone, along the mid-point of the shaft. Skeletal age and the maturity of the finger bones of the thumb, the 3rd and the 5th digits (assigned by anatomical position) was assessed using the 3rd edition of the Tanner-Whitehouse rating system (TW3) [15]. The TW3 rating system is a standardized method for evaluating bone maturity, during which a left hand radiograph is employed to assign a score to each of 27 bones comprising the wrist and hand, contingent on the degree of ossification at the epiphyseal plates. The TW3 scores are summed and standardized to a group of 3,000 healthy boys and girls to generate a 'skeletal age' which may then be compared to chronologic age to assess the pace of maturation.

Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC). Statistical significance was defined as $P<0.05$ for a two-tailed test. Measurement reliability on duplicate measures was assessed using intra-class correlation coefficients (ICC), which characterized the proportion of variability in observed values due to measurement error within-observer. Non-parametric bivariate analysis was employed to evaluate associations between digit ratios, age (chronologic and skeletal) and body mass index (BMI). We used the Student's T-test to examine 2D:4D ratios by race/ethnicity and sex, and the effect of the latter was characterized by Cohen's D using pooled standard deviations [16]. Bone maturity was assessed by taking the difference of TW3 scores for the 3rd and 5th digits within-subject and tested with the Wilcoxon signed-rank test.

3. Results

Of the 81 study participants, there were 75 (92.6%) males and six (7.4%) females, ranging in chronologic age from four to eight and in skeletal age from four to 11 years. Most were Caucasian (71, 87.7 %), with five African American, one Asian and four participants of unidentified racial classification (one of whom was described as being of Hispanic ethnicity). The mean (SD) BMI of participants was 17.9 (3.7), range 13.9 to 34.1.

All ICCs for the metacarpals and phalanges exceeded 0.70 (range 0.71 to 1.00) indicating a degree of measurement error consistent with prior reports [17]. Table 1 displays the mean finger bone length ratios, for the 2nd to 4th digits, by sex for all subjects, as well as the Cohen's D and pooled standard deviation for their differences. The 2D:4D ratio of phalanges for boys was 0.923 (95% confidence limit (CL) 0.918–0.929), and for girls 0.910 (95% CL 0.877–0.943). The 2D:4D ratio of the metacarpals, and sum of metacarpals and phalanges all exceeded 1.00. Compared with girls, boys had larger 2D:4D ratios, for phalanges (0.923 versus 0.910), for the metacarpals (1.192 versus 1.170) and for the sum of metacarpals plus phalanges (1.028 versus 1.013) respectively. These differences corresponded to moderate effect sizes; Cohen's D values exceeded 0.50 but not 0.80. However, no statistically significant differences (i.e., $P>0.05$) were detected between boys and girls, nor by race/ethnicity (data not shown).

Table 2 presents Spearman rank correlation coefficients between 2D:4D ratios, and indicators of growth including chronologic and skeletal ages, and BMI. The 2D:4D ratio of phalanges was significantly correlated with chronologic age ($r=0.30$, $P=0.007$) and skeletal age ($r=0.39$, $P<0.001$), and the 2D:4D ratio of the sum of the phalanges and metacarpals was significantly

correlated with chronologic age (r=0.35, P=0.001), skeletal age (r=0.42, P<0.001), and BMI (r=0.23, P=0.039). However, no significant correlation was detected between chronologic age, skeletal age or BMI and the 2D:4D ratio of metacarpals.

Table 3 presents the results of the bone maturity analysis for the 3rd (i.e., middle) and 5th (i.e., pinky) digits of the left hand. Zero indicates identical bone maturity stages, a positive score indicates greater maturity of the 3rd (i.e., lateral) compared to the 5th (i.e., medial) digit, and negative scores indicate the opposite. Scores ranged from zero to three with all mean differences exceeding zero (P<0.0001 for paired differences). Almost two-thirds (65.4%) of subjects demonstrated a qualitatively immature 5th relative to 3rd metacarpal, and nearly half (48.1%) demonstrated a similar pattern for the middle phalange.

4. Discussion

We here report the detection of statistically significant and positive correlations between left hand 2D:4D ratios, of phalanges and metacarpals plus phalanges, measured in boys and girls diagnosed with ASD and chronologic age, skeletal age and BMI. No statistically differences were detected in 2D:4D ratios by sex, however rating of skeletal maturity using the TW3 method suggested that relative digit development was not complete in our sample of children. This might have caused misinterpretation of the 2D:4D ratio in attempting to determine exposure to androgens *in utero*. The latter is underscored by the absence of associations between chronologic age, skeletal age and BMI with the 2D:4D ratio of metacarpals but the detection of significant positive correlations with the 2D:4D ratio of phalanges (i.e., may reflect differential bone development 'within-digit' at these ages). Left hand 2D:4D ratios among ASD cases may thus not be fixed throughout childhood and, therefore, during this life phase might not accurately reflect prenatal androgen exposure.

Studies of terminated fetuses, at various stages of gestation, have lead to the conviction that sex-specific differences in relative digit length begin as early as three months gestation and become greater over time [18,19]. Sex differences in 2D:4D from as early as one year of age have been reported by several investigators. For example, McIntyre et al. [20] reported sex differences between males and females from data obtained in a longitudinal serial study of 124 subjects, aged one to 17 years of age. Likewise, a mean 2D:4D for the phalanges equal to 0.98 for 400 males aged two to 25, and 1.00 for 400 females of similar age was reported from a cross-sectional study [9]. No such difference was found in the current study using 2D:4D ratios for the phalanges, the metacarpals, or the sum of phalanges and metacarpals, and, in fact, we observed moderate sized effects [16] in the direction opposite of that which we anticipated (i.e., boys demonstrated greater average 2D:4D than girls). We suspect that our observations are a reflection of problems with interpreting 2D:4D data because of the high degree of variability in children whose digits are still maturing. However, the limited sample of girls available for this study (n=6) does not provide sufficient statistical power for the detection of 2D:4D sex differences and thus point estimates for sex-differences are likely to be substantially influenced by sampling error. It is worth noting that our finding of statistically similar metacarpal 2D:4D ratios for boys and girls has been recently reported for metacarpal ratios in African-American and European-American adults [21].

In addition to comprising participants diagnosed with ASD, our study sample was generally younger than those for which statistically significant associations were reported for digit ratio and sex. If a trend towards a sexually dimorphic relative digit length was not in fact in effect within the age range of the majority of our subjects, then variability within-subject may have introduced exposure misclassification into the study and potentially biased our results towards the null hypothesis. The possibility that post-natal factors may influence relative finger bone length has been previously raised [18]. Investigators have speculated that relative finger growth

may not be complete until some time during adolescence [19]. In a longitudinal sample of two to 10 year olds, McIntyre and colleagues [22] reported a declining 2D:4D ratio from subjects six to eight years of age and found that the ratio was an unreliable marker for sex. Thus, while sex-specific differences in relative digit length may be initiated *in utero*, they might vary during childhood growth in keeping with the differential maturation of the digits, to appear fixed after puberty when hand maturation is complete.

Prior to the completion of puberty, the non-uniform pattern of vertebrate digit development (i.e., sequential progression from the lateral to the medial aspect of the hand when in anatomical position) might introduce substantial within-subject variability into 2D:4D ratios [23]. Our findings, though cross-sectional in nature, suggest that digit ratio remains a dynamic quantity until later in development among children with ASD, and may thus not be a useful indicator of prenatal androgen exposure among ASD cases during active phases of growth. This was corroborated by bone maturity estimates employing the 3rd and 5th digits, which indicated that a substantial proportion of study subjects had medial digits that were less mature than those more lateral and could therefore presumed to be shorter relative to their expected size at maturation. This would tend to bias the 2D:4D ratio upward. The statistically significant correlations between 2D:4D and measures for age (i.e., chronologic age) and growth (i.e., skeletal age) further suggest ongoing development of the ratio of digits among subjects in this study. However, the cross-sectional nature of this study precludes assessment of temporality with regard to digit immaturity. While the positive correlations detected between 2D:4D and chronologic age [22] and BMI [24] are not novel, to our knowledge, this report constitutes the first report of a positive correlation between 2D:4D ratio and skeletal age.

There are several limitations to the current study which necessitate caution in the interpretation of the study results. A fundamental condition to our interpretation of the study results is that left-hand 2D:4D ratios are valid markers of androgen exposure *in utero*, a reasonable presumption [25]. However, right hand 2D:4D ratios are known to be more strongly sexually differentiated than left hand 2D:4D ratios and frequently show more pronounced effects with target traits [26,27]; these measures were unfortunately not available for this study. The limited sample size available for this study, with regard to girls and non-Caucasian races/ethnicities in particular, undermined our ability to detect previously reported differences in digit ratios by these characteristics [28]. Moreover, the absence of control group radiographs precluded comparison of digit ratio between ASD cases and controls, an unfortunate consequence of the nature of the parent study from which this secondary analysis was completed.

Our study employed a minority method, hand radiographs, to ascertain 2D:4D [29] and thus limits our ability to evaluate our results in the context of prior studies. Comparative studies employing hand radiographs are limited [30,31]. Differences, in particular between radiographs, photocopies, and direct measures of 2D:4D ratios may be due in part to hand position and incorporation, or lack thereof, of soft tissue, basal and tip fat pads in particular, the development of which may also be responsive to androgens [32]. Thus, comparisons using the results from this study must be made with caution.

This study of boys and girls with ASD raises several questions with regard to the nature of 2D:4D ratios throughout growth and development. We present several indicators of inconsistent digit maturation among our subjects raising the possibility of ongoing relative digit length development among children aged four to eight years and diagnosed with ASD. This study showed no significant difference in 2D:4D ratios between the sexes and point estimates for boys were higher than those for girls, which we suspect is a consequence of dynamic 2D:4D ratios at these ages, in spite of the small number of girls in this study. In conclusion, our study suggests that 2D:4D ratios should be used cautiously as a marker for prenatal androgen

exposure among young children when investigating the ASD hyper-androgenic hypothesis as ongoing 2D:4D development may lead to erroneous interpretation.

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Table 1

Mean of ratios of finger bone lengths (95% CL), for the 2nd to 4th digits (2D:4D), by sex and Cohen's D (SD) for the difference between sexes.

Digit ratio	Phalanges	Metacarpal	Sum
Boys (n=75)	0.923 (0.918–0.929)	1.192 (1.184–1.200)	1.028 (1.023–1.033)
Girls (n=6)	0.910 (0.877–0.943)	1.170 (1.137–1.203)	1.013 (0.986–1.041)
Cohen's D (SD)	0.514 (0.025)	0.620 (0.035)	0.662 (0.022)

NOTE: No statistically significant differences (P>0.05) between boys and girls.

CL, confidence limits; SD, pooled standard deviation; Sum, sum of lengths of the metacarpal and phalanges.

Table 2

Spearman rank correlations coefficients (P-value) between 2D:4D ratio, age, BMI, and sex (n=81).

	Age		BMI	Sex [a]
	Chronologic	Skeletal		
Phalanges	0.30 (0.007)	0.39 (<0.001)	0.14 (0.216)	0.01 (0.230)
Metacarpal	0.09 (0.408)	0.06 (0.569)	0.18 (0.107)	0.02 (0.150)
Sum	0.35 (0.001)	0.42 (<0.001)	0.23 (0.039)	0.01 (0.124)

[a] Mean difference, P-value from Student's T-test.

BMI, body mass index (kg/m^2); Sum, sum of lengths of the metacarpal and phalanges; 2D:4D, length of bone in the 2nd digit divided by that in the 4th digit.

Table 3

Distribution for differences between maturity scores among bones in the 5th and 3rd digits and number of subjects demonstrating immature 5th relative to 3rd digit finger bones (n=81).

	Metacarpal	Proximal phalange	Middle phalange	Distal phalange
Mean (SD) difference	0.35 (0.48)*	0.20 (0.40)*	0.52 (0.59)*	0.22 (0.47)*
n (%) differences >0[a]	53 (65.4)	16 (19.8)	39 (48.1)	15 (18.5)

NOTE: Difference calculated as ordinal scale numeric score assigned to the Tanner-Whitehouse 3 skeletal maturity rating system (TW3) value for finger bones in the 3th digit minus those assigned for the same finger bones in the 5rd digit [15].

[a]Remaining values equal to 0.0 suggesting completion of development for those subjects.

*P<0.0001 for Wilcoxon signed rank test for paired difference.