http:// ijp.mums.ac.ir
Original Article

The Ratio of Second to Fourth Digit Length (2D:4D) in Children with Autistic Disorder

Javad Baharara[1], *Maryam Hojjati [2], Hashem Rasti[3], Malihe Sarabi jamab[4]

[1]Department of Developmental Biology, Animal Developmental of Applied Biology Research Center, Mashhad Branch, Islamic Azad University, Mashhad, Iran.
[2]Head of Noor Hedayat, Center of Autism Spectrum Disorders, Mashhad, Iran.
[3]PhD Student of Developmental Biology, Young Researchers and Elite Club, Mashhad Branch, Islamic Azad University, Mashhad, Iran.
[4] Noor Hedayat, Center of Autism Spectrum Disorders, Mashhad, Iran.

Abstract

Introduction

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 digits (2D:4D) are purported to be markers for prenatal androgen exposure and to be established early in gestation. Ratio of second and fourth digits (2D:4D) is usually used as a proxy for prenatal testosterone.

Methods and Materials

In this study, 2D:4D on 48 children with ASD (Case group) and in 41 normal child (Control group) were measured. Two groups were matched with the gender and age. Both groups were selected by convenience sampling method. All statistical analyses were performed using SPSS version 19 software, considering as significant less than.

Results

Results showed that the average ratio of 2D:4D in ASD children were lower than the ratio in control group ($P<0.05$). 2D to 4D finger-length ratio of the right of children with autism was lower than the normal children ($P<0.05$); while this difference was not significant between the two groups in the left hand ($P>0.05$).

Conclusion

The results indicate that the 2D:4D ratio could be used together with other parameters as an indicator of the likelihood of developing autistic traits in offspring. Results achieved in this research can be valuable in further biological and psychological approaches in neurocognitive research and diagnostics of children from ASD.

Key Words: Autism spectrum disorders , Digit ratio, 2D:4D ratio, Testosterone.

* ***Corresponding Author:***

Dr. Maryam Hojjati, Head of Center of Autism Spectrum Disorders, Mashhad, Iran.
Email: Hojjati_37@yahoo.com
Received date: Jun 15, 2014 ; Accepted date: Jul 22, 2014

Introduction

Autism is a neurodevelopmental disorder characterized by impaired social interaction, verbal and non-verbal communication, and by restricted and repetitive behavior. The diagnostic criteria (1,2) require that symptoms become apparent before a child is three years old (3). Autism affects information processing in the brain by altering how nerve cells and their synapses connect and organize; how this occurs is not well understood (4). It is one of three recognized disorders in the autism spectrum (ASDs), the other two being Asperger syndrome, which lacks delays in cognitive development and language, and Pervasive developmental disorder, not otherwise specified (commonly abbreviated as PDD-NOS), which is diagnosed when the full set of criteria for autism or Asperger syndrome are not met (5-7).

Autism has a strong genetic basis, although the genetics of autism are complex and it is unclear whether ASD is explained more by rare mutations, or by rare combinations of common genetic variants (8). In rare cases, autism is strongly associated with agents that cause birth defects (9). Controversies surround other proposed environmental causes, such as heavy metals, pesticides or childhood vaccines (10); the vaccine hypotheses are biologically implausible and have been disproven in scientific studies (11). The prevalence of autism is about 1–2 per 1,000 people worldwide, and it occurs four to five times more often in boys than girls(12,13). The Centers for Disease Control and Prevention (CDC) report 1.5% of children in the United States (one in 68) are diagnosed with ASD as of 2014 a 30% increase from one in 88 in 2012 (11-15). The number of people diagnosed with autism has been increasing dramatically since the 1980s, partly due to changes in diagnostic practice and government-subsidized financial incentives for named diagnoses (16); the question of whether actual prevalence has increased is unresolved (12).

Parents usually notice signs in the first two years of their child's life (17).The signs usually develop gradually, but some autistic children first develop more normally and then regress (18). Early behavioral, cognitive, or speech interventions can help autistic children gain self-care, social, and communication skills (17). Although there is no known cure (17), there have been reported cases of children who recovered (19).

Results shown a comprehensive understanding of the etiology of ASD remains elusive (20); however reports of excess ASD diagnoses among males, approximately 4:1 compared with females (21), suggest an important role for X-linked risk factors (22-24), such as prenatal androgen exposure. This suggests that ASDs may comprise ‘hyper-male’ phenotypes (25) and motivate the so-called ‘hyperandrogenic’ etiologic hypothesis (Figure.1). 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 (26). During gestation, development of the bones of the hands, the metacarpals and phalanges, are governed by the Homeobox (Hox) genes, which also orchestrate the development of the male reproductive tract, and respond to circulating androgens (27). Excess androgen exposure secondary to fetal testis synthesis at approximately seven weeks of gestation (28) 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 (29). 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 (30).

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 (31). 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 (32).

The most important element of research on autistic children, is avoided of harming to the child while the research; because the autistic children can be severe distress with using the simplest tests and damage to the body. The method that are considered today, is the morphometric characteristics of autistic children compared with normal children (33). These methods according to keep calm the child at the time of study and research ethics, is valuable.

The properties of morphometric characteristics, we can cite to check the size of the head (34, 35), to check the status of curling hair (36) and evaluation of finger length ratio 2D (Index finger) finger length 4D (Ring finger) in autistic children compared to normal children, noticed (37).

The aim of this study was to measurement 2D and 4D finger length in ASD children with healthy children as a control group.

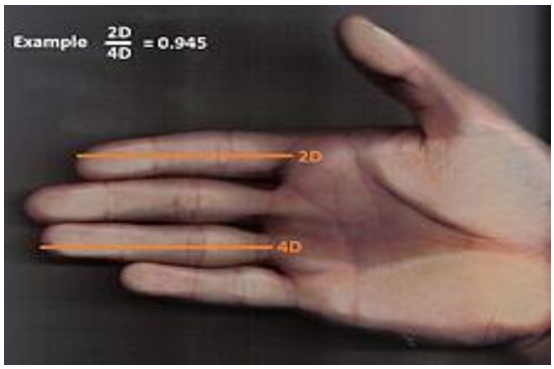

Fig.1: Hand with index finger being shorter than the ring finger, resulting in a small 2D:4D ratio, pointing to a high exposure to testosterone in the uterus

Methods and Materials

This study was a causal-comparative with 48 children in ages 7 to 8 years old (10 girls and 38 boys) with ASD, who were reffered to Rehabilitation Center of Noor Hedayat, Mashhad, Iran and 41 normal children in ages 7 to 8 years old (10 girls and 31 boys) of 3 kindergartens of Mashhad, and these children were elected with random sampling method. Also, kindergartens were selected of areas (1, 4, 6) of Mashhad. The test used in this study was Childhood autism rating scale (CARS).

The diagnosis was made by a child psychiatrist based on DSM-IV-TR criteria and using Autism diagnostic interview-revised (ADIR) and Autism diagnostic observation schedule (ADOS). In this research, Autism rating scale, Childhood autism rating scale (CARS) was used to assess the severity of symptoms in children. The CARS is a behavior rating scale that is utilized to assess symptoms of autistic disorder. In addition, it is able to differentiate children with autistic disorder from other developmental delays. It is conducted as an observation which can be completed during a testing session or in classrooms. However, some items can be answered from parent report or from reports of history. The CARS

contains 15 items that are utilized to compare the behavior of the child being assessed to the behavior of typically developing children. The 15 items include: (1) Relating to people, (2) Imitation, (3) Emotional response, (4) Body use, (5) Object use, (6) Adaptation to change, (7) Visual response, (8) Listening response, (9) Taste, smell, and touch response and use, (10) Fear or nervousness, (11) Verbal communication, (12) Nonverbal communication, (13) Activity level, (14) Level and consistency of intellectual response, and (15) General impressions. Each item is rated on a Likert scale as follows: (1) Within normal limits for a child that age, (2) Mildly abnormal, (3) Moderately abnormal, and (4) Severely abnormal. Midpoints between these values can also be utilized (e.g., 2.5). A total score is computed from the sum of the 15 items. Those with a total score of 30 or above fall within the autistic range (yields an agreement rate of 87%). Psychometric studies on the CARS yield promising results with an internal consistency of α = .94, interrater reliability average of .71 (good agreement), and coefficient kappa of .64 for test retest reliability. In regards to validity, there was high criterion related validity, r = .84 (Schopler et al., 1988). This scale (CARS) can be completed by a clinician or teacher or parent, based on subjective observations of the child's behavior. Each of the fifteen criteria listed above is rated with a 7-point score. Lower scores indicate less severity of Autism. Total CARS scores indicates total scores of severity about autism spectrum disorders (ASD) (6,7).

2D Finger length and 4D finger length in both hands in ASD children was measured by a ruler. The reason for not using a digital caliper to measure, because the autistic children while saw the caliper, had a extreme fear and were not willing to cooperate the study. 2D Finger length and 4D finger length in both hands in normal children, also was measured by a ruler. Data were analyzed using SPSS 16 software and p-value less than 0.05 was statistically considered significant.

Results

In this study 48 children in ages 7 to 8 years old (10 girls and 38 boys) with ASD, and 41 normal children in ages 7 to 8 years old (10 girls and 31 boys) were participated. The mean age of children in the normal group was (7.46±0.3457) and the ASD group was (7.38±0.2816).

Mean right and left hand 2D:4D across the groups is given in (Table.1) and (Figure.2).

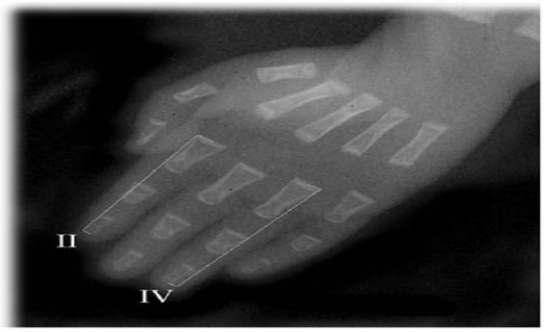

Fig.2: Radiograph of right hand.

Table 1: 2D:4D finger length ratio between left and right hand in ASD group and control group

Variable	Group	Mean	SD	t-test	P value
2D:4D Right hand	Control	0.994	0.032	2.137	0.035*
	ASD	0.973	0.056		
2D:4D Left hand	Control	0.982	0.042	0.928	0.356
	ASD	0.973	0.049		

*P<0.05

Paired t-tests showed the average ratio of 2D:4D in ASD children were lower than the ratio in control group (P<0.05). Results also showed that 2D to 4D finger-length ratio of

the right of children with autism was lower than the normal children (P<0.05); but this difference was not significant between two groups in the left hand (P>0.05) (Table.1).

Discusion

Children with ASD had lower 2D:4D digit ratio than the control group. This finding reflects higher prenatal testosterone levels in ASD children (22-32). The results shown 2D to 4D finger of the right hand of children with ASD was significantly lower than that the normal children. These results are consistent with the findings of Manning, Hönekopp and Milne (38-41). The results of the comparison of 2D to 4D left hand of children with ASD and normal children, showed that despite the lower the proportion of children with autism spectrum disorder, there was no significant difference between the two groups. The lack of significant differences, may be because that the ratio of 2D to 4D finger of the left hand compared with the right hand, the secretion of testosterone in utero is less sensitive (42). Hönekopp and Watson on their research showed that the ratio of finger 2D:4D finger of the right hand is particularly associated with sex differences. We are aware of the fact that our sample is small to generalization results but it is in focus of our future research to collect more data. Another limitation of this study sampling process, some autistic children because of distress, were not willing to cooperate.

Conclusion

The results showed that the mean 2D to 4D finger length ratio in autistic children is lower than that of normal children. It was concluded that 2D:4D ratio may be a possible marker for autism wich could implicate prenatal testosterone in its aetiology.

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgment

The authors would like to thank the staff of Animal Developmental of Applied Biology Research Center, Mashhad Branch, Islamic Azad University, and the staff of Noor Hedayat, Center of Autism Spectrum Disorders, Mashhad, Iran.

References

1. Caronna EB, Milunsky JM, Tager-Flusberg H. Autism spectrum disorders: clinical and research frontiers. Arch Dis Child 2008;93(6):518–23.
2. "DSM-5 News and Updates". Autism Speaks. Retrieved 27 August 2014.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. 4 ed. Washington, DC: American Psychiatric Association; 2000. ISBN 978-0-89042-025-6. OCLC 768475353. Diagnostic criteria for 299.00 Autistic Disorder.
4. Levy SE, Mandell DS, Schultz RT. Autism. Lancet 2009; 374(9701):1627–38.
5. Johnson CP, Myers SM, Council on Children with Disabilities. Identification and evaluation of children with autism spectrum disorders. Pediatrics 2007;120 (5):1183–215.
6. Abrahams BS, Geschwind DH. Advances in autism genetics: on the threshold of a new neurobiology. Nature Reviews Genetics 2008; 9(5):341–55.
7. Hojjati M, Khalilkhaneh M. Evaluate the Ability of Autistic Children to Use Expressive Language and Receptive Language. Int J Peditr 2014; 4-1(2):267-75.
8. Hojjati M. The Effectiveness of Holistic Multi-dimensional Treatment Model (HMTM) in the Treatment of Children with Autism Spectrum Disorder (ASD). Int J Peditr 2014;2-2(2):125-32.
9. Arndt TL, Stodgell CJ, Rodier PM. The teratology of autism. Int J Dev Neurosci 2005; 23(2–3):189–99.

10. Rutter M. Incidence of autism spectrum disorders: changes over time and their meaning. Acta Paediatr 2005; 94(1):2–15.
11. Gerber JS, Offit PA. Vaccines and autism: a tale of shifting hypotheses. Clin Infect Dis 2009; 48(4):456–61.
12. Newschaffer CJ, Croen LA, Daniels J et al. The epidemiology of autism spectrum disorders. Annu Rev Public Health2007; 28:235–58.
13. ASD Data and Statistics. CDC.gov. Archived from the original on 2014-04-18. Retrieved 5 Apr 2014.
14. Prevalence of autism spectrum disorders — autism and developmental disabilities monitoring network, 14 sites, United States, 2008. MMWR Surveill Summ 2012; 61(3):1–19.
15. Stephen J. Blumberg, , et al. Changes in Prevalence of Parent-reported Autism Spectrum Disorder in School-aged U.S. Children: 2007 to 2011–2012. National Health Statistics Reports. March 2013; (65).
16. Stephen J. Blumberg, , et al.. Changes in Prevalence of Parent-reported Autism Spectrum Disorder in School-aged U.S. Children: 2007 to 2011–2012. National Health Statistics Reports. March 2013; (65).
17. Myers SM, Johnson CP. Management of children with autism spectrum disorders. Pediatrics 2007;120 (5):1162–82.
18. Stefanatos GA. Regression in autistic spectrum disorders. Neuropsychol Rev 2008;18 (4):305–19.
19. Helt M, Kelley E, Kinsbourne M et al. Can children with autism recover? if so, how? Neuropsychol Rev 2008;18 (4):339–66.
20. Howlin P, Goode S, Hutton J, Rutter M. Adult outcome for children with autism. J Child Psychol Psychiatry 2004; 45(2):212–29.
21. Szatmari P. The causes of autism spectrum disorders. Br Med J;2003; 326: 173–4.
22. Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. JAMA 2003: 289: 49–55.
23. Stone JL, Merriman B, Cantor RM, Yonan AL, Gilliam TC, Geschwind DH, et al. Evidence for sex-specific risk alleles in autism spectrum disorder. Am J Hum Genet 2004; 75: 1117–23.
24. Manning JT, Kilduff LP, Trivers R. Digit ratio (2D:4D) in Klinefelter's syndrome. Andrology 2013; 1: 94–9.
25. Manning JT, Bundred PE. The ratio of 2nd to 4th digit length: A new predictor of disease predisposition? Medical Hypotheses 2000; 54(5): 855–7.
26. Baron-Cohen S, Knickmeyer RC, Belmonte MK. Sex differences in the brain: implications for explaining autism. Science 2005: 819–23.
27. Manning JT, Stewart A, Bundred PE, Trivers RL. Sex and ethnic differences in 2nd to 4th digit ratio of children. Early Hum Dev2004: 161–8.
28. Kondo T, Zakany J, Innis JW, Duboule D. Of fingers, toes and penises. Nature1997 ;390(6655):29.
29. Siiteri PK, Wilson JD. Testosterone formation and metabolism during male sexual differentiation in the human embryo. J Clin Endocrinol Metab 1974;38(1) 113–25.
30. Manning JT, Scutt D, Wilson J, Lewis-Jones DI. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum Reprod 1998;13(11) 3000–3004.
31. Manning JT, Baron-Cohen S, Wheelwright S, Sanders G. The 2nd to 4th digit ratio and autism. Dev Med Child Neurol 2001;43(3)160–4.
32. De Bruin EI, Verheij F, Wiegman T, Ferdinand RF. Differences in finger length ratio between males with autism, pervasive developmental disorder — not otherwise specified, ADHD, and anxiety disorders. Dev Med Child Neurol 2006; 48: 962–5.
33. Voracek M. Digit ratio (2D:4D) as a marker for mental disorders: low (masculinized) 2D:4D in autism-spectrum disorders, high (feminized) 2D:4D in schizophrenic-spectrum disorders. Behav Brain Sci 2008; 31 : 283–4.
34. Ozgen H, Hellemann GS, de Jonge MV, Beemer FA, van Engeland H. Predictive Value of Morphological Features in Patients with Autism versus Normal Controls. Journal of

Autism and Developmental Disorders 2013; 43(1):147-55.
35. Lainhart JE, Bigler ED, Bocian M, Coon H and et al. Head Circumference and Height in Autism. American Journal of Medical Genetics Part A 2006; 140:2257–74.
36. Surén P, Stoltenberg C, Bresnahan M, Hirtz D and et al. Early Growth Patterns in Children with Autism. Epidemiology 2013; 24(5):660-70.
37. Aksu F, Baykara B, Ergin C, Arman C. Phenotypic Features in Autistic Individuals: The Finger Length Ratio (2D:4D), Hair Whorl, and Hand Dominance. Turkish Journal of Psychiatry 2013; 24(2):94-100.
38. Hönekopp J, Watson S. Meta-analysis of the relation-ship between digit-ratio 2D:4D and aggression. Personality and Individual Differences 2011; 51: 381–6.
39. Manning JT, Baron-Cohen S, Sanders G. The 2nd to 4th Digit Ratio and Autism. Developmental Medicine and Child Neurology 2001; 43: 160-4.
40. Manning JT, Baron-Cohen S, Wheelwright S, Fink B. Is digit ratio (2D:4D) related to systemizing and empathizing? Evidence from direct finger measurements reported in the BBC internet survey. Personality and Individual Differences 2010;48: 767–71.
41. Hönekopp J. Digit Ratio 2D:4D in Relation to Autism Spectrum Disorders, Empathizing, and Systemizing: A Quantitative Review. Autism Research 2012; 5: 221–30.
42. Milne E, White S, Campbell R, Swettenham J, Hansen P, Ramus F. Motion and Form Coherence Detection in Autistic Spectrum Disorder: Relationship to Motor Control and 2:4 Digit Ratio. Journal of Autism and Developmental Disorders 2006;36(3):225-37.
43. Cstho A, Osvath A, Biscak E, Karadi K, Manning J, Kallai J. sex role identity to ratio of second to forth digit length in women. Biology Psychiatry 2002;62: 147-56.
44. Hönekopp J, Watson S. Meta-analysis of digit ratio 2D:4D shows greater sex difference in the right hand. American Journal of Human Biology 2010; 22: 619–30.