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ORIGINAL PAPER

An Exploration of Physical and Phenotypic Characteristics of Bangladeshi Children with Autism Spectrum Disorder

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Abstract

This study explored the physical and clinical phenotype of Bangladeshi children with autism spectrum disorder (ASD). A totally of 283 children who were referred for screening and administered Module 1 of the Autism Diagnostic Observation Schedule (ADOS) were included. Overall, 209 met the ADOS algorithmic cutoff for ASD. A trend for greater weight and head circumference was observed in children with ASD versus non-ASD. Head circumference was significantly ($p < 0.03$) larger in ASD males compared with non-ASD males. A trend was also observed for symptom severity, higher in females than males ($p = 0.068$), with further analyses demonstrating that social reciprocity ($p < 0.014$) and functional play ($p < 0.03$) were significantly more impaired in ASD females than males. The findings help understand sex differences in ASD.

Keywords Autism spectrum disorder · ADOS-2 · Head circumference · Phenotype

Introduction

Autism spectrum disorder (ASD) is genetically and phenotypically a highly heterogeneous disorder that first manifests in early infancy and impacts multiple domains of development (Volkmar and Pauls 2003; Uddin et al. 2014; Tammimieset al. 2015). In the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association 2013) ASD is characterized by persistent deficits in social communication and social interaction along with restricted repetitive patterns of behavior, interests, or activities. Initially, ASD was thought to be

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a relatively rare condition affecting fewer than 1 in 1000 children but more recent studies have estimated the prevalence of ASD at 1 in 59 (Baioet al. 2018). The prevalence of ASD across different countries varies mostly due to methodological variables (Zaroff and Uhm 2012; Baxter et al. 2015). In South Asia a systematic review revealed the prevalence of ASD ranged from 0.09% in India to 1.07% in Sri Lanka (Hossain et al. 2017).Currently there is no systematic review from Bangladesh on ASD prevalence or phenotype characteriztion. ASD is on average four times more frequently diagnosed in males than in females (Fombonne 2003; Solomon et al. 2012; Pisulaet al. 2013). Despite ongoing research efforts, little is known regarding the female phenotype (Kopp and Gillberg 1992; Kim et al. 2011; Mandy et al. 2012), although male–female differences have been reported (Tsai and Beisler 1983; McLennan et al., 1993; Halladay et al. 2015). Such differences may result in later diagnosis (Rivet and Matson 2011) or misdiagnosis (Attwood 2007).

In aetiological terms, ASD is a complex disorder, with both genetic and non-genetic factors contributing, with the former a having a stronger influence (Veenstra-VanderWeele et al. 2004). To date, research points to numerous genetic, neuroanatomical and immune abnormalities along with neurotransmitter dysfunction (Chugani et al. 1999; Hollander et al. 2003; Coutinho et al. 2004; Boyd et al., 2011). Hormonal fetal testosterone (FT) is one possible explanation for sex differences in phenotypic manifestation, with elevated levels of FT identified among children with ASD (Baron-Cohen et al. 2015). Thus, lower FT levels among females may have a protective effect on the manifestation of autistic traits. However, there have been relatively few studies of sex differences in phenotypes and available findings are inconsistent (Werling and Geschwind 2013). Studies have indicated that girls have increased social problems and are less able to perform social imaginative play than boys (Tsai and Beisler 1983; McLennan et al., 1993; Holtmann et al., 2007; Howe et al. 2015; Wang et al. 2017). Other studies failed to observe sex differences in social behavior; indeed, some have found that social behavior is better in girls than boys (McLennan et al., 1993; Carter et al. 2007; Banach et al. 2009). Research findings of communication (McLennan et al. 1993; Holtmann et al. 2007; Banach et al. 2009) and repetitive and stereotyped behaviors (Carteret al. 2007; Holtmann et al. 2007; Banach et al. 2009; Hartley and Sikora 2009; Bölte et al. 2011) are similarly inconsistent from the perspective of male–female differences. Therefore, findings regarding sex differences of symptoms seen in ASD remain ambiguous.

Research on brain development of children diagnosed with ASD has shown consistent findings with respect to abnormal acceleration of head growth among children with ASD than normally developed children (Kanner 1943; Woodhouse et al. 1996; Lainhart et al. 1997, 2006; Aylward et al. 2002; Hazlett et al. 2005). Studies of head circumference (HC) in children with ASD and adults have consistently identified an association between ASD and macrocephaly (i.e. greater than the 98th percentile for HC) (Bailey et al. 1995; Stevenson et al. 1997) with two postmortem studies demonstrating that individuals with ASD have increased brain weight (Bauman and Kemper 1985; Baily et al. 1993). Earlier detection of ASD risk could occur clinically if regular assessment of infants includes neurological indicators in combination with other behavioral markers (Mraz et al. 2007), which is particularly important given that early intensive intervention is associated with better outcomes (Lovaas 1987; McEachin et al. 1993).

The aim of this study was to explore the nature of physical characteristics and clinical phenotype of Bangladeshi males and females with ASD assessed through general physical evaluation and ADOS-2. Based on current knowledge, no such studies have been performed to date among the Bangladeshi population with ASD.

Methods

Participants

This study received ethical approval from the institutional research ethics board (IRB) of the Holy Family Red Crescent Medical College, Dhaka, Bangladesh. From October 2016 to June 2018 a total of four hundred (400) children were referred for ASD screening from pediatricians, neurologists, psychiatrists and therapists. The children were referred for detailed assessment either because of suggestive signs and symptoms of autism spectrum disorder or possible developmental disabilities in several developmental areas such as cognitive, emotional, social, speech and language, motor function, and daily living activities. Among the 400 children, 283 meet the criteria for module-1 administration of ADOS-2 (a gold standard measure of ASD described detailed in later section) based on their chronological age and expressive language level, and constitute the sample of the present study, which comprises 215 males and 68 females (aged 25–137 months). All participants were from different regions of Bangladesh. Table 1 represents the characteristics of participants.

All children were assessed using parental semi-structured interview, diagnostic guidelines of Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association 2013),and ADOS-2 (Lord et al. 2012),administered by experienced clinical psychologists who were certified by Western Psychological Services (WPS) on ADOS-2 administration. All children (among the 283 children) who scored above the algorithmic threshold

Table 1 Demographic characteristics of children with autism spectrum and non-spectrum controls

	Autism spectrum (n = 209)			Non-spectrum (n = 74)			Total (n = 283)		
	Male	Female	Significance of group difference	Male	Female	Significance of group difference	Male	Female	Significance of group difference
N	164	45		51	23	X^{2}=2.73 p = 0.098	215	68	
Age in months									
Mean (SD)	51.97 (18.93)	52.07 (21.48)	F = 0.01 p = 0.976	48.67 (14.25)	51.26 (16.94)	F = 0.467 p = 0.497	51.19 (17.95)	51,79 (19.94)	F = 0.056 p = 0.813
Range	25–122	31–137		31–89	32–87		25–122	31–137	
Inter-quartile range	37–62	37–61		39–58	39–60		37–60	38–60	

	Autism spectrum (n = 209)	Non-spectrum (n = 74)	Significance of group difference
Age in months			
Mean	51.99	49.47	F = 1.022, p = 0.313
(SD)	(19.45)	(15.07)	
Range	25–137	31–89	
Inter-quartile range	37–62	39–58.25	

for an ASD classification on the ADOS-2module 1 algorithm and also classified ASD according to the interview were considered positive for an ASD diagnosis. On the other hand, all the children who did not score above the ADOS-2 module-1 algorithm threshold for ASD were classified as non-ASD. The non-ASD group had the condition of developmental disabilities with ASD symptoms who did not meet the threshold for ASD diagnosis (Wiggins et al. 2015).

Measures

Head Circumference, Body Height, Body Weight, BMI

Occipito-frontal head circumference was measured in centimeters using a non-stretchable plastic tape. Since there is no standardized (approved by healthcare authority) height and weight chart for Bangladeshi children, body height was measured in centimeters using a calibrated non-stretchable tape positioned on a wall with the participant standing with their back against the wall. Body weight was measured in kilograms using a calibrated analogue weight machine. All measurements were carried out by appropriately trained clinical staff. BMI was calculated according to the formula, BMI = weight (kg)/height squared (m^2).

ADOS-2

The ADOS-2 is a semi-structured, standardized assessment of communication, social interaction, play/imaginative use of materials, and restricted and repetitive behaviors. The ADOS-2 is a revision of the Autism Diagnostic Observation Schedule (Lord et al. 1999), a gold standard observational assessment for diagnosing ASD (Ozonoff et al. 2005; Kanne et al. 2008). ADOS-2 has five modules and each module offers standard activities designed to elicit behaviors that are relevant to the diagnosis of ASD at different chronological ages and language abilities. For this study, ADOS-2 Module 1 was administered on 283 participants who did not use phrase speech. The number of participants for the present study was 283 because they were administered Module 1. The Module 1 algorithm uses communication, reciprocal social interaction, and restricted and repetitive behaviors to generate a total score. Elevated scores classify an individual in the autism spectrum or autism diagnostic range based on the severity or the frequency displayed (Fig. 1).

Statistical Analysis

A Chi-square test was used to examine the difference in number of male and female participants between ASD and 'non-spectrum' groups. One way ANOVA was used to examine age, height, weight, BMI, and head circumference differences between males and females for ASD and non-spectrum groups. A *t* test was used to test the difference in autistic featuresbetween males and females in ASD and non-spectrum groups. Effect sizes were calculated using Cohen's d. Correlation analysis was used to test the

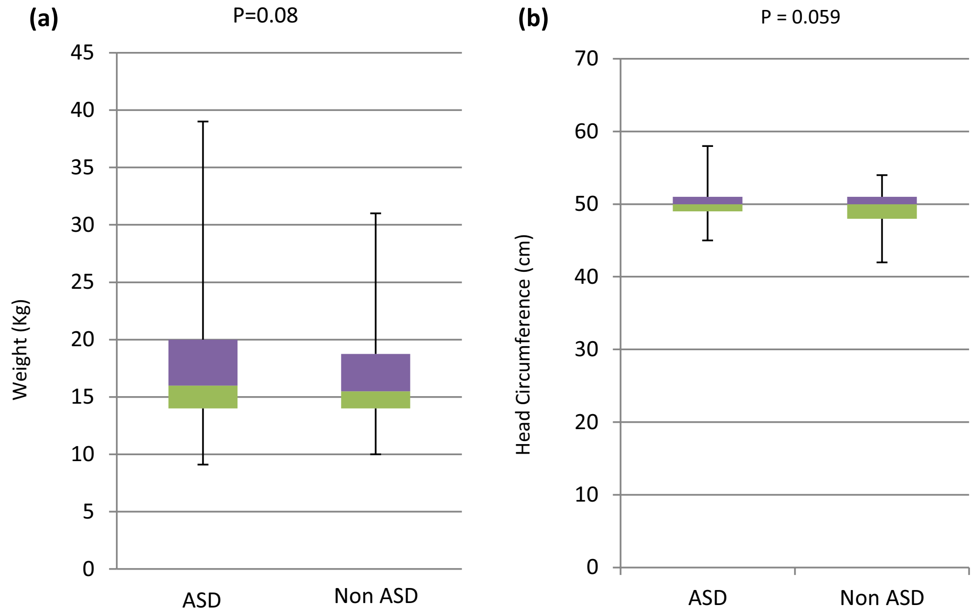

Fig. 1 **a** comparison of autism spectrum and non spectrum participant's weight, the blue color shows the upper quartile and green represents lower quartile, **b** comparison of autism spectrum and non spectrum participant's head circumference

relationship of age, height, weight, BMI, and head circumference with ADOS-2 total score.

Results

Among the 283 participants, 209 meet the criteria for 'Autism' or ASD (164 males, 45 females) based on ADOS-2 classification and interview with the remaining 74 classified as non-ASD. Among ASD positive cases, the male female ratio was 3.64:1, and the mean age for both males and females was approximately 51 months (see Table 1). There were no significant differences between the ASD and non-ASD groups with respect to age, sex, height, weight, head circumference, or BMI (Tables 2, 3). However, a trend for increased weight ($p < 0.08$) and head circumference ($p < 0.05$) was noted among children with ASD (Table 3). Further exploration revealed that head circumference of males with ASD was significantly greater than non-ASD males ($F = 4.35$, $p = 0.03$) (Table 3).

Table 2 Descriptive statistics for general physical characteristics of children with autism spectrum and non-spectrum controls

Phenotype	Autism spectrum			Non-spectrum			Total		
Features	Male	Female	Significance of group difference	Male	Female	Significance of group difference	Male	Female	Significance of group difference
Height (cm)									
N	135	36	F=0.03 p=0.87	47	23	F=0.06 p=0.80	182	59	F=0.16 p=0.69
Mean	102.08	101.66		100.18	99.57		101.59	100.85	
SD	13.80	11.15		9.35	9.70		12.80	10.57	
Weight (kg)									
N	153	39	F=0.08 p=0.78	48	23	F=0.09 p=0.77	201	62	F=0.32 p=0.57
Mean	18.14	17.74		16.42	16.11		17.73	17.13	
SD	8.42	4.89		4.42	3.53		7.68	5.17	
BMI									
N	135	35	F=0.42 p=0.52	47	23	F=0.00 p=0.984	182	58	F=0.15 p=0.70
Mean	16.41	16.73		16.10	16.11		16.33	16.48	
SD	2.44	2.91		2.37	2.99		2.42	2.94	
Head circumference (cm)									
N	152	41	F=0.69 p=0.	47	23	F=0.05 p=0.83	199	64	F=0.20 p=0.66
Mean	50.27	50.83		49.52	49.39		50.09	50.31	
SD	2.20	7.22		2.11	2.13		2.20	5.93	

Table 3 Difference in physical characteristics between children with autism spectrum and non-spectrum controls

Features	Autism spectrum			Non-spectrum			Significance of group difference
	N	Mean	SD	N	Mean	SD	
Height	171	101.99	13.25	70	99.97	9.40	F = 1.338 p = 0.249
Weight	192	18.05	7.95	71	16.31	4.13	F = 3.084 p = 0.080
BMI	170	16.47	2.53	70	16.10	2.57	F = 1.093 p = 0.294
Head circumference	193	50.38	3.83	70	49.47	2.11	F = 3.599 p = 0.059
Sex							
Male							
Height	135	102.07	13.79	47	100.17	9.35	F = 0.768 p = 0.382
Weight	153	18.13	8.41	48	16.41	4.42	F = 1.844 p = 0.176
BMI	135	16.41	2.43	47	16.09	2.37	F = 0.602 p = 0.439
Head circumference	152	50.26	2.19	47	49.51	2.11	F = 4.355 p = 0.038
Female							
Height	36	101.66	11.15	23	99.57	9.70	F = 0.545 p = 0.463
Weight	39	17.73	5.88	23	16.10	3.53	F = 1.499 p = 0.233
BMI	35	16.72	2.90	23	16.10	2.99	F = 0.609 p = 0.438
Head circumference	41	50.82	7.22	23	49.39	2.14	F = 0.864 p = 0.356

Similarly, head circumference of females was also larger than their non-ASD counterparts, albeit non-significantly ($F = 0.864$, $p = 0.356$) (Table 3).

Correlation of age, head circumference, height, weight, and BMI with ADOS-2 total score revealed no significant correlation between autism spectrum and non-spectrum groups. To detect and understand if there were any associations between growth parameters and phenotypic characteristics that might become apparent with an increased sample size, an analysis that combined ASD and non-ASD groups was performed. Here a significant correlation was detected between head circumference distribution ($r = 0.15$, $p = 0.017$), weight ($r = 0.14$, $p = 0.024$) and total ADOS-2 score (Table 4).

Core Autism Symptomatology

Among individuals with ASD, females displayed (Fig. 2) greater impairment of reciprocal social interaction ($t = -2.52$, $p = 0.014$, $d = -0.63$) and functional play ($t = -2.17$, $p = 0.03$, $d = -0.53$) compared with males (Table 5). Additionally, females with ASD displayed more symptom severity compared to male, a difference that was not statistically significant ($t = -1.85$, $p = 0.06$, $d = -0.46$). No significant difference was observed between males and females in the ASD group regardingcommunication ($t = -0.33$, $p = 0.74$) or restricted and repetitive behavior ($t = -1.48$, $p = 0.14$). Likewise, no sex differences were noted with respect to communication, reciprocal social interaction, restricted and repetitive behavior, and functional play when both groups were combined.

Discussion

This study set out to examine the characteristics of a consecutive series of children referred to a developmental clinic in Bangladesh for ASD assessment, including only those who were nonverbal or speaking mainly in single words (i.e. those administered Module 1 of the ADOS-2). It is a seminal study providing a detailed description of patterns of ASD symptoms in this population. A specific focus was

Table 4 Pearson correlation of ADOS total score with age, head circumference, height, weight, and BMI

Parameter	Autism Spectrum		Non-Spectrum		Total	
	N	Correlation (p value)	N	Correlation (p value)	N	Correlation (p value)
Age	209	−0.03 (0.668)	74	−0.05 (0.676)	283	0.02 (0.690)
Head circumference	193	0.08 (0.258)	70	0.16 (0.175)	263	0.15* (0.017)
Height	171	−0.09 (0.253)	70	−0.04 (0.753)	241	0.00 (0.964)
Weight	192	0.09 (0.241)	71	−0.07 (0.565)	263	0.14* (0.024)
BMI	170	−0.08 (0.291)	70	0.19 (0.116)	240	0.03 (0.619)

p value: Significance in two tailed test

*p < 0.05

Table 5 Core and associated features of autism spectrum disorder between males and females

	ADOS-2 features	Male (n = 164) mean (SD)	Female (n = 45) mean (SD)	Effect size Cohen's *d*	Significance of sex effect [t(p-value)]
ASD	Communication	5.71 (1.83)	5.82 (1.98)	−0.08	−0.33 (0.74)
	Reciprocal social interaction	11.01 (3.73)	12.73 (4.14)	−0.63	−2.52 (0.01)
	Restricted and repetitive behavior	2.96 (2.34)	3.56 (2.43)	−0.36	−1.48 (0.14)
	Functional play	1.99 (0.84)	2.31 (0.87)	−0.53	−2.17 (0.03)
	Total score	16.40 (4.68)	17.96 (5.06)	−0.46	−1.85 (0.06)
		Male (n = 51) mean (SD)	Female (n = 23) mean (SD)	Effect size Cohen's *d*	Significance of sex effect [t(p-value)]
Non-ASD	Communication	2.12 (1.62)	2.22 (1.81)	−0.07	−0.23 (0.82)
	Reciprocal social interaction	4.00 (2.20)	3.91(2.09)	0.05	0.16 (0.87)
	Restricted and repetitive behavior	0.80 (1.06)	0.57 (0.79)	0.29	1.08 (0.29)
	Functional play	0.75 (0.80)	0.74 (0.75)	0.01	0.03 (0.98)
	Total score	5.63 (2.65)	5.57 (2.74)	0.03	0.09 (0.93)

Higher scores indicate greater impairment, negative effect size express greater female impairment compared to males

to examine male and female differences in relation to ASD symptoms and growth parameters. The investigations of such ASD symptomatic differences require research into different populations due to ethnic differences. Our study represents the first Bangladeshi ADOS cohort assessing clinical symptoms and growth parameters.

The male female ratio was 3.64:1 among the ASD positive cases similar to that generally found for children with ASD (Baird et al. 2006). There was no significant difference in terms of age at diagnosis, height, weight, and BMI among autism spectrum and non-spectrum males and females. The autism-spectrum group had a larger weight compared to non-ASD group but not statistically significant. However, head circumference was larger in the autism-spectrum group compared to non-ASDgroup; males in the ASD group had significantly larger HC than non-ASD males, and females, a non-significantly larger HC than their non-ASD counterparts.These findings are consistent with previous studies which have demonstrated increased head circumference in children with ASD (Courchesne et al. 2003; Marz et al. 2007; Webb et al. 2007; Fukumoto et al. 2011). Research suggests that the premature acceleration of brain growth in autism occurs at a time when the symptoms and signs of autism are present (Aylward et al. 2002; Dupont et al. 2018).

Interestingly, a small positive correlation existed between ADOS-2 total score and head circumference ($r = 0.15$, $p = 0.017$) when both ASD and non-ASD groups were combined. Specifically, core autism features were more severe among individuals with larger head circumference. However, this finding may represent an artifact of a confound such as age and/or sex. This finding is in contrast with a previous study exploring this same relationship, which reported a small *negative* correlation ($r = -0.21$) between ADI total score and head circumference (Lainhart et al. 1997). These apparently contradictory findings demand further research.

We were particularly interested in the relationship between symptom profile and sex in the ASD group. Girls with ASD demonstrated more severe impairment of reciprocal social interaction and functional play compared with boys. This finding is supported by other studies which also revealed that females with ASD had greater impairment in social reciprocity and peer play based on ADOS or ADI-R scores (Tsai and Beisler 1983; Howe et al. 2015; Wang et al. 2017) and so this may not be due to the nature of the population studied, although this cannot be ruled out. There are potential confounds that might explain this apparent relationship, including the possibility of lower cognitive functioning in girls (Bhasin and Schendel 2007). Unfortunately, we did not have access to IQ scores to further examine this relationship. In contrast to our findings, some studies have also documented that boys with ASD exhibit higher scores on the restricted and repetitive behavior domain than girls (Holtmann et al., 2007; Carter et al. 2007; Banach et al. 2009; Bölte et al. 2011; Mandy et al. 2012). These conflicting results may be attributed to fundamental differences between the populations studied or may represent an artifact of one or more confounds not examined in our study or other studies. Overall, our results suggest that, among those diagnosed in our clinic, females with ASD exhibit a more severe clinical phenotype in certain aspects than males with ASD.

The difference in symptom severity between boys and girls with ASD may be explained by a genetic threshold effect for girls with ASD (Reich et al., 1975; Tsai, Stewart and August 1981). This model assumes that females require a higher 'genetic load' to reach a threshold for symptom manifestation compared with males. Consequently, once formally diagnosed, their cognitive, emotional, and behavioral

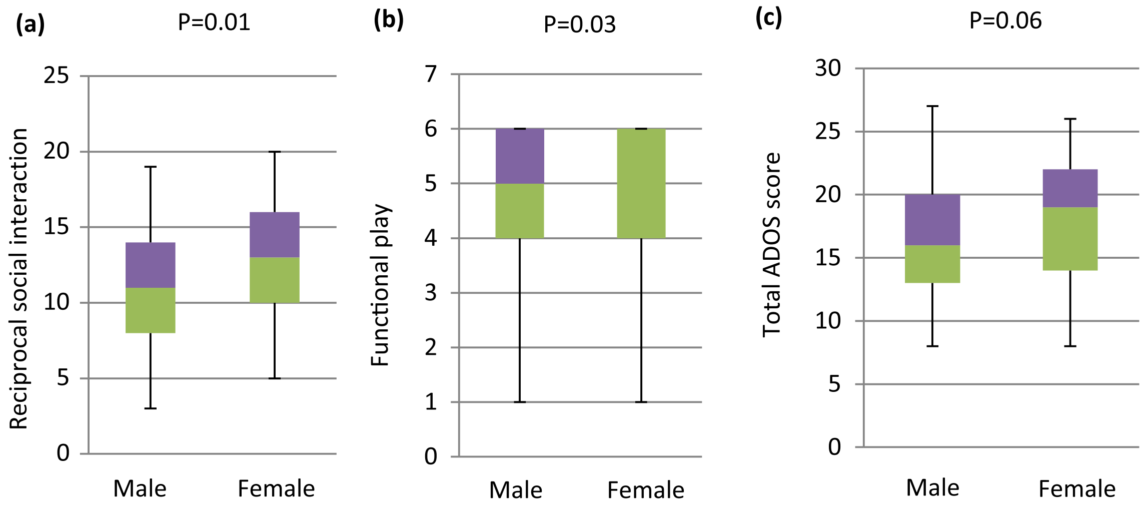

Fig. 2 **a** comparison of autism spectrum disorder affected male and female reciprocal social interaction scores, **b** comparison of autism spectrum disorder affected male and female functional play scores, **c** comparison of autism spectrum disorder affected male and female total ADOS-2scores

functioning will tend to be more severe than in males. Another explanation is that we have only captured more severe females in our cohort, with milder females either not being referred in the first place, or at least not diagnosed using the available diagnostic assessments. As previously described, the diagnostic criteria, and available screening and diagnosis instruments may not be suitably sensitive to capture the phenotypic manifestations among females, who may instead receive a different diagnosis by a process of 'diagnostic substitution'.

Considerable research is warranted to explore the relationship between brain development and the development of cognitive, emotional, and social functioning, as well as sex differences in phenotype expression for ASD. Little research has been done to investigate the differences in clinical presentation of autism symptoms such as communication and language development between different ethnic groups that may represent phenotypic differences across groups (Tek and Landa 2012). Moreover, our study also demonstrates that there may be ethnicity-related differences in phenotypes, and that by studying other populations, new patterns of clinical manifestation may be identified that may, in turn, inform new aetiological mechanisms, genetic or otherwise. The present research, therefore, crucially contributes to this 'bigger picture' of ASD. Importantly, the observation of a particularly severe phenotype among females with ASD needs further examination as it may reflect different genetic architecture underlying in Bangladesh versus other countries. This also, therefore, offers the opportunity to further examine genotype–phenotype relationships. Additionally, the head circumference difference may be related to similar mechanisms.

This study does have some limitations. It lacked standardized height, weight, and head circumference charts by age and sex for Bangladeshi children to be able to compare mean growth percentiles rather than mean measurements between groups and adjust for sex. Participants' IQ level was also not measured, and an age appropriate control group was unavailable. ADOS-2 total score was used instead of comparison score in terms of analyzing symptom severity. The number of female participants was small compared with males, although this is often a problem in ASD research due to its underlying epidemiology.

Conclusions

Our findings support previous observations that children with ASD have increased head circumference compared with non-spectrum counterparts, a relationship that holds particularly true for males. Girls with ASD tend to show more symptom severity than boys in social reciprocity and functional play than boys. These findings contribute to the understanding of sex differences in ASD symptomatology, and may ultimately provide clinical guidance for early screening, diagnosis, and intervention. Furthermore, ethnicity-related differences in epidemiology and clinical presentation are important to document because of their implications for aetiology. With the advent of technologies (i.e. artificial intelligence, precision therapy in neurodevelopmental disorders) (Uddin et al. 2019), detailed clinical observation from ADOS can be useful to explain genotype–phenotype correlations (i.e. severity) by integrating into genetic data.

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Author contribution MAR, and MU conceived the project and desinged all the analysis. ML, MOF, SPK and NJ conducted ADOS-2 and preliminary psychological assessments. KMFU, MAB, SS, MB, MAKAC, MI, NS, MMR and MH recruited the patients and conducted clinical assessments. MAR, MU, CC, MG, and MU conducted and designed statistical experiments. AA, DOR, MW-S, MAR and MU wrote the manuscript and critically reviewed statistical analysis and interpretations.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Holy Family Red Crescent Medical College, Dhaka, Bangladesh). This article does not contain any studies with animal participants performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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