Specific Neurological Phenotypes in Autism Spectrum Disorders Are Associated with Sex Representation

Esther Ben-Itzchak, Shay Ben-Shachar, and Ditza A. Zachor

Autism spectrum disorder (ASD) is a heritable disorder occurring predominantly in males. The aim of this study was to compare sex differences in the prevalence of specific neurological phenotypes commonly described in ASD. The study included 663 participants, aged 18 months to 15 years, diagnosed with ASD. Neurological and behavioral assessments were performed using standardized tests, and obtaining medical, developmental, and familial histories from the parents. Phenotypes under investigation were macro- and microcephaly, developmental regression, minor neurological and musculoskeletal deficits (MNMD), and seizures. Male : female ratio in the ASD group was 6.7:1. No sex differences in autism severity, cognitive ability, and adaptive functioning were noted. Mean head circumference percentile for males (50.1 ± 25.6) was significantly larger than females (43.4 ± 30.2). Micro- and macrocephaly were more frequent in ASD than expected (5.9%; 18.1%, respectively). Microcephaly in females (15.1%) was significantly more prevalent than in males (4.5%). The prevalence of macrocephaly in both sexes did not differ significantly. Regression was noted in 30.2% of the females with ASD, significantly higher than in males (18.9%). MNMD was documented in 73.8% of the females, significantly higher than in males (57.1%). M:F ratio decreased in a group with two or more phenotypes (3.6:1), while male predominance was more significant in the group without phenotypes (13.6:1). Neurological phenotypes associated with ASD are more prevalent in females than in males, resulting in more complex clinical and neurological manifestations in females. Therefore, involvement of different etiologies is suggested in ASD in females. Autism Res 2013, ••: ••–••. © 2013 International Society for Autism Research, Wiley Periodicals, Inc.

Keywords: autism spectrum disorder; male:female ratio; microcephaly; macrocephaly; developmental regression, minor neurological and musculoskeletal deficits, seizures.

Introduction

Autism spectrum disorders (ASD) are a group of neuro-behavioral disorders characterized by a classic triad of symptoms, including impaired social and communication skills, and stereotyped behaviors. It is well accepted now that ASD represents a heterogeneous group of conditions. It is not surprising, therefore, that some individuals show other phenotypes in addition to the core symptoms. ASD is a highly heritable disorder, with heritability indices estimated at 60–92%, suggesting a major role for genetic factors in the etiology of ASD [Schaaf & Zoghbi, 2011].

Accelerated head growth and relative increased head circumference have been documented in ASD in numerous studies [Courchesne & Pierce, 2005; Fombonne, Roge, Claverie, Courty, & Fremolle, 1999; Minshew & Williams, 2007]. Developmental regression has been estimated at 15–30% in individuals with ASD [Baird et al., 2008; Parr et al., 2011]. Children with ASD are often described with clumsiness and motor skills delay [Zachor, Ilanit, & Ben Itzchak, 2010]. In addition, soft neurological signs were frequently documented in ASD [De Jong, Punt, De Groot, Minderaa, & Hadders-Algra, 2011; Ming, Brimacombe, & Wagner, 2007]. The most commonly reported neurological deficits were hypotonia, abnormal reflexes, and cranial nerves dysfunction [De Jong et al., 2011]. Abnormal neurological signs might indicate involvement of multiple brain networks associated with ASD that may affect neurological outcome. Epilepsy has been documented in about 5–46% of individuals with ASD in different studies, suggesting that autism and epilepsy share a common neurobiological basis [Kagan-Kushnir, Roberts, & Snead, 2005; Tuchman & Rapin, 2002].

Male predominance in ASD has been noted in all epidemiological studies and is a well-established fact in the field of ASD. The male : female (M:F) ratio has been reported in many studies in the range of 4–5:1 [Fombonne, 2003; Holtmann, Bolte, & Poustka, 2007; Newsschaefer et al., 2007].

In general, sex differences in autism severity and cognitive abilities have been examined in previous research. Studies looking at sex differences in autism severity found conflicting results even when controlling for IQ. Several studies reported more severe symptoms in girls...
comparing to boys especially in the communication domain [Carter et al., 2007; Hartley & Sikora, 2009], while others reported that boys had more severe symptoms especially in repetitive stereotyped behaviors [Lord, Schopler, & Reivicki, 1982; Mandy et al., 2012; McLeNNan, Lord, & Schopler, 1993; Szatmari et al., 2012]. Others found no sex differences in autism symptom severity [Holtmann et al., 2007; Pilowsky, Yirmiya, Shulman, & Dover, 1998; Zwaigenbaum et al., 2012]. Earlier studies, especially those conducted prior to the use of DSM-IV, found that females had higher rates of intellectual disability compared with boys [Lord & Schopler, 1985; Volkmar, Szatmari, & Sparrow, 1993]. However, several later studies did not find significant sex differences [Mandy et al., 2012; Zwaigenbaum et al., 2012]. Dworzynski, Ronald, Bolton, and Happé [2012] reported that girls, but not boys, meeting criteria for ASD showed more additional problems, such as low intellectual level and behavioral difficulties. Researchers suggested sex bias in the diagnosis of ASD. In the absence of additional intellectual or behavioral problems, girls are less likely than boys to meet diagnostic criteria for ASD at equivalently high levels of autistic-like traits.

Only a few studies have examined the association between M:F ratio and specific neurological phenotypes in ASD. For example, Miles, Hadden, Takahashi, and Hillman [2000] tested 137 individuals with autism, and found no significant difference in sex ratio between normocephalic (M:F 6.9:1) and macrocephalic (M:F 4.3:1) individuals. However, they did find that sex ratio was closer to normal (M:F 1.5:1) in individuals with microcephaly. Epilepsy in ASD was associated with sex (female) [Amiet et al., 2008; Steffenburg & Gillberg, 1986; Tuchman, Rapin, & Shinnar, 1991] and with intellectual disability [Amiet et al., 2008; Bolton et al., 2011]. However, the M:F ratio has not been specifically examined in the subpopulation of ASD and epilepsy. Furthermore, previous studies have not described M:F ratio differences in ASD with developmental regression [Parr et al., 2011; Shumway et al., 2011].

As ASD occurs more frequently in males, we hypothesized that the relatively small group of females with ASD may have a different clinical expression than males. In this study, we aimed at examining the prevalence of females compared with males in several known ASD-related neurological phenotypes. The results of this study may provide better characterization of ASD in females, and insights regarding ASD etiology.

Methods
Participants

The study was conducted at a tertiary autism center that provides diagnosis and treatment services, and is involved in research in the field of ASD.

The study included 690 participants who underwent a full diagnosis for ASD during the years 2002–2011. Participants younger than 18 months (n = 11) or with diagnoses of specific syndromes (n = 16) were excluded from the study. The final cohort included 663 participants (577 males, 86 females) within the age range of 18 months to 15 years. (M = 44.1 m ± 28.7) diagnosed with ASD. Of the cohort, 536 participants (80.8%) were 18 months to 5 years old, 106 (15.9%) were between 5 and 10 years old, and 21 (3.3%) were older than 10 years. This research was approved by the institutional review board of the medical center as required.

Procedure

Participants were referred to the autism center for a comprehensive assessment of a possible diagnosis of ASD. The evaluation included a neurological assessment, and behavioral, cognitive, and functional evaluations. Assessments were conducted by a skilled interdisciplinary team. Pediatric neurologists obtained medical, developmental, and familial histories from the parents, and conducted a comprehensive neurological examination of all the participants.

The diagnosis of autism/ASD was obtained by using two standardized tests: the Autism Diagnosis Interview-Revised (ADI-R) [Rutter, Le Couteur, & Lord, 2003] and the Autism Diagnosis Observation Schedule (ADOS) [Lord, Rutter, DiLavore, & Risi, 1999], and by meeting criteria for autism/ASD based on DSM-IV [American Psychiatric Association, 1994]. All the professionals involved in the diagnostic process established reliability as required. Cognitive and developmental abilities (IQ/DQ) were assessed using the Mullen Scales of Early Learning (Mullen, 1995), Bayley Scales of Infant Development (Bayley, 1993), Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 1989), Stanford–Binet Intelligence Scales (Thorndike, Hagen, & Sattler, 1986), Kaufman Assessment Battery for Children-II (Kaufman, 1983), or Wechsler Intelligence Scale for Children III and IV (Wechsler, 2003), according to the child’s age and language level. Since 2006, developmental and cognitive tests have been obtained, and therefore DQ/IQ scores were available on about half of the ASD cohort (n = 323).

Adaptive skills were assessed using the Vineland Adaptive Behavior Scales (VABS) [Sparrow, Balla, & Cicchetti, 1984]. Since 2004, VABS assessments have been added to each evaluation of ASD, and therefore VABS scores were available only for 528 participants.

Head circumference measurements were performed using standard methods [Deutsch & Farkas, 1994; Deutsch & Joseph, 2003] by a senior child neurologist, and were plotted on normative head circumference growth charts and converted to percentile values [Nellhaus, 1968]. Head circumference data were available.
on 581 participants. Children with ASD were classified further according to whether or not their parents had reported a history of loss of skills (developmental regression) on the ADI-R. The definition of loss within the ADI-R is twofold: it requires that any loss be coded only if the skill was established initially for at least 3 months, and the loss of skill must have lasted at least 3 months. In this study, the occurrence of regression was explored using the coding of definite loss (score = 2) of specified skills in the language, social engagement, constructive or imaginary play, and motor skills in the ADI-R. Minor neurological and musculoskeletal dysfunction (MNMD) referred to findings of abnormal neurological and musculoskeletal findings that were detected during a comprehensive neurological examination, without the use of standardized procedures, by two pediatric neurologists. These findings included muscle tone (hypotonia, hypertonia), deep tendon reflexes (weak, exaggerated), cerebellar dysfunction (Romberg test, Finger-to-nose test, Heel-to-shin test, diadochokinesis), and hyperluxity of joints, not related to a major neurological disorder. Data were available on 616 participants with ASD. Seizures were defined as one or more episodes of idiopathic seizures not related to a febrile illness or a traumatic event. Documentation of seizures was based on the neurological assessment by one of the certified pediatric neurologist at the autism center, previous reports from the neurologist who made the diagnosis of seizures, and on the results of the Electroencephalogram recording if available. An abnormal EEG recording was not required for a child to be considered to have a seizure disorder. Data on seizures were available on 634 participants with ASD.

Data Analysis

To investigate the differences in M:F ratio between the ASD subgroups with and without the specific phenotypes (microcephaly, macrocephaly, developmental regression, MNMD, seizures), chi-square tests were used. To compare the head circumference percentiles of males and females in the ASD group while controlling for age, one-way analysis of covariance was used. To compare the percentiles of males and females in our cohort. No significant differences were noted between the percentage of verbal males (39.6%) and females (37.2%), and therefore ADI scores between the sexes could be compared. Table 1 summarizes the characteristics of males and females in our cohort. No significant differences were noted between males and females in all the above examined measures.

Of the male participants, 47.1% received a diagnosis of ASD and 52.9% received a diagnosis of autism. Of the female participants, 52.3% received a diagnosis of ASD and 47.7% received a diagnosis of autism. The distribution of autism diagnostic categories, autism, and ASD did not differ between males and females [χ²(1) = 1.2, P > 0.05].

The overall mean head circumference centile in the ASD group was 49.2% ± 26.4. We divided the ASD group into two subgroups: one with HC >3rd percentile (n = 620) and a microcephaly group with HC ≤3rd percentile (n = 39). There were no age differences between the groups with and without microcephaly. The study revealed that the ASD group had higher representation (5.9%) of microcephaly than the 3% expected in the general population [χ²(4) = 19.3, P < 0.001]. We then divided the ASD group into two subgroups: one with HC <97th percentile (n = 540) and a macrocephaly group.

Table 1. Autism Symptoms Severity and Adaptive Functioning in Males and Females with ASD

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>M (SD)</td>
<td>n</td>
<td>M (SD)</td>
<td>F</td>
</tr>
<tr>
<td>Age (months)</td>
<td>577</td>
<td>43.8 (29.1)</td>
<td>86</td>
<td>44.9 (26.6)</td>
</tr>
<tr>
<td>ADOS severity scale</td>
<td>577</td>
<td>7.4 (2.1)</td>
<td>86</td>
<td>7.4 (2.1)</td>
</tr>
<tr>
<td>ADI-R Social</td>
<td>577</td>
<td>16.3 (11.2)</td>
<td>86</td>
<td>16.9 (7.2)</td>
</tr>
<tr>
<td>Communication</td>
<td></td>
<td>10.8 (3.8)</td>
<td>10.1 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Repetitive behavior</td>
<td></td>
<td>4.8 (2.4)</td>
<td>4.3 (2.0)</td>
<td></td>
</tr>
<tr>
<td>VABS composite scores</td>
<td>460</td>
<td>69.9 (10.9)</td>
<td>68</td>
<td>67.3 (12.3)</td>
</tr>
<tr>
<td>IQ/DQ</td>
<td>283</td>
<td>78.8 (21.8)</td>
<td>40</td>
<td>75.7 (21.7)</td>
</tr>
</tbody>
</table>

ADOS, Autism Diagnosis Observation Schedule; ADI-R, Autism Diagnosis Interview-Revised; VABS, Vineland Adaptive Behavior Scales; IQ/DQ, cognitive and developmental abilities.
with HC ≥97th percentile (n = 119). There were no age differences between the groups with and without macrocephaly. The study revealed that the ASD group had higher representation than expected of macrocephaly (18.1%) \(\chi^2(1) = 513.5, P < 0.001\).

Comparing head circumference percentiles in males and females while controlling for age revealed that the mean head circumference percentile for males (50.1 ± 25.6, n = 501) was significantly larger than for females (43.4 ± 30.2, n = 80) \(\chi^2(1) = 6.2, P < 0.01, n^2 = 0.021\). To examine whether the difference in mean head size is not a function of having more females at the extremes of small head size, we examined the distribution of head size in the female group using skew and kurtosis analyses. Values of skew \((Z = 1.18)\) and kurtosis \((Z = −1.06)\) were found in the proper range \((-1.96 < Z < 1.96)\). Given these results, we further investigated the M:F ratio in different head circumference (HC) groups. M:F ratio was significantly lower (2.0:1) in the microcephaly group compared with the >3rd percentile group (7.5:1). These results indicate an increased rate of microcephaly among females with ASD compared with males (Table 2). We then compared the M:F ratio in the ≥97th percentile (defined as macrocephaly) group (9.8:1) with the <97th percentile group (6.2:1) in the ASD sample. The differences in M:F ratio in these two groups were not statistically significant (Table 2).

To examine the prevalence of macro- and microcephaly in males and females separately, the differences between the observed and expected HC in the general population were compared using \(\chi^2\) goodness-of-fit test. Microcephaly was noted in 4.5% of the males in the ASD group and was significantly higher than the 3% expected by definition \(\chi^2(1) = 4.3, P < 0.05\). For females, the rate of microcephaly was five times more pronounced than expected, with 15.1% of the female group having HC ≤3rd percentile \(\chi^2(1) = 42.1, P < 0.001\). Macrocephaly was more frequent in males (18.8%) than in females (12.8%), but this difference was not statistically significant. Among both males and females, macrocephaly representation was significantly higher than the expected 3% [males \(\chi^2(1) = 594.6, P < 0.001\); females \(\chi^2(1) = 28.3, P < 0.001\)] (Fig. 1).

Assessing the developmental trajectory (yes/no regression) in the ASD group revealed that 20.4% of the sample had a history of regression. There were no age differences between the groups with and without developmental regression. The rate of developmental regression was significantly higher for females (30.2%) than for males (18.9%). The M:F ratio in the developmental regression group (4.2:1) was significantly lower than in the non-regressive group (7.8:1) (Table 2). Examining the specific domains of regression revealed that the M:F ratio in the group with \((n = 92)\) and without language regression did not differ significantly. However, the M:F ratio (2.5:1) in the group with social regression \((n = 67)\) was significantly different from the M:F ratio (7.9:1) in the group without regression, indicating more females in the social regression group \(\chi^2(1) = 15.5, P < 0.001\) (Fig. 2).

Of the ASD group, 59.3% of the participants had minor neurological deficits (MNMD). Hyperlaxity of joints (52.5%) and hypotonia (26.3%) were the most frequent abnormalities, followed by abnormal deep tendon reflex (21.1.0%) and cerebellar dysfunction (18.2%), while hypertonia (1.6%) was infrequently found. The group with MNMD was older \((M = 46.5 ± 30.6\) months) than the group without MNMD \((M = 41.1 ± 25.9)\) \(\chi^2(1, 515) = 6.5, P < 0.05, n^2 = 0.009\). Looking at the sex distribution, significantly higher rates of females (73.8%) in comparison to males (57.1%) had MNMD. Calculating the M:F ratio, a significantly lower ratio was found for the group with MNMD \((5.2:1)\) compared with the group without MNMD \((11:1)\) (Table 2).

Of the ASD group, 5.4% were reported to have seizures, significantly more than the 1% expected in the general population \(\chi^2(1) = 57.0, P < 0.001\). In general, the group with seizures was older \((M = 64.3 ± 40.2\) months\) than the group without seizures \((M = 43.4 ± 27.9)\) \(\chi^2(1, 633) = 17.1, P < 0.001, n^2 = 0.026\). The rate of seizures among females with ASD was 9.5%, which was twice as high as the rate of

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**Table 2. Distribution of Neurological Phenotypes among Males and Females in the ASD Cohort and M:F ratio for the Groups with and without the Neurological Phenotypes**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Males</th>
<th></th>
<th>Female</th>
<th></th>
<th>M:F</th>
<th></th>
<th>M:F</th>
<th></th>
<th>(\chi^2(1))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N)</td>
<td>%</td>
<td>(N)</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcephalic</td>
<td>26</td>
<td>4.5</td>
<td>13</td>
<td>15.1</td>
<td>2.0:1</td>
<td>7.5:1</td>
<td>15.0***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrocephalic</td>
<td>108</td>
<td>18.8</td>
<td>11</td>
<td>12.8</td>
<td>9.8:1</td>
<td>6.2:1</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>26</td>
<td>4.7</td>
<td>8</td>
<td>9.5</td>
<td>3.3:1</td>
<td>6.9:1</td>
<td>3.3*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental regression</td>
<td>109</td>
<td>18.9</td>
<td>26</td>
<td>30.2</td>
<td>4.2:1</td>
<td>7.8:1</td>
<td>5.9**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNMD</td>
<td>306</td>
<td>57.1</td>
<td>59</td>
<td>73.8</td>
<td>5.2:1</td>
<td>11.0:1</td>
<td>8.0***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASD, autism spectrum disorder; MNMD, minor neurological and musculoskeletal deficits.

***P < .001, *P < .05, ∧P < .1.
Figure 1. Percentage of head circumference percentiles (≤3%; ≥97%) in males and females with autism spectrum disorder. The horizontal line represents the expected three centiles.

Figure 2. Percentage of developmental regression in language, socialization, and motor skills in males and females with autism spectrum disorder. ***$P < .001$. 

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**Figure 1.** Percentage of head circumference percentiles (≤3%; ≥97%) in males and females with autism spectrum disorder. The horizontal line represents the expected three centiles.

**Figure 2.** Percentage of developmental regression in language, socialization, and motor skills in males and females with autism spectrum disorder. ***$P < .001$. 

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**INSAR**

Ben-Itzchak et al./Specific phenotypes in females with ASD
4.7% in the male population. The M:F ratio in the group with a history of seizures was lower (3.3:1) than the sex ratio of the ASD group without seizures (6.9:1), showing a trend for significant differences (Table 2). Since the peaks of seizures in ASD may occur after the age of 4, the percentage of seizures was investigated in this age group separately and was found to be higher (10.2%) than for the entire group. However, the M:F ratio for this age range for groups with and without seizures was not different from the findings in the entire ASD group. Overall, 24.3% of ASD group (n = 161) did not have any of the examined phenotypes, 50.7% (n = 336) had a single neurological phenotype, and 25.1% (n = 166) had two or more of the examined phenotypes. M:F ratio significantly decreased as the number of the examined phenotypes increased. M:F ratio for the ASD group without phenotypes was 13.6:1, for the ASD group with one phenotype it was 7.6:1, and for the ASD group with two or more phenotypes it was 3.6:1. No age differences were noted between the groups with and without the neurological phenotypes.

**Discussion**

ASD is a heterogeneous group, associated with multiple clinical presentations and etiologies. ASD is considered one of the most common neurodevelopmental disorders, affecting about 1% of the population. Although ASD has been proven to have a major genetic component, only about 20–30% of cases have a known etiology [Schaaf & Zoghbi, 2011]. During the last few years, a vast effort has been made to assess biological and medical conditions that co-occur frequently in ASD, and can shed light on the pathogenesis of ASD. The present study, conducted on a large series of children with ASD, found a decreased M:F ratio, with relatively more females in the majority of clinical phenotypes that are associated with autism.

Accelerated head growth in early childhood resulting in relatively enlarged head circumference has been reported in numerous studies. It is hypothesized that the brain in children with autism undergoes an abnormal growth trajectory that includes a period of early overgrowth. This theory is supported by neuroimaging and neuropathological findings [Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2007; Mraz, Green, Dumont-Mathieu, Makin, & Fein, 2007; Webb et al., 2007]. In general, our study found that the representation of both sexes in the macro- and microcephalic groups was higher than the 3% expected in the general population (18.1% and 5.9% respectively). Regarding sex differences in head circumference, we show for the first time that the average head circumference in females with ASD is smaller than in males. Moreover, among the group with microcephaly, the M:F ratio was significantly lower, with relatively more representation of females. We did not observe the same pattern in the group with macrocephaly, where the M:F ratio was not significantly different from the rest of the ASD group. Similar findings regarding the role of sex in ASD with microcephaly were previously reported in a relatively small cohort [Miles et al., 2000]. Previous studies reported increased rate of microcephaly in ASD [Miles et al., 2005, –5%; Fombonne et al., 1999, −15.1%], but only Miles et al. [2005] reported more female representation in this group. Microcephaly is, in many instances, a sign of abnormal brain development, seen in multiple genetic and nongenetic conditions. Our finding of a higher proportion of microcephaly in females compared with males is highly interesting as ASD is usually associated with enlarged head circumference. These results suggest that a subgroup of ASD with microcephaly is more prevalent in females and might point to a unique etiology for ASD in this group.

We further examined another common clinical condition unique for ASD, developmental regression, noted in 15–30% of cases with autism in different studies [Parr et al., 2011; Shumway et al., 2011; Stefanatos, 2008]. In our ASD group, about 20% had a history of regression, which is in accordance with previous reports. The phenomenon of regression was significantly more common in females than in males. This pattern was especially noted in social development regression, but no differences in sex ratio were found for language development regression. Currently, there is no evidence for clear pathogenetic mechanisms that can explain developmental regression in ASD. Genetic and environmental factors have been suggested as a possible etiology for regression in ASD. Interestingly, one of the known genetic disorder that is associated with developmental regression and symptoms of autism among females is Rett syndrome, which is caused by mutations in the MeCP2 gene. The high prevalence of developmental regression in females in our study strengthens again the possible contribution of unique genetic or neurological processes in females with ASD, which are less prominent in affected males.

We further looked at brain abnormalities in ASD as manifested in MNMD found during the medical examination. High rates of joint hyperlaxity, hypotonia, abnormal DTR, and cerebellar dysfunction were documented, suggesting involvement of various parts of the brain in ASD. These findings are in accordance with recent studies that documented frequent specific dysfunctions in ASD (95%) in comparison to the general population (20%) [De Jong et al., 2011]. The group with MNMD was older than the group without MNMD, which may be explained by the increased minor neurological signs, i.e. cerebellar dysfunction, with age. About three quarters of the females and half of the males had neurological dysfunctions, adding to our previous findings that point to more extensive involvement of brain dysfunction in females.
A history of seizures was documented in about 5.4% of the entire ASD population and in about 10% for children above the age of 4 in our study. These rates are nearly 5–10 times more than the reported rate (1%) in the general population. Higher rates of epilepsy have long been reported in ASD, with prevalence estimates that vary from 5% to 46% [Kagan-Kushnir et al., 2005; Tuchman & Rapin, 2002]. Our finding of a seizure rate lying in the lower range in ASD may stem from the age of the studied population and the type of referrals. In our study, the ASD population included mostly young children (mean age = 44.1 months); therefore, the described second peak of epilepsy among individuals with ASD that appears during mid-adolescence was not reflected in our population. The finding that the ASD group with a history of seizures was older than the group without seizures supports the above explanation. In addition, the tertiary autism center receives referrals for diagnosis of possible ASD in a heterogenic population with general developmental problems, while most of the studies on autism and epilepsy came from specialty neurology and epilepsy clinics that assess populations with seizures as the main problem [Hughes & Melyn, 2005; Rossi, Parmeggiani, Bach, Santucci, & Visconti, 1995; Tuchman & Rapin, 2002], and thus are at a higher risk for ascertainment bias regarding the prevalence of seizures. In the current study, the history of seizures was about twice more frequent in females than in males with ASD. However, these differences were almost statistically significant, which may be explained by the small number of individuals with seizures. A trend of a greater frequency of seizures in females with ASD compared with males was described in previous studies [Bolton et al., 2011; Steffenburg & Gillberg, 1986; Tuchman et al., 1991]. Amiet et al. [2008], in their meta-analysis on epilepsy in females with autism, reported that the pooled prevalence of epilepsy in all the studies they reviewed was of 34.5% in females vs. 18.5% in males. The M:F ratio of autism comorbid with epilepsy was close to 2:1, whereas M:F ratio of autism without epilepsy was 3.5:1.

Overall, a minority of the ASD population had none of the ASD-related phenotypes. However, sex ratio in this group revealed extreme male predominance (13.6:1) that might represent idiopathic ASD. In contrast, the trend toward normalization of M:F ratio when one or more of the examined phenotypes exist may suggest different etiologies for this subgroup. These findings complement the study conclusions that secondary complex etiologies are more associated with female ASD.

Our study found no sex differences in autism severity, as well as cognitive and adaptive skills, in a large ASD population. Therefore, sex differences found in the representation of neurological phenotypes in this study cannot be explained by differences in these behavioral, cognitive, and functional domains. Earlier studies reported that girls with ASD tend to have a lower mean IQ and higher rates of severe intellectual disability compared with boys [Lord & Schopler, 1985; Volkmar et al., 1993]. However, several recent studies that focused on very young children diagnosed with ASD reported less pronounced or no sex differences in cognitive abilities [Carter et al., 2007; Hartley & Sikora, 2009; Mandy et al., 2012; Zwaigenbaum et al., 2012]. The differences between the results of earlier vs. more recent studies might be related to the use of different diagnostic measures, before and after the implementation of International Classification of Disease (ICD)-10 and DSM-IV diagnostic criteria. Several studies assessing autism severity using standardized tests reported no sex differences [Holtmann et al., 2007; Pilowsky et al., 1998; Zwaigenbaum et al., 2012]. Other studies did report sex differences in autism severity, but with conflicting result; some reported more severe symptoms in males [Lord et al., 1982; McLennan et al., 1993], while others reported more severe presentation in females [Carter et al., 2007; Hartley & Sikora, 2009]. In several studies, females had less repetitive stereotyped behavior compared with males with similar levels of social and communication disorders [Mandy et al., 2012; Szatmari et al., 2012].

Social-communication impairments and stereotyped behaviors characterize, by definition, all the individuals with ASD, both males and females. However, ASD is commonly associated with other phenotypes. Miles et al. [2005] divided autism to essential and complex groups; the latter included children with significant dysmorphology and microcephaly. The “complex autism group” had poorer outcome, with lower IQ, more seizures and abnormal EEG, more brain magnetic resonance imaging (MRI) abnormalities, and relatively more females than the “essential autism” group. In the current study, we examined specific neurological phenotypes, including microcephaly, in ASD in a sex-specific manner, in a large, well-characterized population with ASD. We showed that the abnormal neurological phenotypes are consistently associated with female sex.

This study has some limitations, including the lack of complete DQ/IQ data on all the participants, and the use of comprehensive neurological examination but not a standardized protocol for assessment of MNMD. The convergence of our findings indicates that, in addition to the core symptoms, females with ASD present with a higher prevalence of clinical and neurological manifestations compared with males. The investigated neurological phenotypes, microcephaly, developmental regression, and other neurological signs are likely associated with more extensive neurological deficits. It is possible, therefore, that whereas “prototypic” ASD is typically seen in males, the ASD manifestation in many females may result from a different

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disorder associated with more extensive brain dysfunction. It might be that females are more protected than males from “prototypical” ASD [Levy et al., 2011], and therefore a higher prevalence of ASD that is a secondary manifestation of other disorders is found in affected females.

Recent advances in genetic testing, such as the current extensive use of microarray techniques, may reveal new microdeletions/duplications in DNA that are responsible for ASD with complex neurological phenotypes. Such genetic aberrations affect both sexes equally resulting in more female representation in this subgroup.

These compelling results should alert clinicians when assessing a female with ASD to conduct a more comprehensive neurological assessment, and to consider brain imaging and EEG as part of the evaluation.

The proposed hypothesis of a “complex ASD phenotype in females” that involves extensive brain dysfunction should be further analyzed by other methods and approaches, such as a functional MRI and a comprehensive genetic evaluation using advanced methods. Further molecular investigation of the nature of ASD with complex neurological phenotypes is required to improve our understanding of the mechanisms associated with ASD, and might show better success than that seen in the extensive studies performed on the general ASD population, which predominantly consists of males.

References


