Elevated rates of testosterone-related disorders in women with autism spectrum conditions

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Abstract

The androgen theory of autism proposes that autism spectrum conditions (ASC) are in part due to elevated fetal testosterone (FT) levels, which are positively correlated with a number of autistic traits and inversely correlated with social development and empathy. A medical questionnaire was completed by $n=54$ women with ASC, $n=74$ mothers of children with ASC, and $n=183$ mothers of typically developing children to test whether women with ASC have an increased rate of testosterone-related medical conditions, and to see whether mothers of children with ASC show similar abnormalities, as part of the 'broader autism phenotype'. Compared to controls, significantly more women with ASC reported (a) hirsutism, (b) bisexuality or asexuality, (c) irregular menstrual cycle, (d) dysmenorrhea, (e) polycystic ovary syndrome, (f) severe acne, (g) epilepsy, (h) tomboyism, and (i) family history of ovarian, uterine, and prostate cancers, tumors, or growths. Compared to controls, significantly more mothers of ASC children reported (a) severe acne, (b) breast and uterine cancers, tumors, or growths, and (c) family history of ovarian and uterine cancers, tumors, or growths. These results suggest current hormone abnormalities in women with ASC and their mothers. Direct investigations of serum testosterone levels and genetic susceptibility to high testosterone production or sensitivity in women with ASC would illuminate the origin of these conditions. The relationship between FT and current testosterone levels also needs to be clarified. The present results may be relevant to understanding the increased male risk to developing autism.
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Introduction

Autism is a spectrum of neurodevelopmental conditions characterized by difficulties in social development, abnormalities in communication, and the presence of repetitive behaviors/obsessive interests (APA, 1994). Asperger Syndrome (AS) shares these features, but children with AS do not show the delay in language acquisition or general intellectual impairment of classic autism. It has been argued that autism and AS are essentially the same condition but with varied degrees of language development or IQ (Wing, 1988). Together they constitute two major subgroups of autism spectrum conditions (ASC).

Four males are diagnosed with autism for every female, and AS males are nine times as common as AS females (Wing, 1981). This sex difference suggests that there may be a male vulnerability to developing ASC, a hypothesis supported by multiple lines of evidence. For example, individuals with ASC tend to display a hypermasculine profile on many cognitive tasks (Baron-Cohen, 2002). On the Embedded Figures Test and on measures of 'intuitive physics', they perform better than typical males, who perform better than typical females (Jolliffe and Baron-Cohen, 1997; Lawson et al., 2004). On tests involving empathy or 'intuitive psychology', they perform worse than typical males, who perform worse than typical females (Baron-Cohen et al., 1999; Happe, 1995; Baron-Cohen et al., 2001a). Typical males also have more autistic traits on average than typical females, as measured by the Autism-Spectrum Quotient (AQ) (Baron-Cohen et al., 2001b; Wheelwright et al., 2006). These findings have led to the idea that the autistic brain may be

an 'extreme' of the typical male brain (Baron-Cohen, 2002), a theory that is also currently being explored at the level of neural connectivity (Baron-Cohen et al., 2005).

At the biological level, higher levels of fetal testosterone (FT), measured in amniotic fluid, are inversely correlated with amount of eye contact at 12 months of age (Lutchmaya et al., 2002a), vocabulary size at 18 and 24 months (Lutchmaya et al., 2002b), and quality of social relationships at 4 years (Knickmeyer et al., 2005). FT levels are correlated with number of autistic traits as measured on the Childhood Asperger Screening Test (CAST) and the Child Autism Spectrum Quotient (AQ-C) (Auyeung et al., submitted for publication), higher scores on the Child Systemizing Quotient (SQ) (Auyeung et al., 2006), and lower scores on the Child Empathizing Quotient (EQ) (Chapman et al., 2006). Individuals with ASC also have lower-than-expected 2nd to 4th digit (2D:4D) ratios (Manning et al., 2001), which is correlated with higher ratios of FT to fetal estrogen (Lutchmaya et al., 2004), as well as lower verbal and higher numerical intelligence (Luxen and Buunk, 2005).

Some neuroanatomical studies comparing the brains of individuals with and without ASC reveal structural differences associated with high levels of FT, including hemispheric asymmetries (Herbert et al., 2005). Finally, girls with abnormally high FT levels as a result of congenital adrenal hyperplasia (CAH) have a higher number of autistic traits than their unaffected sisters (Knickmeyer et al., 2006a). These findings have led to the androgen theory of ASC, which proposes that elevated FT contributes to differences in brain development that underlie the cognitive traits found in autism (Baron-Cohen et al., 2004; Geschwind and Galaburda, 1985).

Studies of women with ASC, though less common, are consistent with the androgen theory. Women with ASC score similarly to men with ASC on the EQ (Baron-Cohen and Wheelwright, 2004; Wheelwright et al., 2006), the SQ (Baron-Cohen et al., 2003; Wheelwright et al., 2006), and the AQ (Baron-Cohen et al., 2001b; Wheelwright et al., 2006). On average, girls with ASC show an 8-month delay in the onset of menarche (Knickmeyer et al., 2006b) and are more likely to display male-typical play preferences (Knickmeyer et al., submitted for publication). One study found elevated testosterone levels in a subgroup of children with ASC and aggressive behavior (Tordjman et al., 1997). The single pubertal female with ASC in this study had testosterone levels 24% higher and adrenal androgen levels 500% higher than control means.

There is also evidence for cognitive hyper-masculinization in the *parents* of individuals with ASC, who often display traits that reflect the 'broader autism phenotype'. They score higher on the AQ than people without autism, though not high enough to be in the ASC range, and mothers score similarly to control males on items pertaining to social skills (Bishop et al., 2004). Additionally, having both a mother and a father who score in the upper quartile on the Social Responsivity Scale (SRS), another measure of autism spectrum traits, results in an elevenfold increase in the prevalence of meeting clinical criteria for an ASC (Constantino and Todd, 2005). Mothers and fathers of individuals with ASC perform as well as typical males on the Embedded Figures Test and poorer than control females on a test

of reading facial expressions of emotions from the eyes (Baron-Cohen and Hammer, 1997), and findings from a preliminary neuroimaging study suggest that they display a masculine pattern of brain activity while performing these tasks (Baron-Cohen et al., 2006). There is also some evidence for elevated FT levels in parents of children with autism: like their children, they have lower 2D:4D ratios than expected (Manning et al., 2001).

Both the androgen theory and the extreme male brain theory predict that women with ASC might manifest physical masculinization, and be more vulnerable to conditions associated with elevated levels of androgens. In addition, because of the evidence of psychological hyper-masculinization in mothers of children with autism, they too might share some of these vulnerabilities. The survey reported here was developed to investigate whether this was the case.

Methods and materials

The Testosterone-related Medical Questionnaire (TMQ)

The TMQ (see Appendix A) was developed by our research group based on a literature search of endocrine conditions and relevant traits or symptoms, particularly those that have documented associations with androgens. Participants responded either via e-mail or by filling out the survey on a secure Web site. Below we justify the inclusion of each of the 35 items (italicized here) in the TMQ.

Several conditions were included in the TMQ because of their direct effect on sex hormone levels. *Polycystic ovary syndrome (PCOS)*, for example, is an endocrine disturbance in which the ovaries produce atypically high levels of androgens. Excess androgens are also a primary feature of *congenital adrenal hyperplasia (CAH)*, a condition in which they build up due to an enzymatic block, most commonly a 21-hydroxylase deficiency.

Androgens are also a crucial part of sexual development. The *onset of puberty* is characterized by an increase in androgen production (Hiort, 2002), resulting in adolescent *growth spurt*, acne, deepening voice, and body and pubic hair growth. Hyperandrogenism is associated with extreme variants of these developments, including *hirsutism* (Azziz et al., 2000) and *severe acne* (Archer and Chang, 2004). Excess androgens have also been linked to menstrual problems including *amenorrhea* (lack of periods), *irregular menstrual cycle, abnormal uterine bleeding*, and *dysmenorrhea* (severe menstrual cramps) (Caufriez, 1991), while low levels of estrogen are thought to precipitate *premenstrual syndrome* (PMS) (Fink et al., 1996). Many of these problems can be treated through the use of androgen suppressors such as *oral contraceptives* (Yamamoto and Okada, 1994) and are frequently comorbid with conditions such as PCOS (Balen, 1999).

Other factors that can affect the onset of puberty include *thyroid gland abnormalities* and body weight. *Obesity* is a common symptom of PCOS, and there is evidence that obese girls (before and after puberty) have higher levels of androgens than normal-weight girls (Reinehr et al., 2005). Obesity can lead to hyperinsulemia (insulin resistance), making overweight women susceptible to metabolic problems including *diabetes mellitus* and *atherosclerotic disease*.

Another condition thought to be modulated by sex hormones is *epilepsy*. Estrogen is thought to increase neuronal excitability and certain androgens appear to have a suppressive effect on epileptic activity, but this may depend on the balance of conversion from testosterone to dihydrotestosterone, estradiol, and other androgenic metabolites (Herzog, 1999). As a result, seizures in women often fluctuate in frequency and severity over the course of reproductive development, including at puberty, throughout the menstrual cycle, during pregnancy, and at menopause (Morrell, 1999).

Later in life, excess androgens can lead to reproductive complications. Hyperandrogenism, such as in PCOS or CAH, may disrupt ovarian function and can lower fertility (Spiliotis, 2003; Stikkelbroeck et al., 2003), and higher levels of serum testosterone have been found in women with preeclamptic pregnancies, as compared to those with uncomplicated pregnancies (Troisi et al., 2003).

Hormone levels are also linked to tumors, cancers, and other abnormal growths in the sex organs. Higher levels of testosterone are associated with the development and progression of *prostate cancer* (Ko and Balk, 2004), *breast cancer* (Somboonporn and Davis, 2004), *ovarian steroid tumors* (Reedy et al., 1999; Takeuchi et al., 1999), and the most common form of uterine cancer, *endometrial cancer* (Kaaks et al., 2002). Risk of prostrate cancer may also be correlated with the length of the CAG repeat in the androgen receptor gene (Nelson and Witte, 2002), although some studies have found this association to be weak (Zeegers et al., 2004).

Finally, several items on the TMQ address potential behavioral effects of sex hormone levels, for example *tomboyism*, *gender identity disorder (GID)*, and *sexual orientation/preference*. While no definitive link has been established between testosterone and tomboyism, high levels of prenatal androgens have been linked to masculine preferences in toys, activities, and playmates in girls (Hines, 2003). As mentioned earlier, in a study of play toy-preferences, girls with autism were more likely to show a preference for 'male'-typical toys (Knickmeyer et al., submitted for publication). Androgens may also be important determinants of male gender role behavior and gender identity (Wilson, 2001). Female-to-male *transsexuals* have been found to have a higher rate of hyperandrogenic disorders than control women (Bosinski et al., 1997) and there are several single case reports of females with AS having GID or developing transsexualism (Kraemer et al., 2005; Landen and Rasmussen, 1997).

The relationship between testosterone and sexuality is debated. Females with CAH show reduced interest in marriage, motherhood, and physical appearance (Dittman et al., 1990; Ehrhardt and Baker, 1974) and reduced heterosexual behavior and fantasy (Hines et al., 2004; Zucker et al., 1996), although the majority do identify themselves as heterosexual. Several studies have shown a relationship between lower 2D:4D ratios and homosexuality, implicating FT, but other studies reported conflicting results which vary as a function of ethnicity (McFadden et al., 2005). Animal studies have shown that early testosterone injections lead to masculinized sexual behavior in female rats, guinea pigs, ferrets, pigs, zebra finches, and rhesus monkeys (Harris and Levine, 1962; de Jonge et al., 1988; De Vries and Simerly, 2002; Wallen, 1996; Wallen and Baum, 2002; Mansukhani et al., 1996). These findings demonstrate that testosterone is involved in the development of sexual behavior in many non-human animals. However, these findings may not apply to sexual interest and partner preference in humans. Although the role of testosterone should not be discounted in the development of human sexual orientation/preference, it is likely that other environmental, psychological, and social factors are involved as well.

The original TMQ sent out contained some items relating to pregnancy but these items were dropped from the analysis because it was not possible to discern whether the individuals in the ASC group had ever been, or attempted to become, pregnant. It also included an item related to anorexia, but because the relationship between androgens and anorexia is unclear, results from this item are not reported here but are reported elsewhere (Ingudomnukul et al., submitted for publication).

Participants

Three groups participated in this study. All groups consisted of individuals who are registered with research databases held at the Autism Research Centre and the Department of Experimental Psychology in Cambridge University. Participants were directed to register via either the Autism Research Centre volunteers Web site (for **Groups** 1 and 2) or a general population psychology research volunteers Web site (for Group 3). Adverts were placed in relevant clinics, newsletters, or Web sites for people with ASC, or in the general press. This study was approved by the Cambridge Psychology Research Ethics Committee. Consent was assumed when participants filled out the questionnaire.

Group 1 (ASC) comprised 54 adult women with autism, with a mean age of 38.2 years (SD=10.8, range 19.0–63.2). All participants in this group were diagnosed by psychiatrists using established criteria for autism or AS (APA, 1994), the vast majority (50) having AS, 3 having HFA, and 1 having PDD-NOS. Thirty-five additional women with ASC were contacted about the study but did not complete the survey, yielding a response rate of 60.7%. This is a good response for survey research. Responders and non-responders did not differ significantly in terms of age ($F=2.0$, $P<0.161$) or autism-related diagnoses ($\chi^2=2.43$, $P<0.488$).

Group 2 (Mothers) comprised 74 mothers of children with ASC, with a mean age of 40.3 years (SD=6.3, range 26.2–56.8). One had a diagnosis of AS, and 4 others expressed suspicions that they might have AS but had never received an official diagnosis. Seventy-three additional mothers were contacted about the study but did not complete the survey, yielding a response rate of 50.3%. Again, this is a good response for survey research. Responders and non-responders did not differ significantly in terms of age ($F=0.016$, $P<0.899$) or autism-related diagnoses ($\chi^2=0.402$, $P<0.818$).

Group 3 (controls) comprised 185 mothers of children without autism and had a mean age of 43.4 years (SD=6.1, range 26.5–58.5). Two expressed suspicions that they might have AS but had never received an official diagnosis. Insufficient information was obtained from non-responders to compare them to responders. Two women in the control group claimed to be transsexuals but did not provide sufficient information regarding the status of their condition, i.e., whether they were pre-op or post-op. Because sex change procedures require intensive hormone therapy that could cause or affect many of the symptoms or conditions in the TMQ, these two women were excluded from the analyses, leaving an N of 183. A one-way ANOVA with post hoc comparisons showed that groups did not differ significantly in age ($P<0.165$) or level of education ($P<0.426$).

Statistical analysis

The data were summarized and compared with published prevalence statistics in order to ensure that participants were unlikely to be misreporting. Chi-square tests were used to compare the women with ASC and mothers of children with ASC groups to the controls. In comparisons where fewer than 5 cases were present in one or more cells, the Fisher's Exact Test was used to control for sample size.

Results

The reported rates of medical conditions investigated in this sample of controls were consistent with prevalence rates reported in the literature (Table 1). The exceptions to this were the rates for epilepsy and congenital adrenal hyperplasia (CAH), which were reported to be higher in this control sample than expected.

Compared to controls, women with autism reported higher rates of hirsutism ($\chi^2=29.0$, $P<0.0001$), medical diagnosis of polycystic ovary syndrome (PCOS) (FET, $P<0.018$), diagnosis of epilepsy (FET, $P<0.026$), diagnosis of delayed puberty (FET, $P<0.010$), irregular menstrual cycle in adulthood ($\chi^2=15.2$, $P<0.0001$), unusually painful periods in adulthood ($\chi^2=5.2$, $P<0.023$), severe acne problems in the past ($\chi^2=17.0$, $P<0.0001$), and having been considered a tomboy in the past ($\chi^2=4.3$, $P<0.039$). More women with autism reported having one or more close relatives with ovarian cancer, tumors, or growths (FET, $P<0.01$), uterine cancer, tumors, or growths (FET, $P<0.013$), or prostate cancer ($\chi^2=4.4$, $P<0.040$). They were much less likely to have taken oral contraceptives than controls ($\chi^2=17.8$, $P<0.0001$). They also reported a different range of sexual preferences than did controls ($\chi^2=47.9$, $P<0.0001$), being less likely to prefer only males and more likely to consider themselves either bisexual or asexual.

Compared to the control group, significantly more mothers of children with autism reported severe acne problems in the past ($\chi^2=3.8$, $P<0.05$) and a history of breast cancer, tumors, or growths (FET, $P<0.035$) and uterine cancer, tumors, or growths (FET, $P<0.019$). They also reported having one or more close relatives with ovarian cancers, tumors, or growths

Table 1
Summary of chi-square tests comparing adult women with autism spectrum conditions (ASC) and mothers of children with ASC (Mothers) to adult female controls (Controls)

Item	Condition, symptom, or trait	Percent of group represented			Prevalence statistics
		ASC ($n=54$)	Mothers ($n=74$)	Controls ($n=183$)	
A1.	Pre-menstrual syndrome (PMS)	25.9%	18.9%	14.8%	8% have severe PMS/PMDD, and another 15% experience moderate or threshold symptoms (Freeman, 2003)
A2.	Polycystic ovary syndrome (PCOS)	11.3%*	6.7%	2.7%	22–33% of women aged 18–25 have polycystic ovaries, but only 5–10% express the syndrome (Balen, 1999)
A3.	Diabetes	5.6%	4.0%	3.8%	4.5% of total US population are diagnosed, and another 1.8% remain undiagnosed (Centers for Disease Control and Prevention, 2003)
A4.	Epilepsy	7.4%*	1.4%	1.1%	0.5% in adolescents, 0.6% in adults, 0.7% in the elderly (Forsgren et al., 2005)
A5.	Cardiac arrhythmia, atrial fibrillation, or other cardiac conditions	11.3%	8.1%	4.4%	Too broad for prevalence figures
A6	Thyroid gland abnormalities	11.1%	5.3%	8.8%	Hypothyroidism: 1–2% of total population but 10 times more common in women than men and 8% of women are considered subclinical (Vanderpump and Tunbridge, 2002); affects 5–20% of elderly women (Laurberg et al., 2005) Hyperthyroidism: 2% of women (Miehle and Paschke, 2003)
A7.	Congenital adrenal hyperplasia (CAH)	0.0%	0.0%	1.1%	1:15,000 births, or up to 1:100 for non-classical forms in certain populations (Forest, 2004)
A8.	Precocious puberty	0.0%	1.4%	1.6%	~1–3% of women (Tanner and Davies, 1985)
A9.	Delayed puberty	7.4%**	0.0%	0.5%	~1–3% of women (Tanner and Davies, 1985)
A10.	Breast cancer, tumors, or growths	7.4%	8.0%*	2.2%	5.6% of women develop breast cancer by age 65, 10.9% of women over lifetime (Quinn et al., 2000)
A11.	Ovarian cancer, tumors, or growths	7.5%	8.1%	2.7%	~1.5% of women, but rises to 3–4.5% if cohort has one relative with prior history, or 15% if cohort has two or more relatives with prior history (Bell et al., 1998)
A12.	Uterine cancer, tumors, or growths	9.3%	12.0%*	3.8%	0.6% of women develop uterine cancer by age 65, 1.4% of women over lifetime (Quinn et al., 2000)
A13.	Any medical condition involving a hormonal treatment	24.1%	25.7%	18.7%	Too broad for prevalence figures
B1.	Any close relatives with breast cancer, tumors, or growths	43.4%	26.0%	29.1%	5.6% of women develop breast cancer by age 65, 10.9% of women over lifetime (Quinn et al., 2000)
B2.	Any close relatives with ovarian cancer, tumors, or growths	11.3%**	9.5%*	2.2%	~1.5% of women, but rises to 3–4.5% if cohort has one relative with prior history, or 15% if cohort has two or more relatives with prior history (Bell et al., 1998)
B3.	Any close relatives with uterine cancer, tumors, or growths	18.9%*	17.8%*	6.6%	0.6% of women develop uterine cancer by age 65, 1.4% of women over lifetime (Quinn et al., 2000)
B4.	Any close relatives with prostate cancer	18.9%*	15.1%	8.8%	7% of men (Cancer Research UK, 2002)
C1.	Excessive bodily or facial hair (hirsutism) in adulthood	29.6%***	11.0%	4.4%	5–15% of women depending on definition (Azziz et al., 2000)
C2.	Irregular menstrual cycle in adulthood	57.4%***	39.2%	28.6%	~15% of women aged 20–35 (Solomon et al., 2002); 58% of women aged 45–46 (Astrup et al., 2004)
C3.	Unusually painful periods in adulthood	44.4%*	28.8%	28.0%	52–90% of women have dysmenorrhea, but only severe enough to cause absenteeism in 13–51% of women (Weissman et al., 2004)
C4.	Excessive menstrual bleeding or endometriosis in adulthood	37.0%	34.2%	34.1%	2–22% of asymptomatic women and 40–50% of women with dysmenorrhea have endometriosis (Farquhar, 2000); ~30% of women complain of heavy menses (Oehler and Rees, 2003)
D1.	Periods started before age 10	5.7%	0.0%	2.2%	~1–3% of women (Tanner and Davies, 1985)
D2.	Periods started after age 16	7.4%	1.4%	4.4%	~1–3% of women (Tanner and Davies, 1985)
D3.	Any history of severe acne	27.8%***	14.9%*	7.1%	50% of UK girls age 14–16 have acne, but only 11% have moderate or severe symptoms (Smithard et al., 2001)
D4.	Early growth spurt (e.g., being one of the tallest in your class at school)	25.9%	30.1%	26.4%	Too broad for prevalence figures
E1.	Ever used contraceptive pill	68.5%***	90.4%	91.2%	54% of single women, 26% of married or cohabitating women, 22% of widowed, divorced, or separated women are currently using the pill (Taylor et al., 2006)
G1.	Ever considered a tomboy as a child	53.7%*	39.7%	37.9%	No official figures, but studies range anywhere from 10–63% of heterosexual women and 70–82% of lesbian women (Devor, 1997)
G2.	Ever been diagnosed with a gender identity disorder (GID)	1.9%	0.0%	0.5%	1/34,000 MF; 1/108,000 FM (Hoenig and Kenna, 1974)
G3.	Transsexual	0.0%	0.0%	0.0%	1/34,000 MF GID; 1/108,000 FM GID (Hoenig and Kenna, 1974)
G4.	Sexual preference	***			
	Males	67.9%	98.6%	97.3%	4.1% of women have had same-sex preferences since age 18
	Females	1.9%	0.0%	1.1%	(Laumann et al., 1994); ~1% of population is asexual (Bogaert, 2004)
	Either/Bisexual	13.2%	1.4%	1.6%	
	Neither/Asexual	17.0%	0.0%	0.0%	

Significant differences as compared to the control group are indicated. *$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

(FET, $P<0.015$) and uterine cancers, tumors, or growths ($\chi^2=6.1$, $P<0.013$).

Discussion

The results of the study are consistent with the androgen theory of autism and suggest that heightened testosterone levels and/or activity may exist in individuals with ASC into adulthood, manifesting in other conditions. Although some of these clinical conditions appear at increased rates in this sample of individuals with autism, there is no suggestion that one of these conditions (e.g., PCOS) causes autism (or vice versa). Rather, we assume that these conditions and autism share a common risk factor: elevated T levels.

Medical conditions

Several androgen-related conditions were found at a higher rate in the ASC group, including PCOS, hirsutism, severe acne, and menstrual dysfunctions such as irregular menstrual cycle and dysmenorrhea. To confirm that the potential overlap of PCOS with some of the aforementioned symptoms was not driving the statistical effects of these variables, we repeated the chi square tests after excluding all individuals who had reported a diagnosis of PCOS, with the result that all the differences previously found remained significant. As these conditions present themselves primarily in adolescence or adulthood, these findings suggest that androgen levels may be raised not only prenatally but also at later points in the life span of many individuals with ASC.

Significantly more women with autism than controls reported having been diagnosed with delayed puberty; however, while only 1.1% of the control group had a diagnosis of delayed puberty, 4.9% did not begin periods until after age 16, a criterion that is usually sufficient for the diagnosis of delayed puberty. This inconsistency may be due to the fact that controls were less likely to seek out or receive a diagnosis of delayed puberty during adolescence. When these women are counted as having been diagnosed with delayed puberty, the difference between the ASC group and controls is no longer significant (FET, $P<0.339$). Since low body weight may affect T levels, Body Mass Indices were calculated from height and weight data, and a one-way ANOVA with post hoc comparisons revealed no significant differences between groups ($P<0.108$).

More women in the ASC group reported having had a medical diagnosis of epilepsy. This is consistent with previous reports that there is an increased risk of epilepsy in autism which varies depending on age, cognitive level, and language ability (Tuchman and Rapin, 2002). Because testosterone's relationship to epilepsy may depend on its rate of conversion to other androgenic metabolites, this finding is difficult to interpret with our current knowledge of this connection. Also complicating the matter is the fact that some antiepileptic treatments, especially valproate, are thought to cause endocrine disturbances that may cause PCOS and other reproductive disorders (Rasgon, 2004). To confirm that such side effects were not

driving our statistical results, we repeated the chi square tests after excluding individuals with epilepsy and found once again that all differences previously found remained significant, including the group differences in PCOS, hirsutism, severe acne, irregular menstrual cycles, and dysmenorrhea.

Another finding from this study that merits further investigation because of its seriousness (as well as its potential relevance to causality) is that relatives of the ASC group and mothers of individuals with autism had higher rates of certain cancers, tumors, or abnormal growths than the control group. The Mothers group also had a higher incidence of acne problems. It is therefore possible that close relatives of individuals with autism, who may have the 'broader autism phenotype' (Piven et al., 1997), may also have elevated testosterone levels later in life, compared to a control group. These results need to be replicated and explored in more detail.

Behavioral traits

The ASC group also differed from controls in two behavioral traits: tomboyism and sexual orientation/preference. Regarding the former, women with an ASC were more often considered tomboys during childhood. Regarding the latter, women with an ASC were more likely to show bisexual interests or reduced sexual interest. We acknowledge that the control group consists of mothers, who are more likely to have had a heterosexual relationship and to prefer males; however, the difference between the ASC group and controls is sufficiently large to merit follow-up. Also noteworthy is the high percentage (17%) of the ASC group who stated that they were asexual or had a sexual preference for neither sex. This may be relevant to the finding that women with ASC are much less likely to have ever used oral contraception. It is unclear whether these women consider themselves asexual because they are disinterested in sex or because sex typically requires social challenges that might be too great for them. Studies of asexuality in humans are sparse, and it is unclear whether any relationship exists between asexuality and hormones. One study of a British sample found that 1% of individuals were asexual and that being female, having poor health, and having a later onset of menarche were among the factors associated with asexuality (Bogaert, 2004). These results are interesting given the current focus on hormonal conditions.

Limitations

When evaluating the results of this study, it is important to keep in mind that because the TMQ covered a wide array of conditions, it is statistically likely that some significant differences between the groups could have been found by chance. However, the strongest findings (hirsutism, history of severe acne, irregular menstrual cycle in adulthood, sexual preference) remained unaffected by using Bonferroni-adjusted alpha levels of .0017 per test (.05/30). We have opted to report the uncorrected P-values as they may reflect trends that should be explored in future studies.

Because the TMQ was distributed electronically and because individuals who were more affected by these conditions were probably more likely to fill out the survey, it should be noted that this sample may not necessarily be representative of the general population. It would be ideal in future studies to recruit a broader sample and to match the ASC and control groups for marital and reproductive status. We also relied on self-report of clinical conditions. Future studies could confirm these findings via clinical examination and medical records checks.

In conclusion, we found an increased rate of medical conditions and behavioral traits associated with elevated androgen levels in women with ASC. Mothers of children with ASC shared some of the same vulnerabilities. These findings are consistent with the androgen theory of autism and suggest several avenues for future research. Direct measures of testosterone from blood samples from women with autism are needed, as are studies of genetic susceptibility to high testosterone production or sensitivity. Such studies are underway in our lab. Furthermore, the relationship between FT, current testosterone levels, and actual testosterone activity needs to be clarified. Finally, focused investigations of the clusters of conditions that appear to be more prevalent in a population with autism (gonadal cancers, and the cluster of symptoms related to PCOS) may help tease apart the specific common hormonal or genetic control mechanisms.

Acknowledgments

Appendix A. The Testosterone-related Medical Questionnaire (TMQ)

Your name:

For each question, please type Y for yes and N for no.

A. Have you ever been diagnosed by a medical doctor with any of the following medical conditions? If yes, please specify.

	Y/N

1. Pre-menstrual syndrome (PMS)
2. Polycystic ovary syndrome (PCOS)
3. Diabetes
4. Epilepsy
5. Cardiac arrhythmia/atrial fibrillation/other cardiac conditions
6. Thyroid gland abnormalities
7. Congenital adrenal hyperplasia (CAH)
8. Precocious puberty
9. Delayed puberty

	Y/N

10. Breast cancer/tumors/growths
11. Ovarian cancer/tumors/growths
12. Uterine cancer/tumors/growths
13. Any medical condition involving a hormonal treatment

B. Have any of your close relatives (i.e., parents, siblings, grandparents, children) been diagnosed with any of the following? If yes, please specify which relative.

	Y/N

1. Breast cancer/tumors/growths
2 Ovarian cancer/tumors/growths
3. Uterine cancer/tumors/growths
4. Prostate cancer

C. Have you had any of the following problems in adulthood? If yes, please specify:

	Y/N

1. Excessive bodily or facial hair (hirsutism)
2. Irregular menstrual cycle
3. Unusually painful periods
4. Excessive menstrual bleeding or endometriosis

D. Did you have any of the following in the past?

	Y/N

1. Your periods started before the age of 10 years
2. Your periods started after the age of 16 years
3. Severe acne
4. Early growth spurt (e.g., being one of the tallest in your class at school)

E.

	Y/N

1. Have you used the contraceptive pill?

F.

	Y/N

1. How tall are you?
2. How much do you weigh?

G.

	Y/N

1. Were you considered a tomboy as a child?
2. Have you ever been diagnosed with gender identity disorder (GID)?
3. Are you transsexual? If yes, please specify.
4. Is your sexual preference for males, females, either or neither?

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