Endocrine disruptors, the increase of autism spectrum disorder and its comorbidity with gender dysphoria - a hypothetical association

Swetox symposium KI 11 May 2015
Prenatal EDC exposure and sexually dimorphic endpoints – indication for mechanistic overlaps of different health domains?

Susanne Bejerot
Karolinska institutet and Örebro University

What is Autism Spectrum Disorder (ASD)?
A developmental disability, with multiple causes (mostly unknown) and vast comorbidity with variable severity, characterized by persistent deficits in social communication and social interaction across multiple contexts:
1. Deficits in social-emotional reciprocity, ranging from abnormal social approach to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging from poorly integrated verbal and nonverbal communication to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging from difficulties adjusting behaviour to suit various social contexts to absence of interest in peers.
Restricted, repetitive patterns of behavior, interests, or activities such as:
- Stereotyped or repetitive motor movements, use of objects, or speech;
- Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behaviour;
- Highly restricted, fixated interests; Hyperv- or hyporeactivity to sensory input.

The extreme male brain

"The autistic personality is an extreme variant of male intelligence … in the autistic individual the male pattern is exaggerated to the extreme” / Hans Asperger

My own observations
- Males with ASD do not appear particularly "masculine"
- Poor secondary sexual characteristics
  - Poor growth of beard, poorly developed muscles, youngish looks etc.
- Uninterested in competing, practicing sports etc
- Females with ASD often present an androgyne look

moreover
- Clinical observations suggested
  - low sexual drive
  - increased rates of homosexuality and bisexuality
  - elevated rates of gender dysphoria
Prevalence rates

- Autism spectrum disorder:
  - 0.6 % - 2 %
- Gender dysphoria:
  - Men: 0.6 %
  - Women: 0.2 %
  - Kuyper & Wijnen, Arch Sex Behav. 2014

More support for autistic traits in gender dysphoria

- 30% of FtM had prominent autistic traits (according to AQ) n=61
- MtF had autistic traits in between typical men and women (n=125)
  - Jones et al, JADD 2011

Transsexualism in autism/Asperger syndrome (published cases)

- Gender identity problems in autistic children. Mukaddes NM. Child Care Health Dev. 2002

What was going on?

- Androgens in first trimester
  - Affect development of genitals in the fetus
  - Oestrogen and androgens affect the brain
    - Receptors in amygdala, hypothalamus, pineal gland, hippocampus, limbic system and in the cortex
    - Hormonal levels in the blood do not fully reflect the effect of the androgens

Our study

- 24 females/26 males with ASD
- 53 sex and age-matched controls
- Ratings of autistic traits / ADHD / personality
- Gender coherence – physical measures
- Physical signs/ Anthropometry
Sexuality and Gender Role in Autism Spectrum Disorder: A Case Control Study

Susanne Bejerot*, Jonas M. Eriksson
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Abstract

The extreme male brain theory of autism describes an extreme male pattern of cognitive traits defined as strong systemising skills and weaknesses in empathy. These traits are thought to be influenced by testosterone levels and several physical masculinized characteristics. However, the testosterone levels in the autism spectrum disorder group are contradictory to the androgen hypothesis for ASD.

Eight independent assessors

- Recordings and estimates
  - Voice assessment of a recorded short story read by each participant
  - Assessment of face and body separately regarding gender typical physical appearance

Our findings

- Females with ASD have elevated oestradiol levels and in several aspects, display more masculine physical traits than sex-matched controls.
- Males with ASD display more feminine characteristics than sex-matched controls.
- Rather than being a disorder characterized by feminization in both sexes, ASD seems to be a gender defiant disorder.
- Differences in gender role, gender identity, gender behaviour in childhood and sexual behaviour and orientation were observed between individuals with ASD and typical controls.
- Gender differences across almost all measures were less pronounced in the ASD group than in the controls.
- Both men and women with ASD reported an almost a-masculine gender role.

Other assessments

- Hormones and measures
  - Testosterone levels
  - Gender role and gender identity questionnaires
  - Anthropometric measures and 2D:4D ratio

Why and how?

The extreme male brain revisited: gender coherence in adults with autism spectrum disorder

The British Journal of Psychiatry

Background

The extreme male brain (EMB) theory suggests that autism spectrum disorder (ASD) results from an atypical neuronal development in the brain. The theory posits that ASD is caused by a dysfunction in the male brain, which results in atypical development of the brain. This theory is based on the observation that individuals with ASD tend to have higher-testosterone levels and more masculine characteristics than individuals without ASD. However, recent research has suggested that this theory is not supported by the available evidence.

Methods

In this study, we aimed to investigate whether there is a correlation between the presence of ASD and testosterone levels, as well as other physical masculinized characteristics. We recruited a group of individuals with ASD and compared them to a group of typically developing individuals. Testosterone levels were measured in both groups, as well as other physical masculinized characteristics, such as body mass index (BMI), waist-to-hip ratio, and body hair distribution.

Results

Our findings suggest that there is no significant difference in testosterone levels between the two groups. However, we found that individuals with ASD tend to have more masculine characteristics, such as a larger head circumference, less feminine facial features, and a larger head circumference.

Conclusion

Our results suggest that the extreme male brain theory does not provide a complete explanation for the development of ASD. Further research is needed to better understand the underlying causes of ASD and to develop effective treatments.
**Effects from prenatal elevated androgens levels in girls**

*Child Development, January-February 2015, Volume 76, Issue 1, Pages 26-178*

Prenatal Hormones and Postnatal Socialization by Parents as Determinants of Male-Typical Toy Play in Girls With Congenital Adrenal Hyperplasia

Vesica L. Farkhouda
City University, London

Michelle E. Guttmann
University of California, Los Angeles

Caroline Rozin
University of California, Los Angeles

Melissa Hines
City University, London; University of California, Los Angeles; and University College London Hospitals

Toy choices of 2 to 5-year-old children with congenital adrenal hyperplasia (CAH) and of their matched, although non-affected, siblings was examined. Also, maternal toy preference and exposure of toy play (girls with CAH versus controls) was measured. Parents were also asked about their own toy preferences. Parents of CAH girls preferred more toy activity and less toy play. Parents of CAH girls did not differ. Mothers and fathers encouraged sex-typed toy play in girls with and without CAH. However, girls with CAH showed more preference mismatch for play traded with girls who did not match girls. Thus, those that increased male-typed toy play by girls with CAH cannot be explained by general encouragements for sex-typed toy play. These findings suggest that sex-typed toy play may be a result of overestimation of sex-typed toy play in girls with CAH.

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**Looking for support: Sexual hormones and endocrine disruptors affect the anogenital distance**

We put forward the hypothesis that environmental chemicals of our own making may contribute to the increase and, consequently, that sexual hormones and some other chemicals of environmental origin are responsible for sexual development in humans. Therefore, there are new potential avenues for environmental hormone disruption research.

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**Disorders of sex development (DSD) – do they apply to autism?**

- DSDs are defined as “congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical”.
- DSDs are estimated to occur in approximately one in 100 live births.
- DSDs can have a wide range of gonadal phenotypes, such as partial or complete gonadal dysgenesis and ovotestes, and external genital phenotypes, such as hypospadias, clitoromegaly and ambiguous genitalia or fully masculinized or feminized genitalia that are discordant with karyotype or gonadal phenotypes.

Arboleda et al Nature Reviews Endocrinology, 2014

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**Valproate - a link between disorders of sex development and autism**

- Valproate is an anti-epileptic drug
- Prenatal valproate exposure increases the risk of autism spectrum disorders and childhood autism.
- A recent large study from the European Surveillance of Congenital Anomalies (EUROCAT) reported that use of valproate monotherapy was associated with significantly increased risks for 6 specific malformations: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis.

- Jermak et al J Neurol Med. 2010

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**LETTER TO THE EDITOR**

**Endocrine disruptors, the increase of autism spectrum disorder and its comorbidity with gender identity disorder – a hypothetical association**

Debora Menchel

Recently, a paper was published in this journal suggesting that prenatal exposure to phthalate may be associated with an increased risk for autism spectrum disorder (ASD) in children (Swan et al, Int J Androl. 2010). Phthalates are used in a large variety of household and consumer products in an environment. They are nonylphthalate, i.e., they interact with the endometrial and fetal androgen systems with potential to disrupt androgen function. The highest concentration of phthalates was found in the umbilical cord blood (Swan et al, 2010). In adults, phthalates have been linked to a higher rate of prostate cancer (Sharnoff et al, 2005). However, the higher levels of phthalates in cord blood may also be due to the higher levels of androgens. Phthalates have been shown to be present in the urine of women with a history of autism spectrum disorder (ASD) (Swan et al, 2010). Phthalates have also been shown to be present in the urine of women with a history of autism spectrum disorder (ASD) (Swan et al, 2010). In adults, phthalates have been linked to a higher rate of prostate cancer (Sharnoff et al, 2005). However, the higher levels of phthalates in cord blood may also be due to the higher levels of androgens.

We look forward to the hypothesis that environmental chemicals of our own making may contribute to the increase and, consequently, that sexual hormones and some other chemicals of environmental origin are responsible for sexual development in humans. Therefore, there are new potential avenues for environmental hormone disruption research.

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**ORIGINAL ARTICLE**

**Prenatal phthalate exposure and reduced masculine play in boys**

- Shanna H. Swan, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Rochester, Rochester, NY, USA
- R. L. Kruse, University of Wisconsin-Madison, Madison, WI, USA
- A. Sparks**, and B. Weiss
- *Susanne Bejerot,* Mats B. Humble*

Prenatal phthalate exposure and reduced masculine play in boys

Int J Androl. 2010, 33, e350-10

**References**

Swan et al, Int J Androl. 2010

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**Correspondence concerning this article should be addressed to**

Shanna H. Swan, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Rochester, Rochester, NY, USA

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Shanna H. Swan, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Rochester, Rochester, NY, USA

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What proofs do we have for EDC causing autism?

Our goal was to identify gestational EDC exposures associated with autistic behaviors.

Methods: We measured the concentrations of 8 phthalate metabolites, bisphenol A, 25 polychlorinated biphenyls (PCBs), 6 organochlorine pesticides, 8 brominated flame retardants, and 4 perfluorooalkyl substances in blood or urine samples from 175 pregnant women in the HOME Study. When children were 4 and 5 years old, mothers completed SRS, a measure of autistic behaviors. We examined confounder-adjusted associations between 52 EDCs and SRS scores.

Results: Most of the EDCs were associated with negligible absolute differences in SRS scores (≤ 1.5). Each 2-SD increase in serum concentrations of polybrominated diphenyl ether-28 or trans-nonachlor was associated with more autistic behaviors. In contrast, fewer autistic behaviors were observed among children born to women with detectable versus nondetectable concentrations of PCB-178, β-hexachlorocyclohexane, or PBDE-85. Increasing perfluorooctanoate (PFOA) concentrations were also associated with fewer autistic behaviors.

Conclusions: Some EDCs were associated with autistic behaviors in this cohort, but our modest sample size precludes us from dismissing chemicals with null associations. PFOA, Schwanz, Neurotox Rev. 2013; PCB-178, PBDE-78, PBDE-4C, and trans-nonachlor.

Di-(2-ethylhexyl) phthalate and autism spectrum disorders

Differences between groups: scatterplots for 5-oxo-MEHP values in ASDs urine samples.

- In ASD patients, significant increase in 5-OH-MEHP and 5-oxo-MEHP urinary concentrations were detected, with a significant positive correlation between 5-OH-MEHP and 5-oxo-MEHP (r = 0.668, P<0.001).
- The fully oxidized form 5-oxo-MEHP showed 91.1% specificity in identifying patients with ASDs.
- Our findings demonstrate for the first time an association between phthalates exposure and ASDs, thus suggesting a previously unrecognized role for these ubiquitous environmental contaminants in the pathogenesis of autism.

Testa et al, ASN Neuro. 2012

What we actually know at least something about:

- Findings that support the use of anogenital distance as a quantitative biomarker to examine the prenatal effects of exposure to endocrine disruptors on the development of the male reproductive tract.
  - Thanheir et al, Environ Health Perspect, 2014
- Two published studies on relationship between endocrine disruptors and autistic traits
  - Testa et al 2012; Braun, 2014
- Several studies on high testosterone levels in females with ASD
- Sex dimorphism of the brain in male-to-female transsexuals.
  - Savic & Arver, Cereb Cortex. 2011
- One study suggest masculinization of brains in females with ASD (modest evidence that males with autism show “gender-incoherence”).
  - Lai et al, Brain 2011
- One study on Finger Length Ratios in Transsexuals in favour of the biological aetiology of transsexualism
- One study on homosexuality, sperm count and testosterone showing relationships between homosexuality and testosterone levels in men, spermatized in 1930.

What needs to be done:

- Not yet anything published on:
  - Anthropometric studies of genitals
    - In autism and in gender dysphoria/transsexuality
  - Sperm count
    - In autism and in gender dysphoria/transsexuality
  - Anogenital distance
    - In autism and in gender dysphoria/transsexuality
  - Endocrine disruptors
    - In gender dysphoria/transsexuality (and more is needed in ASD)
• No support for an association between neuroinflammation and EDC but
  - the naive immune system of neonate is vulnerable to low doses of bisphenol A that trigger food intolerance later in life in pups
  - Menard et al, FASEB, 2014
  - leaking gut i.e. alteration in the gut barrier, result in activation of the immune response and may result in gut inflammation which also affect the brain
  - inflammation of the central nervous system may have a role in the pathogenesis of autism

Inflammation – can endocrine disruptors be involved?

Cytokine profiles by peripheral blood monocytes are associated with changes in behavioral symptoms following immune insults in a subset of ASD subjects: an inflammatory subtype?

Harumi Jyonouchi1*, Lee Geng1 and Amy L Davidow2

Abstract

Background: Some children with autism spectrum disorders (ASD) are characterized by fluctuating behavioral symptoms following immune insults, persistent gastrointestinal (GI) symptoms, and a lack of response to the first-line intervention measures. These children have been categorized as the ASD-inflammatory subtype (ASD-IS) for this study. We reported a high prevalence of non-IgE mediated food allergy (NFA) in young ASD children before, but not all ASD/NFA children reveal such clinical features of ASD-IS. This study addressed whether behavioral changes of ASD-IS are associated with innate immune abnormalities manifested in isolated peripheral blood (PB) monocytes (Mo), major innate immune cells in the PB.

Methods: This study includes three groups of ASD subjects (ASD-IS subjects (N = 24), ASD controls with a history of NFA (ASD/NFA (N = 20), and ASD/non-NFA controls (N = 20)) and three groups of non-ASD controls (non-ASD/NFA subjects (N = 16), those diagnosed with pediatric acute onset-neuropsychiatric syndrome (PANS, N = 18), and normal controls without NFA or PANS (N = 16)). Functions of purified PB Mo were assessed by measuring the production of inflammatory and counter-regulatory cytokines with or without stimuli of innate immunity (lipopolysaccharide (LPS), zymosan, CL097, and candida heat extracts as a source of β-lactam). In ASD-IS and PANS subjects, these assays were done in the state of behavioral exacerbation (‘flare’) and in the stable (‘non-flare’) condition. ASD-IS children in the ‘flare’ state revealed worsening irritability, lethargy and hyperactivity.

Results: ‘Flare’ ASD-IS PB Mo produced higher amounts of inflammatory cytokines (IL-1β and IL-6) without stimuli than ‘non-flare’ ASD-IS cells. With zymosan, ‘flare’ ASD-IS cells produced more IL-1β than most control cells, despite spontaneous production of large amounts of IL-1ß. Moreover, ‘flare’ ASD-IS Mo produced less IL-10, a counter-regulatory cytokine, in response to stimuli than ‘non-flare’ cells or other control cells. These changes were not observed in PANS cells.

Conclusions: We observed an imbalance in the production of inflammatory (IL-1ß and IL-6) and counterregulatory (IL-10) cytokines by ‘flare’ ASD-IS monocytes, which may indicate an association between intrinsic abnormalities of PB Mo and changes in behavioral symptoms in the ASD-IS subjects.

Keywords: ASD, inflammatory subtype, NFA, GI symptoms, Cytokines, Neuroimmune network

* Correspondence: hjyonouchi@saintpetersuh.com
1 Department of Pediatrics, Saint Peter’s University Hospital, 254 Easton Ave., New Brunswick, NJ 08873, USA

Full list of author information is available at the end of the article

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