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A potential explanation of some established major risk factors for autism

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ABBREVIATIONS
ADHD Attention-deficit-hyperactivity disorder
ASD Autism spectrum disorder

Baron–Cohen hypothesized that a cause of autism in infants is exposure to high concentrations of intrauterine testosterone concentrations. Some of the subsequent research on this hypothesis has focused on the possibility that the source of this testosterone is the fetus; however, this review shows that if the source is taken to be the mother, then many of the established risk factors for autism could be explained. If that were correct, it would follow that high maternally derived intrauterine androgen concentrations may be a major environmental cause of autism.

There is good evidence that the causes of autism are multifactorial (genetic plus environmental).[1,2] Moreover, although the evidence for a genetic aetiology is strong,[3] the individual genetic elements are apparently weak, numerous, and perhaps overestimated.[4] At any rate, genetic factors may be of little immediate practical consequence in the tasks of treating the condition and of reducing its incidence. At present, therefore, it would seem prudent to direct research at elucidating the environmental cause(s) of autism.

Gardener et al.[5] compiled a list of prenatal risk factors for autism on the basis of a comprehensive meta-analysis. These authors identified more than 50 factors with which autism had been reported to vary. They suggested that this variation is reliable in respect of the following six factors: (1) advanced parental age at birth; (2) maternal prenatal medication use; (3) maternal bleeding; (4) gestational diabetes; (5) being firstborn versus third or later born; and (6) having a mother who was born abroad.

To these six factors, Voracek[6] added another: exposure of the fetus to high androgen levels. He did so for the following reason. Manning et al.[7] had studied the finger length ratio, *R*, where *R*=2D/4D, where 2D and 4D are the lengths of the second and fourth fingers. They found that the *R* values of children with autism, their siblings, and both of their parents were all significantly less than population values. *R* is a putative measure of fetal hormone exposure, so these authors accordingly inferred that fetuses with autism had been exposed to high androgen levels. Voracek's suggestion was made on the ground that the finding of Manning et al.[7] had been independently replicated by 10 further studies.[8] It is fair to say that there has been little success in explaining the established risk factors for autism adduced by Gardener et al.[5]

In this review, I shall first consider terminology. Then I shall discuss the hypothesis of Baron–Cohen[9] and recent evidence for it. Lastly, I shall adduce evidence to suggest that Baron–Cohen's hypothesis might account for all the foregoing risk factors for autism, and for others subsequently identified. If that were substantially correct, it would suggest that exposure to high concentrations of intrauterine androgens is a major environmental cause of autism.

TERMINOLOGY

There are a number of neurodevelopmental disorders that elude exact definition, which show some behavioural overlap, which are thought to be of multifactorial origin, and which occur more frequently in males than in females. Terms used to denote these disorders include 'reading disability', 'autism spectrum disorder' (ASD), 'pervasive developmental disorder–not otherwise specified' (PDD-NOS), 'attention-deficit–hyperactivity disorder' (ADHD), 'developmental language disorder', and 'oppositional defiant disorder'. With this proliferation of diagnostic terms, there is no guarantee that different authors use a term in exactly the same sense. However, since (as will be documented) there is an overall suspicion that all these conditions share a cause (intrauterine exposure to androgens), little purpose is served in sharpening the various diagnoses before that suspicion has been tested. Genome investigations of the first three of the above categories suggest a possible genetic overlap.[10] Moreover, the suspicion above was generated by the suggestion that high intrauterine levels of testosterone are associated not only with autism,[7,9,11] but also with ADHD, oppositional defiant disorder, and PDD-NOS.[12]

An immediate problem is that of taxonomy: how should these categories be classified? Are we to 'lump' or 'split'? Here, as suggested above, the solution will be first to 'lump'. By doing this initially, we may hope to avoid a type II error (that of accepting the null hypothesis when it is, in fact, false) contingent on too small a sample size. If significance is

achieved by 'lumping', then we may choose to 'split' to determine whether each of the different diagnostic categories is associated with the criterion under test.

BARON–COHEN'S HYPOTHESIS AND RECENT EVIDENCE FOR IT

The hypothesis proposed that autism was caused by high intrauterine testosterone levels.[9] Although intrauterine hormone levels are sometimes available,[13] Baron–Cohen's hypothesis was initially tested by measuring offspring finger length ratios.[7] In contrast with a comparison group, these were significantly more masculine in children with autism and in their siblings and parents. These data were generally interpreted to suggest, in conformity with Cohen–Bendahan et al.,[13] that the fetus (rather than the mother) was the source of the testosterone hypothesized to be responsible for autism. This perspective on the hypothesis continues to be the subject of discussion.[14]

Here I suggest a means of testing the effect of the testosterone contributed by the mother (as opposed to the fetus). This possibility arises as follows: there is now very substantial evidence that the sexes of mammalian (including human) offspring are partially determined by the hormone levels of both parents around the time of conception.[15–18] According to this hypothesis, high testosterone levels in either parent around the time of conception are associated with the subsequent production of male offspring. It follows that if a congenital disorder were at least partially caused by high intrauterine testosterone levels, it would be expected to occur more frequently in males. Moreover, testosterone levels in females persist across time.[19] So, Baron–Cohen's hypothesis could be tested by examining the sex ratio (proportion of males) of the siblings of probands with autism. If this sibling sex ratio were significantly high too, this would constitute evidence that mothers of such probands are predisposed to produce the disorder and male children (both, according to this hypothesis, via high testosterone levels). I have previously cited studies using this form of argument to implicate maternal hormone levels in the aetiology of the following sex-biased congenital disorders: polydactyly, transposition of the great arteries, oral clefts, and pyloric stenosis.[20] In that paper,[20] I also adduced evidence that (when the data are pooled) there is a statistical excess of brothers among the siblings of probands with reading disabilities, ADHD, and ASD. Moreover, this finding has been confirmed in respect of developmental language disorder[21] and ASD.[22] So, the evidence is very strong that Baron–Cohen's hypothesis is substantially correct–at least in regard to some of these diagnostic categories. That being so, it seems reasonable to try to assess whether his hypothesis identifies a major (or merely a minor) aetiological factor. This may be done by examining whether it can be reconciled with most (or all) of the established risk factors for autism.

RISK FACTORS FOR AUTISM IDENTIFIED BY GARDENER ET AL.

In female mammals, the major source of androgens is the adrenals. [5] These react to stress of many sorts, for example infectious disease, psychotic disorder, surgical trauma, and strenuous exercise.[23] Hence, high androgen levels have been reported in women who are chronically stressed,[24] chronically fatigued,[25] chronically depressed,[26] or exposed to fear-relevant stimuli during pregnancy.[27] This phenomenon of stressed women producing adrenal androgens underlies many of the following comments on the individual risk factors for autism. The factors of Gardener et al.[5] will now be treated in order.

What this paper adds

- This paper offers a hypothesis that might explain the major risk factors for autism.
- It adds to the evidence for Baron–Cohen's hypothesis that testosterone is a cause of autism.
- It suggests that the primary source of this testosterone is the mother.

Advanced parental age

When a congenital pathology correlates with advanced parental age, it is not clear whether this is due to a current parental condition associated with age or to one associated with past subfertility. Testosterone does not increase with age in either males or females.[28,29] However, parents may be old because they are subfertile (having been exposed to the risk of pregnancy but having failed to achieve one in the past). If so, such a process would select for female hyperandrogenism, because this is associated with female subfertility, as will now be shown.

Obstetric suboptimality

The next two risk factors (maternal prenatal medication and maternal bleeding) adduced by Gardener et al.[5] may be subsumed into a category of 'obstetric suboptimality', a term coined by Haglund and Kallen,[30] who reported that preterm birth, low Apgar score, and growth restriction were all positively and significantly associated with autism. Of the causes of suboptimal obstetric conditions, the most important is pre-eclampsia, which has itself been reportedly linked to autism.[31,32] It is established that androgen levels are significantly high in early[33] and late[34] pre-eclamptic pregnancies. From the present perspective, the causal direction is not important. However, in human beings, high pregnancy testosterone levels are reportedly associated with growth restriction in utero; [35] moreover, high prepregnancy androgens are associated with subsequent miscarriage.[36] In addition, when testosterone was injected into pregnant ewes, they produced growth-retarded lambs.[37,38] Pregnancy in ewes is commonly used as a human model, so one may provisionally infer that testosterone is a causal agent in this process. In short, it is suggested that the association between autism and reproductive suboptimality is secondary to associations of both with high maternal testosterone levels.

Gestational diabetes

Hyperandrogenism in women is associated with gestational diabetes. This is illustrated by the high prevalence of gestational diabetes in women with polycystic ovary syndrome.[39] Grounds have been given for proposing that the placenta in such pregnancies is partly responsible for the high testosterone

levels.[40] Accordingly, it is suggested here that this testosterone may be responsible for the additional risk of autism following gestational diabetes.

Birth order

Gardener et al.[5] judged that birth order is a reliable risk factor for autism: firstborns are at greater risk than those born later. Firstborns are reportedly exposed to higher levels of maternal testosterone in the first trimester[29] and at term[41] than those born later. So, it seems reasonable to ascribe the additional risk of autism in firstborns to their additional exposure to testosterone in utero.

Migration

The suggestion of Gardener et al.[5] that migration is a risk factor for autism has been since confirmed.[30,42,43] We usually have no data on the psychological status of females who migrate. However, in the absence of evidence to the contrary, one may suggest that in the case of some, there had been stressful conditions in their countries of origin and that later attempts to cope with Western society also occasioned stress. Dealberto[42] also noted the additional risk of autism to offspring of veiled females, i.e. women who might particularly be expected to experience stress in an unfamiliar Western environment. It is noteworthy, too, that Zhang et al.[44] noted 'maternal unhappy emotional state' as a risk factor for autism. I suggest that the association between maternal migration (with its attendant stress) and infant autism is mediated by high maternal adrenal androgen concentrations.

FURTHER RISK FACTORS FOR AUTISM

The six risk factors identified by Gardener et al.[5] all seem amenable to the proposal that they may be explained by high maternal androgen levels. In the following sections, I deal with a number of further risk factors identified simply by their having been reported at significant statistical levels.

Birthweight

Autism spectrum disorder is reportedly associated with low birthweight.[32,45] The same authors also reported a highly significant association between ASD and maternal eclampsia/pre-eclampsia (p=0.0005). I suggest that the common factor underlying (and possibly causing) the pre-eclampsia/eclampsia, the birthweight, and the autism is a high level of maternal testosterone.

Duration of gestation

It has been reported that the risk of autism is inversely associated with duration of gestation.[46,47] Short gestations are associated with pre-eclampsia, and both are associated with fetal growth retardation and high maternal androgen concentrations. I suggest that the autism is at least partially caused by these androgens.

Maternal obesity

It has been reported that maternal body mass index correlates positively with the risk for infant autism.[48,49] Moreover, it is established that obese women have high androgen levels.[50,51] I suggest that the autism is due to the androgens.

Maternal occupation

Windham et al.[52] reported that, in contrast to mothers in other white-collar occupations, those in highly technical occupations (engineering, computer programming, and science) had an adjusted odds ratio of 2.5 [95% confidence interval (CI) 1.2–5.3] of producing an infant with autism. The comparable figure for fathers was 1.3 (95% CI 0.79–2.1). There are good grounds for supposing that people in technical ('systemizing') occupations have higher testosterone levels than those who are not.[53] So, these data suggest that high maternal (as opposed to paternal) testosterone is associated (presumably causally) with autism in offspring.

Breastfeeding

It has been reported that autism is significantly associated with an absence of breastfeeding.[47,54] Carlsen et al.[55] reported that midpregnancy androgen levels are negatively associated with subsequent breastfeeding. It seems reasonable to propose that high androgen levels caused the autism and the failure to breastfeed.

Race

It has been reported that race is independently associated with a high risk for autism.[42,43] Pregnant black women have reportedly higher testosterone levels than white women.[56] I suggest that the higher risk for autism in the offspring of black women is this higher androgen level.

Time trend

Rutter[57] commented on the recent widespread increase in reported incidence rates of autism. Clearly, part of this trend is due to improved recognition and consequent earlier and more frequent diagnosis. However, following Howard,[58] I suggested that this reported increase in rates of autism may be also due to increasing rates of obesity and diabetes, both of which in females are associated with increased testosterone levels.[59]

Maternal chronic or acute medical condition unrelated to pregnancy

This risk factor was identified by Zhang et al.[44] and would be explained by the excess androgens secreted by stressed women.

SUMMARY

It has been shown that if Baron–Cohen's hypothesis were true, then some established risk factors would be explained viz: advanced parental age, maternal medication, maternal bleeding, gestational diabetes; birth order, and migration. Other reported (but less well established) risk factors may also be reconciled with the hypothesis, namely birthweight, duration of gestation, maternal obesity, maternal occupation, breastfeeding, race, time trend, and maternal chronic or acute medical conditions unrelated to pregnancy. It would seem curious if so much evidence could be adduced to support a hypothesis that is substantially false.

REFERENCES

1. Grafodatskaya D, Chung B, Szatmari P, Weksberg R. Autism spectrum disorders and epigenetics. *J Am Acad Child Adolesc Psychiatry* 2010; **49:** 794–809.
2. Levy SE, Mandell DS, Schultz RT. Autism . *Lancet* 2009; **374:** 1627–38.
3. Bailey A, Le Couteur A, Gottesman I, et al. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med* 1995; **25:** 63–77.
4. Chamak B. Autism: overestimation of the genetic origins. *Med Sci Paris* 2010; **26:** 559–662.
5. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. *Br J Psychiatry* 2009; **195:** 7–14.
6. Voracek M. Fetal androgens and autism. *Br J Psychiatry* 2010; **196:** 416.
7. Manning JT, Baron-Cohen S, Wheelwright S, Sanders G. The 2nd to 4th digit ratio and autism. *Dev Med Child Neurol* 2001; **43:** 160–4.
8. Voracek M. Digit ratio (2D:4D) as a marker for mental disorders: low (masculinized) 2D:4D in autism spectrum disorders, high (feminized) 2D:4D in schizophrenia-spectrum disorder. *Behav Brain Sci* 2008; **31:** 283–4.
9. Baron-Cohen S. The extreme male brain theory of autism. *Trends Cogn Sci* 2002; **6:** 248–54.
10. Smalley SL, Loo SK, Yang MH, Cantor RM. Towards localizing genes underlying cerebral asymmetry and mental health. *Am J Med Genet Neuropsychiatr Genet* 2005; **135:** 79–84.
11. Baron-Cohen S, Knickmeyer RC, Belmonte MK. Sex differences in the brain: implications for explaining autism. *Science* 2005; **310:** 819–23.
12. De Bruin EI, Verheij F, Wiegman F, Ferdinand RF. Differences in finger length ratio between males with autism, pervasive developmental disorder – not otherwise specified, ADHD and anxiety disorders. *Dev Med Child Neurol* 2006; **48:** 962–5.
13. Cohen-Bendahan CCC, Van Goozen SHM, Buitelaar JK, Cohen-Kettenis PT. Maternal serum steroid levels are unrelated to fetal sex: a study in twin pregnancies. *Twin Res Hum Genet* 2005; **8:** 173–7.
14. Auyeung B, Baron-Cohen S, Ashwin E, Knickmeyer R, Taylor K, Hackett G. Fetal testosterone and autistic traits. *Br J Psychol* 2009; **100:** 1–22.
15. James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels at the time of conception. *J Theor Biol* 1996; **180:** 271–86.
16. James WH. Further evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels around the time of conception. *Hum Reprod* 2004; **19:** 1250–6.
17. James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels around the time of conception. *J Endocrinol* 2008; **198:** 3–15.
18. James WH. Behavioural and biological determinants of human sex ratio at birth. *J Biosoc Sci* 2010; **42:** 587–99.
19. Apter D, Vihko R. Endocrine determinants of fertility: serum androgen concentrations during follow-up of adolescents into the third decade of life. *J Clin Endocrinol Metab* 1990; **71:** 970–4.
20. James WH. Further evidence that some male-based neurodevelopmental disorders are associated with high intrauterine testosterone concentrations. *Dev Med Child Neurol* 2008; **50:** 15–18.
21. Mouridsen SE, Hauschild KM. The sex ratio of siblings of individuals with a history of developmental language disorder. *Logoped Phoniatr Vocol* 2010; **35:** 144–8.
22. Mouridsen SE, Rich B, Isager T. Sibling sex ratio of individuals diagnosed with autism spectrum disorder as children. *Dev Med Child Neurol* 2010; **52:** 289–92.
23. Kemper TD. Social Structure and Testosterone. London: Rutgers University Press, 1990.
24. Powell LH, Lovallo WR, Matthews KA, et al. Physiologic markers of chronic stress in premenopausal middle-aged women. *Psychosom Med* 2002; **64:** 502–9.
25. Goldberg M. High androgen levels in chronic fatigue patients. *J Clin Endocr Metab* 1995; **80:** 3390–1.
26. Baischer W, Koinig G, Hartmann B, Huber J, Langer G. Hypothalamic–pituitary–gonadal axis in depressed pre-menopausal women: elevated blood testosterone concentrations compared to normal controls. *Psychoneuroendocrinology* 1995; **20:** 553–9.
27. Roos A, Robertson F, Lochner C, Vythilingum B, Stein DJ. Altered prefrontal cortical function during processing of fear-relevant stimuli in pregnancy. *Behav Brain Res* 2011; **222:** 200–5.
28. Gray A, Berlin JA, McKinlay JB, Longcope C. An examination of research design effects on the association of testosterone and male aging: results of a meta-analysis. *J Clin Epidemiol* 1991; **44:** 671–84.
29. Troisi R, Hoover RN, Thadhani R, et al. Maternal, prenatal and perinatal characteristics and first trimester maternal serum hormone concentrations. *Br J Cancer* 2008; **99:** 1161–4.
30. Haglund NGS, Kallen KBM. Risk factors for autism and Asperger syndrome: perinatal factors and migration. *Autism* 2011; **15:** 163–83.
31. Wallace AE, Anderson GM, Dubrow R. Obstetric and parental psychiatric variables as potential predictors of autism severity. *J Autism Dev Disord* 2008; **38:** 1542–54.
32. Mann JR, McDermott S, Bao H, Hardin J, Gregg A. Pre-eclampsia, birth weight and autism spectrum disorders. *J Autism Dev Disord* 2010; **40:** 548–54.
33. Carlsen SM, Romundstad P, Jacobsen G. Early second trimester maternal hyperandrogenemia and subsequent pre-eclampsia: a prospective study. *Acta Obstet Gynec Scand* 2005; **84:** 117–21.
34. Serin IS, Kula M, Basbug M, Unluhizarki K, Gucer S, Tayyer M. Androgen levels of pre-eclamptic patients in the third trimester of pregnancy and six weeks after delivery. *Acta Obstet Gynec Scand* 2001; **80:** 1009–13.
35. Carlsen SM, Jacobsen G, Romundstad P. Maternal testosterone levels during pregnancy are associated with offspring size at birth. *Eur J Endocrinol* 2006; **155:** 365–70.
36. Cocksedge KA, Saravelos SH, Wang O, Tuckerman E, Laird SM, Li TC. Does free androgen index predict subsequent pregnancy outcome in women with recurrent miscarriage? *Hum Reprod* 2008; **23:** 797–802.
37. Manikam M, Crespi EJ, Doop DD, et al. Fetal programming: prenatal testosterone excess leads to fetal growth retardation and postnatal catch-up growth in sheep. *Endocrinology* 2004; **145:** 790–8.
38. Steckler T, Wang J, Bartol FF, Roy SK, Padmanabhan V. Fetal programming: prenatal testosterone causes intrauterine growth retardation, reduces ovarian reserve and increases follicular recruitment. *Endocrinology* 2005; **146:** 3185–93.
39. Vanky E, Stridsklev S, Skokoy K, et al. PCOS – what matters in early pregnancy? – Data from a cross sectional multicenter study *Acta Obstet Gynec Scand* 2011; **90:** 398–404.
40. Uzelac PS, Li X, Lin J, et al. Dysregulation of leptin and testosterone production and their receptor expression in the human placenta with gestational diabetes mellitus. *Placenta* 2010; **31:** 581–8.
41. Maccoby EE, Doering CH, Jacklin CN, Kramer H. Concentration of sex hormones in umbilical cord blood: their relation to sex and birth order of infants. *Child Dev* 1979; **50:** 632–42.
42. Dealberto M-J. Prevalence of autism according to maternal immigrant status and ethnic origin. *Acta Psychiatr Scand* 2011; **123:** 339–48.
43. Keen DV, Reid FD, Arnone D. Autism, ethnicity and maternal immigration. *Br J Psychiatry* 2010; **196:** 274–81.
44. Zhang X, Lv C-C, Tian JA, et al. Prenatal and perinatal risk factors for autism in China. *J Autism Dev Disord* 2010; **40:** 1311–21.
45. Luyster RJ, Kuban KCK, O'Shea TM, Paneth N, Allred EN, Leviton A. The Modified Checklist for Autism in Toddlers in extremely low gestational age newborns: individual items associated with motor, cognitive, vision and hearing limitations. *Paediatr Perinat Epidemiol* 2011; **25:** 366–76.
46. Buchmayer S, Johansson S, Johansson A, Hultman CM, Sparen P, Cnattingius S. Can associations between preterm birth and autism be explained by maternal or neonatal morbidity? *Pediatrics* 2009; **124:** e817–25.
47. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. *J Pediatrics* 2010; **156:** 525–31e2.
48. Dodds L, Fell DB, Shea S, Armson BA, Allen AC, Bryson A. The role of prenatal, obstetric and neonatal factors in the development of autism. *J Autism Dev Disord* 2011; **41:** 891–902.
49. Lyell K, Pauls DL, Santangelo S, Spiegelman D, Ascherio A. Maternal early life factors associated with hormone levels and the risk of having a child with autism spectrum disorder in the Nurses Health Study II. *J Autism Dev Disord* 2011; **41:** 618–27.
50. Kaergaard A, Hansen AM, Rasmussen K, Andersen JH. Association between plasma testosterone and work-related neck and shoulder disorders among female workers. *Scand J Work Environ Hlth* 2000; **26:** 292–8.
51. Sutton TK, Zhao X, Santoro N, et al. Reproductive hormones and obesity: 9 years of observations from the Study of Women's Health Across the Nation. *Am J Epidemiol* 2010; **171:** 1203–13.
52. Windham GC, Fessel K, Grether JK. Autism spectrum disorders in relation to parental occupation in technical fields. *Autism Res* 2009; **2:** 183–91.
53. Baron-Cohen S. The Essential Difference. London, Allen Lane, 2003.

54. Schultz ST. Breastfeeding, infant formula supplementation and autistic disorder: the results of a parent survey. *Int Breastfeeding J* 2006; **1:** 16.

55. Carlsen SM, Jacobsen G, Vanky E. Midpregnancy androgen levels are negatively associated with breastfeeding. *Acta Obstet Gynec Scand* 2010; **89:** 723–5.

56. Henderson BE, Bernstein L, Ross RK, Depue RH, Judd HL. The early *in utero* oestrogen and testosterone environment of blacks and whites: potential effects on male offspring. *Br J Cancer* 1988; **57:** 216–18.

57. Rutter M. Commentary: fact and artefact in the secular increase in the rate of autism. *Int J Epidemiol* 2009; **38:** 1238–9.

58. Howard JM. This could be due to maternal testosterone. *Arch Dis Child* 2006; **91:** 622–3.

59. James WH. A potential cause of the reported increase in rates of autism. *Int J Epidemiol* 2010; **39:** 1676–7.