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Interaction of genes and nutritional factors in the etiology of autism and attention deficit/hyperactivity disorders: A case control study

Scott S. Field *

Huntsville Hospital, University of Alabama in Birmingham (Huntsville Campus), United States

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ABSTRACT

Objective: To compare risk factors of attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) to age/sex-matched controls with particular attention to family history, parental age and nutrition.
Method: 31 ASD and 81 ADHD patients were compared to 612 age/sex-matched controls by reviewing charts for parental age, sibling order, gestational age, and early feeding, and by parental interview for early feeding and family history of psychopathology on affected patients and 139 of those controls.
Findings: Parental age affected ASD and ADHD females but not males. First-born males were at increased risk for both disorders even though their siblings had older parents and their parents were not more likely to stop having children. Breastfeeding in the absence of parental psychopathology reduced ADHD risk, but breastfeeding of first-born males by older mothers with psychopathology was a risk for ASD. Breastfeeding was only a risk for ADHD if the mother had psychopathology. Parent emigration from a place of high fish consumption was a significant ASD risk factor.
Resulting hypotheses: ADHD and ASD share risk factors due to shared genetic and nutritional interactions, likely revolving around deficiencies of omega-3 fatty acids (n3FAs) during brain development. Fatty acid metabolism genes are important in that process. The 4:1 male to female ratio for both disorders results from hormonally driven fat metabolism differences. Risk factors for both disorders including maternal smoking, prematurity, and gestational diabetes may also be attributed to their effect on n3FA supplies. Breastfeeding can be a risk factor when the mother's genes and/or age affect her milk quality. Parental age and gene defects may affect female more than male offspring. Childbirth with adequate spacing and breastfeeding can override maternal age and protect subsequent offspring. Genetic variations in fat metabolism can be influenced by cultural/geographic diet, causing deficiencies in offspring with migration-influenced diet changes. Interaction of n3FA deficient diets, delayed child-bearing, and breastfeeding by mothers with psychopathology may be important factors in the rising incidence of ASD and ADHD in recent decades. Partial prevention through diet and supplements may be possible.

Introduction

Autism is a developmental disorder of social communication that also involves repetitive inflexible behavior [1]. Autism spectrum disorder (ASD) includes most commonly the classical autism disorder (AD), Asperger disorder (ASP), and Pervasive Developmental Disorder (PDD). Attention deficit/hyperactivity disorder (ADHD) is a developmental disorder involving inattention/distractibility and/or impulsivity/hyperkinesis that starts before age 7, persists in multiple environments, and causes significant functional impairment [1]. Over the past 30 years, there has been an increase in both ASD [2–5] and ADHD [6]. They are both disorders of brain function occurring 3–5 times as often in males as females [5,7–9], but the ratio is lower with lower function (AD and mental retardation) and prematurity [10] and higher with ASP [11]. Other shared risk factors include prematurity, low birth weight, gestational diabetes and maternal smoking [2,5,10,12–15]. They both have strong genetic influences, but lack full concordance in monozygotic twins, pointing to concomitant environmental factors [4,11,16]. There is strong co-morbidity found between them.

ASD studies have found higher risk with older parents of each sex [7,8,17] although significance has been limited when controlling for the opposite parent's age in other studies [2,5]. Parental age has risen significantly in the US [7,8]. One study found

* Address: Field Pediatrics, PC, 1106 Gleneagles Drive, Huntsville, AL 35801, United States. Tel.: +1 256 881 9355 (office), mobile: +1 256 656 8819; fax: +1 256 881 5084.
E-mail address: scottfieldmd@gmail.com

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a correlation between older paternal age and ASD but not with ADHD, yet fathers 15–24 years old had lower rates of children with ADHD compared to controls and fathers 35–44 years old had non-significantly higher rates of children with ADHD [18].

Deficiency of omega-3 fatty acids (n3FAs) may play a significant role in the etiology of ADHD and ASD [19–23]. ADHD symptoms have been linked to low blood levels of n3FAs [21]. Premature babies from Japan demonstrated higher red blood cell (rbc) membrane levels of docosahexaenoic acid (DHA), a 22-carbon chain n3FA, in breastfed vs. formula-fed premature babies 1 month after birth and then significantly better executive functioning in areas of mental processing, distractibility, impulsivity, and hyperactivity at 5 years of age [24]. Fish oil supplementation during pregnancy and the first 3 months of lactation resulted in significantly better mental processing at 4 years of age compared to controls [25]. Most DHA accumulation in the developing brain occurs in the last trimester and the first few months postpartum [26]. Prior to DHA supplementation in infant formulas, breastfed babies had higher brain DHA levels than bottle-fed babies and had much more DHA in the forebrain where most dysfunction occurs in both autism and ADHD [27]. Infants born prematurely missed out on this relatively large supply of n3FAs. Variation of the delta-6 desaturase (D6D) gene involved in converting 18 carbon essential FAs into long chain polyunsaturated FAs (LC-PUFAs) like DHA can make women's breast milk lower in DHA [28] including women who eat more fish [29]. So even breastfed term babies could be at risk for n3FA deficiency, a risk only compounded by the typical American diet being low in n3FAs [22,30]. Lower rbc or plasma levels of n3FAs have been found in ASD patients than controls [31–33]. Several studies have indicated clinical benefit in treating young ASD patients with n3FA supplements [31,32,34,35]. Associated FA levels and supplementation benefits have also been found with schizophrenia [36] and ADHD [13,21,37] and ADHD symptoms in children with other developmental disorders [38,39]. An n3FA deficiency has also been implicated in the etiology of autism and IQ deficits associated with phenylketonuria [40] for which supplementation has demonstrated some neuro-functional benefit [41].

This is an exploratory study examining factors associated with ADHD and ASD compared to controls, testing the hypothesis that they share etiologies involving parental age, nutritional factors, and genes as reflected by psychopathology in the family history.

Methods

Patients in a pediatric practice with *Diagnostic and Statistical Manual Disorders*, fourth edition (DSM-IV-TR) [1]-based diagnoses of ASD ($n = 31$) and ADHD ($n = 81$) were enrolled. Age/gender-matched controls ($n = 612$) were selected by chart review starting in January of birth years 1985 through 2003. Those years were chosen because the oldest ASD patient was born in 1985 and both ASD and ADHD are often not diagnosed before 7 years of age. The controls were only accepted if they did not have ADHD or ASD, had been followed for at least 5 years and their parent's birth dates were known. The ADHD patients only included those who had been seen and treated in the past couple years which included patients born between 1991 and 2005. Patients with ASD were excluded from the ADHD cohort.

Parental age, co-morbid psychological problems, gestational age (GA), multiple births, birth order, race and sex were noted. GA was determined by hospital records and/or parental recall at the first office visit. Early feeding history was obtained from the medical record of 320/406 (79%) male and 152/206 (74%) female controls. Family history (FH) of the following psychopathology (PP) was obtained by the author from parents of affected patients and 139 age- and sex-matched controls: ADHD, autism, depression, schizophrenia, obsessive compulsive disorder (OCD), anxiety disorder, tic disorder, dyslexia and bipolar disease.

Early feeding history was also obtained from all affected and the 139 age/sex matched controls above. This was corroborated with the medical record when possible. Infant feeding was categorized as breastfeeding at more than twice a day for at least 4 months (Br) or not (Bt), the latter usually bottle-fed most if not all of that time period. Informed consent was obtained for all patients from whom FHs and early feeding data was collected and the forms used were approved by the local Institutional Review Committee.

Two-tailed Student's *t*-test was used to evaluate parental age factors. Effect size was calculated for that data by difference in mean affected and control ages divided by the standard deviation of controls. Two-tailed Fisher's exact was used for statistical comparison of other variables; $p < 0.05$ was considered significant. Variables which are known to or have good reason to support a suspected common underlying etiology could be considered as supportive rather than confounding variables. Thus traditional multivariate analysis was not deemed applicable. Nevertheless as an exploratory study with large numbers of variables, the statistical values obtained should be viewed with caution and larger studies should be done for validation.

Results

A total of 26 males and 5 females diagnosed with ASD were included. Three were diagnosed AD, 11 PDD, and 17 ASP. Seven of the 8 low or medium functioning males were first-born, and the other was born over 11 years after his half-sister to a 33-year-old (yo) mother. One patient also had Duchene's muscular dystrophy. Five patients (16%), including the only affected male/female sibling pair, had a mother and/or father born in a foreign country compared to 34/612 (5.6%, OR 3.3, $p = 0.033$) controls. Four of these five patients were the only black ASD patients in the study, and all foreign parental origins (Nigeria, Vietnam, and two Caribbean islands) were places where the parents said fish was a major part of the diet.

Parental age by itself was only found to be a significant risk factor for ASD females (Table 1). Mean maternal age was more significant ($p = 0.003$, effect size 0.78) than paternal ($p = 0.035$, effect size 0.49) or combined parental ages ($p = 0.008$, effect size 0.68). By contrast the effect size by each parental mean age on ASD males was <0.12. All 5 ASD females were born to mothers over 30 yr ($M > 30$). ADHD female mean maternal age ($p = 0.074$, effect size 0.55) and combined parental age ($p = 0.097$, effect size 0.45) were marginally statistically greater than that of controls. Of the 5 ADHD females who were only children ($p = 0.029$ compared to controls), the average combined parental mean age was 77.4 yr.

ASD male patients were significantly more likely than controls to be born prematurely; 31% vs. 6.7% <37 week ($p < 0.001$) and 50% vs. 30% <39 week ($p = 0.049$) GA. There were less born at $\geqslant$41 week GA; 4% vs. 13%. ASD females were all term, but 2/5 (40%) were <39 week GA compared to control females 48/206 (23%). GA in ADHD patients did not differ significantly from controls.

Two (6%, $p = 0.097$) ASD patients were male twins, both fraternal, with 1 female unaffected sibling and 1 male ADHD sibling. This compared with 7/406 (1.7%) male and 2/206 (1.0%) female controls that were multiples. ADHD multiple gestations in males (5/64; 7.8%, $p = 0.015$) and females (1/17; 5.9%) were also more common than in controls.

Besides the black patients with at least one parent of foreign origin, black patients were underrepresented in the ADHD (3%) and ASD (0%) male groups compared to 9% of controls. Whites were

Table 1
Effect of parental age, gestational age, race, and sibling order on ASD and ADHD.

Parameter	Male			Female		
	Controls	ADHD	ASD	Controls	ADHD	ASD
N	406	64	26	206	17	5
Mean paternal age (yr)	32.7	32.9	33.3	32.2	33.9	34.9[b]
Mean maternal age (yr)	30.4	30.2	30.1	30.0	32.6[a]	33.7[b]
Combined mean age (yr)	63.1	63.1	63.3	62.2	66.5[a]	68.6[b]
# (%) with						
<37 week Gest. Age	27 (6.7)	5 (7.8)	8 (31)[c]	7 (3.4)	1 (5.9)	0
<39 week Gest. Age	123 (30)	24 (38)	13 (50)[b]	48 (23)	7 (41)	2 (40)
⩾41 week Gest. Age	54 (13)	6 (9)	1 (4)	35 (17)	2 (12)	0
Multiple gestation	7 (1.7)	5 (7.8)[b]	2 (8)[a]	2 (1.0)	1 (5.9)	0
White	351 (86)	60 (94)	22 (81)	180 (87)	16 (94)	4 (80)
Black	35 (9)	2 (3)	3 (11)	19 (9)	1 (6)	1 (20)
Birth order: 1	178 (43)	38 (59)[b]	18 (67)[b]	95 (46)	9 (53)	1 (20)
Birth order: 2	155 (38)	22 (34)	8 (30)	78 (38)	5 (29)	3 (60)
Birth order: 3	62 (15)	4 (5)[a]	0[b]	30 (15)	2 (12)	1 (20)
Only child	45 (11)	11 (17)	2 (8)	20 (9.7)	5 (29)[b]	0
0 Later siblings	217 (53)	27 (42)	7 (27)[b]	108 (52)	11 (65)	3 (60)
1 Later sibling	140 (34)	26 (41)	15 (58)[b]	71 (34)	5 (29)	2 (40)
2 Later siblings	44 (11)	8 (12.5)	3 (12)	23 (11)	1 (6)	0

Two-tailed Student's *t* test applied to mean parental ages. Fisher's exact test applied to the rest. Superscript letters denote *p* values: a < .1, b ⩽ .05, c ⩽ .001. Gest. = Gestational.

overrepresented in ADHD (94%) males compared to 86% of controls.

Both ADHD (59%, $p = 0.022$) and ASD (67%, $p = 0.014$) males were more likely than controls (44%) to be first-born and less likely (5%, $p = 0.079$ for ADHD and 0%, $p = 0.037$ for ASD) than controls (15%) to be third-born. Only 2 ASD patients (both males) were only children (6.5%) compared to 10.6% of 612 controls. Less ASD males (27%, $p = 0.014$) than controls (53%) were the last child. ASD (58%, $p = 0.021$) and ADHD (41%) males were more likely than controls (34%) to have one later sibling, and just as likely as controls to have 2 subsequent siblings. Four ASD males who were the products of second or third pregnancies were preceded by fetal or neonatal demises (Potter's Syndrome, anencephaly, a set of triplets, and 2 previous miscarriages).

Two second-born ASD males were born at least 9 years after the first-born child to a $M > 30$. ADHD females born under those conditions (1/17; 6%) compared to 4/206 (1.9%) controls, but 1/64 (1.6%) ADHD males were not more frequent than 8/406 (2.0%) controls. The only group close to significance ($p = 0.116$) was ASD males.

Breast feeding at least 4 months (Br) was not significantly different in any group except 4 of 5 ASD females were Br. All 4 were born to mothers between 32 and 34 yr. The Bt ASD female's parents were both over 36 yr. Eleven of 26 ASD males were Br. All but 3 had $M > 30$. One of the younger mothers ($M < 30$) who Br had a previous neonatal demise, another's husband was from a foreign country, and the third had psychopathology.

Breastfeeding at least 4 months occurred significantly more with $M > 30$ than $M < 30$ for both control and ASD groups, but not for ADHD groups. (Table 2) Bottle-feeding occurred at approximately equal rates for $M > 30$ vs. $M < 30$ controls, but at non-significantly higher rates for $M < 30$ vs. $M > 30$ for ADHD patients and ASD males. Psychopathology in either parent was significantly associated with ADHD males and females, and with ASD males compared to controls. Maternal PP with $M > 30$, Br was significantly more common than controls in both males and females with ASD and ADHD. First-born males with $M > 30$, Br were at lower risk of ADHD if there was no MPP, but were at significant risk for ASD with MPP. Second-born males with $M > 30$, Br and MPP were not seen more commonly with ASD than with controls, but second-born ASD females with MPP, $M > 30$, Br were more common ($p = 0.013$) than controls. Lack of PP in both parents with $M < 30$, Br was found less often, however not significantly in ADHD ($p = 0.071$) and ASD ($p = 0.054$) males than controls. Lack of psychopathology in both parents with $M > 30$, Br was found less often in ADHD males ($p = 0.001$) and females ($p = 0.076$).

ADHD was found commonly among siblings (especially male) of patients with ADHD. Of 11 ADHD females with any full siblings over age 5, 4 had ADHD-diagnosed siblings; 2 sisters and 2 brothers. Three of the 7 girls with no diagnosed sibling were bottle fed and had only sisters. One Br ADHD female had an older brother and mother with symptoms of ADHD, not diagnosed. The other 3 were Br, had one or more unaffected brothers, and each of their mothers experienced postpartum depression only while breastfeeding the affected girl. Of 34 ADHD males with brothers, 19 (56%) had at least one brother with ADHD, 17 (89%) of whom were Br and 4 of whom had mothers with ADHD. Of the 15 ADHD males without ADHD brothers, 3 had brothers no more than 5 years old that have ADHD symptoms and 1 brother had ASD without ADHD. Six of the other 11 (55%) were Br and none had maternal ADHD. Of 23 ADHD males with sisters, only 2 had a sister with ADHD, one of whom was a 28 week GA triplet sibling.

Discussion

Role of hormones and converting enzymes

A deficiency of essential fatty acids (precursors for LC-PUFAs) as the cause of ADHD was proposed 32 years ago [42]. Accumulating evidence has since supported that hypothesis along with the idea that n3FA deficiency may also play a major role in the etiology of ASD [19,20,22,23]. The male to female ratio between 3 and 5 for both disorders found in this study as well as in the literature [2,5,7–9] goes along with the finding that females are born with more n3FAs than males [42] and are also better able to convert the shorter (18 carbon) chain n3 alpha-linolenic acid (ALA) to the longer (20 carbon) eicosopentanoic acid (EPA) and DHA [44,45]. In 1987, Mitchell, et al. noted that male animals require 3 times as much EFAs as females for normal development and said that could explain the high male to female ratio in hyperactive children [13]. The different conversion rates by sex were also recently suggested as the reason for male predominance in ASD [19,22]. The conversion rate from ALA to EPA in men ranges 0.3–8% vs. up to 21% in women, and EPA to DHA less than 4% or undetectable in

Table 2
Interaction of early feeding with parental age and psychopathology.

	Male			Female		
	Controls	ADHD	ASD	Controls	ADHD	ASD
# Feeding histories	320	64	26	152	17	5
M < 30	138 (43)	35 (55)	12 (46)	71 (47)	8 (47)	0 (0)[a]
M < 30,Br	51 (16)	15 (23)	3 (12)	27 (17)	2 (12)	0 (0)
M > 30,Br	93 (29)	16 (25)	9 (35)	45 (30)	5 (29)	4 (80)[b]
M < 30,Bt	87 (27)	20 (31)	9 (35)	44 (29)	6 (35)	0 (0)
M > 30,Bt	89 (28)	13 (20)	5 (19)	36 (24)	4 (24)	1 (20)
# Family histories	104	64	26	35	17	5
MPP	17 (16)	33 (52)[c]	12 (46)[b]	4 (11)	13 (76)[c]	2 (40)
PPP	10 (10)	28 (44)[c]	12 (46)[c]	6 (17)	10 (59)[b]	2 (40)
MPP,*M* < 30,Br	4 (4)	7 (11)	0 (0)	1 (3)	2 (12)	0 (0)
MPP,*M* > 30,Br	2 (2)	7 (11)[b]	4 (15)[b]	1 (3)	4 (25)[b]	2 (40)[b]
MPP,*M* > 30,Br,1st	2 (2)	4 (6)	4 (15)[b]	0 (0)	1 (6)	0 (0)
MPP,*M* > 30,Br,2nd	0 (0)	2 (3)	0 (0)	0 (0)	1 (6)	2 (40)[b]
M > 30,Br,1st,xMPP	13 (13)	1 (2)[b]	2 (7)	2 (6)	1 (6)	1 (20)
PPP,*M* > 30,Br,1st	3 (3)	2 (3)	5 (19)[b]	0 (0)	1 (6)	1 (20)
M > 30,Br,1st,xPPP	12 (12)	3 (5)	1 (4)	2 (16)	1 (6)	0 (0)
M < 30,Br,xPP	19 (18)	5 (8)[a]	1 (4)	5 (14)	0 (0)	0 (0)
M > 30,Br,xPP	25 (24)	3 (5)[c]	4 (15)	11 (31)	1 (6)[a]	1 (20)

Results reported as # (% of feeding or family histories obtained); histories limited in controls. Abbreviations used: *M* < 30 = mothers less than 30 years old, *M* > 30 = mothers over 30 years old, Br = breastfed at least 4 months, Bt = bottle-fed or breastfed less than 4 months, MPP = maternal psychopathology, PPP = paternal psychopathology, 1st = 1st born, 2nd = 2nd born, *x* = without, PP = psychopathology in either parent. Superscript letters denote 2-tailed Fisher's *p* values as follows: a < .1, b ⩽ .05, c ⩽ .001.

men versus up to 9% in women [45]. The latter two n3FAs are mostly found in fish, so non-fish-eaters depend largely on their conversion ability for their supply of LC-PUFAs. EPA is an important precursor of anti-inflammatory prostaglandins and leukotrienes and DHA is instrumental in membrane fluidity and cell function in cerebral cells, especially at synaptic junctions [30]. DHA is also an important intracellular signaling molecule [46] and is involved in gene regulation [30]. Gene defects associated with the X chromosome such as fragile X syndrome have been suspected as possible causes of the male predominance in autism, but only account for 2–6% of ASD patients, and levels of the deficient protein don't correlate with severity of autism symptoms [47]. Some argue that conversion rates are too insignificant for the proper fetal accretion of DHA in the absence of maternal and/or formula DHA supplementation [45], but D6D messenger RNA levels have been found much more in the brain than in any other tissue including liver [46]. There may be much more conversion taking place at end organs like brains, placentas, and breasts than previously thought that could supply needed DHA without direct DHA supplementation.

Estrogen enhances converting enzymes whereas testosterone inhibits them [44]. It is possible that the resulting difference in conversion rates between males and females may be responsible for basic differences in brain function/personalities, thus making females more verbal and in-tune to other's feelings and making males generally more active, often with less fine-motor skills. ADHD and ASD may be extremes of some male traits caused by an excess deficiency of long chain n3FAs. There has been an association between mothers with clinical conditions indicating higher testosterone levels and ASD offspring [48]. Smoking during pregnancy has also been linked to higher fetal testosterone and increased risks for ASD and ADHD [12]. The negative effect on DHA production found with smoking [26] may occur indirectly by its tendency to increase testosterone.

Maternal fetal transfer of DHA: role in cause of prematurity and inadequacies as a cause of ADHD and ASD

Since normal baby brains require substantial quantities of DHA [26], it is important for females to be able to build up their supplies and replenish their losses after pregnancies [43]. Two possible mechanisms to help them accomplish this naturally are; (1) estrogen which is higher during pregnancy enhances EFA conversion, and (2) prolactin which is secreted in large quantities during lactation regulates some enzymes that may help track fatty acids to particular intracellular brain sites [46]. It is possible that relatively recent generations of women may be at increased risk of developing Alzheimer disease because they did not breastfeed their babies. The measured drop of serum DHA between 28 weeks gestation and birth in a relatively high fish consumption and breastfeeding population was restored such that parity was positively associated with serum DHA [49]. That repletion of DHA may explain why subsequent brothers to first-born breast-fed ASD and ADHD males in this study were often unaffected even though their parents were older. Conflicting risk factors of parental age versus birth order has been previously described [8]. First-born males being overrepresented in the ASD population is supported by larger studies [8,9,17] and might be explained by insufficient stores of DHA from poor diet, recent fetal demise, poorer conversion in older women (decreased D6D activity with age) [46] and/or lack of conditioning of the uterus and breasts from at least one previous pregnancy. There is animal data to indicate that DHA transfer to offspring may be better with subsequent pregnancies [50]. Long intervals (>9 yr) between child-bearing as found with 2 of the ASD patients in this study may also be a risk factor for less supportive uteri and breasts in supplying longer chain EFAs. Close child spacing found recently to be a risk factor for ASD [51] may be explained by inadequate maternal DHA repletion. Both ASD and ADHD males were more likely to be first-born and less likely to be third-born. ASD males were less likely than controls to be the last child. Speculation that more ASD patients were first-born because parenting difficulties lead to fewer subsequent children (stoppage) [8] is not supported in this study.

This study's finding of a shift in gestational age not only to more premature but less post-date affected ASD and ADHD patients (only statistically significant in ASD males for <37 and <39 week GA) goes along with the major DHA accretion of babies in the last trimester of pregnancy. Maternal supplies of LC-PUFAs may have an influence on gestation length; prematurity could be a maternal survival technique as normal fetal accretion of DHA in the third trimester may be a threat to women of limited supplies. Although DHA supplementation has not had major influences on overall gestational age, it has been associated with less significant (under

34 weeks) prematurity [25,52]. GA is a significant nutritional factor.

Rates of Br in male ASD patients were similar to controls. Combined with other factors like MPP and older maternal age, breastfeeding was associated with significant differences for both ASD and ADHD groups compared to controls, but it actually was a detriment rather than a benefit. There are genetic factors as well as environmental factors (low n3FA diet, maternal n3FA deficiencies, maternal age and genes [28,29,53] affecting uterine and breast provision of DHA) that could negate an otherwise beneficial effect of breastfeeding. Breast milk content of EPA and DHA should be studied in relationship to maternal age, maternal PP, and child spacing. It would be interesting to look at the D6D genotypes in the mothers of breastfed ASD and ADHD children. There were significantly less breastfed first-born ADHD males of $M > 30$ mothers without PP than controls while the presence of MPP with first-born males Br by $M > 30$ was significantly associated with ASD in males. There was also a significant risk for ASD and ADHD in males and females of $M > 30$, MPP, Br. Differing n3FA breast milk content among women may explain the conflicting results of ASD risk with breastfeeding [54,55].

Increased prevalence of multiple gestations in this study for males with ADHD and ASD would go along with limited supplies of DHA from mothers for simultaneously developing brains. That risk was more pronounced with older mothers in one ASD study [7]. Previous fetal or early postnatal demise cases prior to the birth of 4 ASD patients in this study goes along with the idea that maternal DHA depletions from previous non-breastfed pregnancies may put the next child at risk for ASD. Further investigation is warranted.

Gestational diabetes has been found to be a risk factor for both ASD [15] and ADHD [14]. Placental transport limitations in that condition may explain fetal plasma LC-PUFAs being significantly lower than maternal levels [53]. Those lower levels may be a reason it is a risk factor. LC-PUFA transport gene activity during pregnancy as measured by messenger RNA techniques may be useful in understanding ASD links to gestational diabetes, older mothers and first versus later pregnancies.

Some of the maternal-fetal transfer of DHA is through breastfeeding. Five of the 8 ADHD girls with $M < 30$ were bottle-fed with non-DHA-supplemented formula. Of patients followed from birth in the author's practice, 17 ASD cases were born in years 1992–2001 whereas only 4 to 6 (2 left the practice without a definitive diagnosis) were born in years 2002–2011, a trend recently indicated also in Norway [56]. Part of that difference could be attributed to ascertainment limitations. It is possible that the incidence of ASD may already be on the decline since 2002–2003 when DHA was added to infant formulas. Autism has been significantly associated with non-supplemented formula versus supplemented formula or breast milk [55]. Breastfeeding has also been implicated as a possible risk factor for autism [54]. Perhaps much greater strides in prevention could be achieved by maternal n3FA supplementation before, during, and after pregnancy, and by supplementation of breast milk for babies of mothers >30 yr and those with psychopathology.

Role of ASD and ADHD linked genes in fatty acid metabolism/supplies

Twin studies have demonstrated the genetics of both ADHD [11,57] and ASD [16]. It is becoming more apparent that high comorbidity and shared family histories of these and other mental disorders indicate shared genes [57]. Research focusing on genes for neurotransmitters in ADHD has shown that many genes are probably involved, each with small effect [58]. Over 100 genes involving phospholipid metabolism and their respective chromosomal locations have been identified, with over half of them associated with various mental disorders [46]. All FH brain disorders evaluated in this study were represented in that list. Chromosome site 11q22–23 contains the genes for desaturases (including D6D) involved in FA conversion which are linked to ADHD and autism, as well as a dopamine receptor gene that is linked to bipolar disease [58]. Brooks, et al. [59] found a significant association with a single nucleotide polymorphism (SNP) in the gene for D6D and ADHD. Sites in the 6p21–23 region containing genes involved with fatty acid metabolism are associated with schizophrenia, bipolar disorder, ADHD, and autism [46]. Sites at 12q21–23 linked to bipolar disorder and autism are near the genes for phospholipase A2s which are enzymes linked to neurotransmitter receptors that break off the Sn2 long-chain fatty acid from the membrane phospholipid to produce cell-signaling free FA molecules (intracellular neurotransmitters) [46]. Sites on 5p which contains a 5α-reductase gene are associated with both autism [46] and ADHD [58]. It is no wonder that most ASD and ADHD children in this study had stronger family histories of other brain disorders than controls (unpublished data). This also goes along with a significant increased risk of autism for children born to mothers taking psychiatric medication [17]. In that situation, mother's faulty genes passed to her child as well as her gene-induced limited n3FA stores and conversion abilities could all play a role in the child's development of ASD. The medicine itself may have less to do with the risk.

As in other studies, [2,5,8,18] parental age was found to be a risk factor in ASD, less so with ADHD, but in this study only with females. The lack of association in males may be due to type 2 error from inadequate sample size. There is little data in the literature looking at parental age effect on either disorder by sex of the affected child, so this finding must be examined by other investigators. The significantly greater number of only child ADHD females was probably due to their conception later in their parent's lives. A recent ASD study did show a greater difference in affected vs. control proportions for females than for males at maternal and paternal ages 35–39 [5]. If the female parental effect holds up in further studies, it might indicate that genetic effects are more important for females and environmental (like n3FA supplies) effects are relatively more important in males. ASD males in the present study had younger fathers (<30 yr) less commonly (23%) than controls (33%). ASD females also had fewer fathers <30 yr (0% vs. 33%) and more combined parental age of $\geqslant$65 yr (80% vs. 38% controls). Paternal age risk is likely caused by *de novo* gene defects that are more likely to occur with continued gametogenesis throughout a male's life, whereas maternal age is more likely to be a risk factor due to body aging factors affecting the fetal environment such as the aging effect on maternal D6D activity [46]. That in turn could be due to *de novo* gene defects in somatic cells that express genes involved in FA metabolism. Female gametogenesis occurs mostly prior to the mother's birth and thus is less apt to pass on gene replication errors to the offspring. The ASD male with muscular dystrophy had a completely negative family history for PP or muscular dystrophy but had an older father (38) and mother (36). Muscular dystrophy has been associated with ADHD and ASD [60]. Delayed child-bearing may be a significant factor in the recent increased incidence of ASD and ADHD.

Diet alone as a factor in the etiology of ASD and ADHD

Inuits from Northern Quebec, population 12,000, with very high fish consumption had *no* autism per physicians working with them from 1991 to 2006 [61]. When mercury was studied in California as a possible risk factor for autism, it was found that there was less autism in the children with higher mercury levels and that was attributed to them having eaten more fish [62]. Breastfeeding duration has correlated with less ADHD symptoms on parent and teacher Conner scales while lower plasma levels of EPA and DHA

were found in ADHD patients compared to controls [63]. In the present study, breastfeeding was identified as a potential risk factor in older mothers and in mothers who had PP. It remains to be determined if that association is due to decreased levels of LC-PUFAs in their milk. Autism rates rose directly with exclusive 6-month breastfeeding rates in the US between 2000 and 2004 [54]. For Br patients, more ADHD male's mothers were >30 yr (16) than <30 yr (14); for females 5 vs. 2, for ASD males 8 vs. 3, and for ASD females 4 vs. 0. In contrast, there were more $M < 30$ of Br control males (51 vs. 31) and control females (27 vs. 15) compared to $M > 30$. Breastfeeding by younger mothers, especially in absence of PP, may protect against ADHD and ASD. For mothers >30 yr and those with PP, n3FA supplementation of their milk may turn out to be beneficial but that needs to be studied more. Other benefits of breastfeeding outweigh bottle feeding even in those circumstances.

Regression has been reported to occur in 25–50% of children with autism [4] usually in the 2nd or 3rd year after birth when most children's nutrition quality decreases significantly. ASD patients have been found to have restrictive diets from 15 months on, eating less vegetables, salad and fresh fruit [64]. Nutrition from conception through the first year or two after birth is probably most important in the development of ASD and ADHD, yet later nutrition may affect their clinical courses. Antioxidants found in fruits and green vegetables are known to protect LC-PUFAs from oxidation, which may explain their role in prevention and treatment of brain disorders. Oxidative stress is associated with ASD and antioxidant placebo-controlled trials have shown behavioral benefits [65]. Breath ethane which is associated with n3FA oxidation was found in greater quantities in a small case control ADHD study [66]. The American diet is deficient in n3FAs; 90% of EFAs come from the omega-6 FA linoleic acid [30]. Deficiencies of n3FAs can come from inadequate diet, inadequate FA metabolism, and excessive destruction by oxidation which in turn can be caused by both poor diet and antioxidant related genes.

More study is needed to determine optimal FA balances and doses for supplementation [22]. Using only DHA for supplementation could have a negative effect on other FAs since DHA strongly down-regulates the converting enzymes [30,45]. Two studies of solely or predominantly DHA supplementation in ADHD children found no benefit [67,68] while studies using a combination of fish oil and evening primrose oil containing DHA, EPA, and γ-linolenic acid (GLA) did show improvement [37–39].

Interaction of genes and nutritional factors

An interesting genetic/environmental interaction was found with the high rate of ASD patients (5/31; 16%) born to parents who emigrated from other countries, all of which happened to be places where fish was a prominent part of their diet. This risk factor was found previously but was not attributed to diet changes [69]. Populations with a high long chain n3FA diet for many generations could have more gene variants limiting conversion from ALA (because the better conversion was not needed) such that when they move to a place like inland North America and consume much less EPA and DHA (from fish), their children are deficient in those nutrients and develop ASD and/or ADHD. That might explain why the children of immigrant parents in this study had a high rate of siblings with ASD or ADHD symptoms (4/5), yet their FH was otherwise unremarkable (4/5). This compared to strong FHs of PP in 23/26 ASD children born to both parents from the United States. In the South London boroughs of Lambeth and Wandsworth, increased rates of autism were found in children of mothers from Africa, Caribbean, and Asia, with the highest risk being from the Caribbean [69]. The risks were a little higher in Lambeth than Wandsworth. Googling the nearest fish market to those two boroughs revealed one place serving both boroughs and it was closer to Wandsworth than to Lambeth. Another interesting corollary is the report that Californian children of mothers who were born in Mexico had a 40% *decreased* risk of autism over those to mothers born in California [17]. This might be explained by populations not used to eating fish having better fatty acid metabolism genes than average such that their mental health is not as dependent on dietary intake of EPA and DHA to compensate for gene deficits. Other than black patients whose parents came from other places where fish consumption is high, black patients were underrepresented in both ASD and ADHD groups, which may indicate that they could be better converters on average than whites of European descent. Blacks were significantly underrepresented in a recent neonatal intensive care unit graduate ASD study [70] and had lower risk than whites in a large ASD survey study [3].

SNPs of the D6D gene can limit breast milk content of n3FAs [28,29]. The same gene is associated with ADHD [59] and neighboring genes are associated with ASD [46]. Those genes may contribute to mothers not only having PP, but may also contribute to the risk found in this study of MPP, Br for ASD and ADHD patients. I am not aware of any other study that has looked at maternal psychopathology interacting with breastfeeding as a possible risk for ASD or ADHD. That as well as a possible association of post-partum depression in mothers only during breastfeeding of their ADHD daughters yet having unaffected breast-fed sons deserves further study.

Schmidt, et al showed that genes for one carbon metabolism interact with prenatal vitamin consumption as a risk for ASD [71]. The suspected most important interacting nutrient was folic acid. Unfortunately, DHA intake was not included in the analysis, yet DHA supplementation for pregnant women was being used at the time of the study and DHA is intimately involved in those metabolic pathways [72]. DHA has been found to up-regulate enzymes upstream of products like methionine and cysteine [72] which were low in AD patients [73] and to down-regulate an enzyme downstream of methionine. Folic acid, DHA, vitamins B12, B6, and D probably all interact with genes for enzymes in their metabolic pathways and with each other in brain development and health.

Somatic gene defects associated with aging are inhibited by n3FA consumption [74]. Such defects present in organs involved with fetal and infant nutrition could explain an increased risk in older mothers whether or not breastfeeding. Add that to poor nutrition and genetic defects in the mother and those passed to the patient from either or both parents, and the risk can be magnified. It is possible that n3FA supplementation of mothers and babies may override genetic defects and help prevent both ADHD and ASD.

Conclusion

Deficiencies of n3FAs caused by genes as well as environmental factors could be major etiologies of both ADHD and ASD. Parental diet and age along with patient diet early in life are perhaps the most important environmental risk factors that could explain the growing incidence of both disorders in recent decades. The addition of long-chain n3 and n6 FAs to formulas since 2002 may already be having a positive impact on the incidence of ASD. Breastfeeding mothers with psychopathology, even when younger, were significantly associated with ADHD male and female children. Previously described risk factors for ASD such as prematurity, multiple births, birth order, child spacing, smoking, gestational diabetes and even ancestral genetic background could be explained by their effects on n3FA status. Most of those risk factors have also been described for ADHD. Hormonally driven essential FA

conversion rate gender differences may explain the male predominance found in both ASD and ADHD. Breastfeeding by younger mothers is probably not only helpful for their first children, but may enhance their own health by facilitating repletion of FA stores, which along with conditioning of her uterus and breasts may protect subsequent children. Breast-feeding without FA supplementation by older women, especially in the presence of parental psychopathology, may be a risk factor for ASD and ADHD. Fat metabolism gene variations may differ geographically such that moves causing significant fish intake changes may increase or decrease ASD and ADHD risks in offspring. An evidence-based etiological model of ASD and ADHD is presented here that explains most risk factors for each which are shared by both. More research is needed, but there is sufficient evidence of the safety and importance of LC-PUFAs in normal brain function that supplementation and/or improved diets should be recommended for those affected by brain dysfunction and for pregnant mothers and their young children. Those interventions may compensate for genetic fatty acid metabolism inefficiencies and potentially help prevent these disorders.

Conflicts of interest and source of funding

No conflicts of interest; unfunded.

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