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REVIEW

Nutritional and Environmental Approaches to Preventing and Treating Autism and Attention Deficit Hyperactivity Disorder (ADHD): A Review

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ABSTRACT

Objectives: The purpose of this study was to concisely review the available literature of nutritional and environmental factors on autistic spectrum and attention deficit hyperactivity disorder (ADHD).

Design and methods: Review of journal articles found on the PubMed database and from information from several conference proceedings.

Results: Many, but not all, studies link exposure to toxins such as mercury, lead, pesticides, and *in utero* smoking exposure to higher levels of autism and/or ADHD. Some studies have reported many nutritional deficiencies in autism/ADHD patients. Numerous studies have reported that supplemental nutrients such as omega-3 fatty acids, vitamins, zinc, magnesium, and phytochemicals may provide moderate benefits to autism/ADHD patients. Avoidance of food allergens, food chemicals, and chelation therapy may also provide some relief to autism/ADHD patients.

Conclusions: Autistic spectrum disorders and ADHD are complicated conditions in which nutritional and environmental factors play major roles. Larger studies are needed to determine optimum multifactorial treatment plans involving nutrition, environmental control, medication, and behavioral/education/speech/physical therapies.

INTRODUCTION

Autism, a chronic disorder with onset before 3 years, presents with a wide range of stereotyped, repetitive behaviors, social difficulties, and language abnormalities.[1–3] The recent total prevalence of autism, Asperger's syndrome, and related developmental disorders is estimated at between 40 and 60 per 10,000 children.[4] Attention deficit hyperactivity disorder (ADHD) is an extremely common condition affecting 8% to 12% of children worldwide.[5] About 40% to 80% of autistic spectrum children also have ADHD as a comorbid disorder.[6–9]

Psychosocial factors certainly play a significant role in autism and ADHD disorders. Many studies have indicated that behavioral therapy and medications are often at least partially helpful for children with autistic spectrum and/or ADHD.[10–16] However, much recent research has suggested that nutritional and environmental factors also play a major role in the development of autism and ADHD disorders.

This paper will attempt to provide a broad review of the available literature on nutritional and environmental aspects of the epidemiology, etiology, prevention, and treatment of autistic spectrum disorders and ADHD. A second paper by the same authors will describe a pilot study of multi modal treatment (nutrition, chelation, environmental control, and

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psychosocial therapies) of 10 children with a combined diagnosis of autistic spectrum and ADHD.[17]

MATERIALS AND METHODS

This review is based upon extensive review of the PubMed database, as well as information from proceedings from several conferences on autism and/or ADHD.

RESULTS AND DISCUSSION

Toxic chemicals and autism

Much attention has focused on possible links between exposure to mercury, lead, and other toxics and autism. Some studies have found that exposure to vaccines with the mercury-containing preservative thimerosal is associated with significantly higher rates of autism,[18] while other studies have found no association between thimerosal-containing vaccines and autism.[19–21] A British prospective study of 13,647 singleton births recorded whether or not children received thimerosal-containing vaccines by 93 or 124 days after birth.[21] This study also analyzed whether or not children developed any of 23 behavioral, fine motor, speech, and other problems relating to autistic spectrum.[21] Of 46 analyses, receiving thimerosal-containing vaccines was associated with a significantly increased incidence of 1 adverse effect (reduced prosocial behavior by children who received vaccine before 93 days), no statistically significant effect in 41 comparisons, and associated with a significantly reduced adverse effect for 4 comparisons (conduct problems and fine motor skills in children receiving thimerosal before 93 days and tics and development of special needs in those children who received thimerosal vaccines before 124 days).[21] A review by the U.S. Food and Drug Administration (FDA) in 2001 concluded that there was no evidence of risk of thimerosal in vaccines apart from local hypersensitivity reactions.[22] A study 1047 children 7–10 years of age found that exposure to thimerosal-containing vaccines prenatally or up to age 7 months was rarely associated with any significant positive or negative outcomes in 42 neuropsychologic tests.[23] Higher prenatal thimerosal exposure was associated with 1 significantly positive and 1 significantly negative neuropsychologic outcome in 42 tests as compared to unexposed children.[23] Higher exposure to thimerosal-containing vaccines from birth to 7 months was associated with 2 significantly positive and no significantly negative neuropsychologic outcomes.[23] The incidence of autistic spectrum disorders was not measured in this study.[23]

Hair mercury levels averaged 15 times higher in 40 Kuwaiti autistic children as compared to 40 healthy controls (4.50 versus 0.30 μg/g hair, $p < 0.001$).[24] On the other hand, a Singapore study reported little difference in mean hair mercury in 82 autistic children versus 55 controls (2.26 versus 2.07 μg/g hair, $p = 0.79$).[25] An Arizona study found that levels of mercury in baby teeth were 2.1 times as high in a group of 15 autistic children as compared to 11 healthy controls ($p < 0.05$).[26] Levels of zinc and lead were similar in both autistic and control children.[26] Average antibiotic use in first year of life was 3.6 in the autistic children and 1.5 in the controls ($p < 0.001$).[26]

A study of 1184 Texas elementary/ high school districts found that higher levels of environmentally released mercury were associated with significantly higher levels of autism rates and rates of special education services.[27] A California study of 284 autistic children and 657 controls found that living in areas with higher outdoor air concentrations of mercury, cadmium, vinyl chloride, and trichloroethylene were all associated with significantly higher rates of autistic spectrum disorder.[28] A California case–control study reported that children born to mothers who lived within 500 m of agricultural organochlorine spraying had an odds ratio risk of autistic spectrum disorders of 6.1 (95% confidence interval (CI) of 2.4–15.3) as compared to children whose mothers did not live near areas of agricultural organochlorine spraying.[29]

Several studies have examined urinary levels of metals in autistic children following oral chelation therapy with meso-2,3-dimercaptosuccinic acid (DMSA). A Maryland study determined urinary metal levels following DMSA challenge in a group of 7 autistic children with no known mercury exposures except from thimerosal in vaccines.[30] Urinary mercury levels exceeded the reference level of 3 μg Hg/g creatinine in all 7 patients, and urinary lead levels exceeded the reference level of 15 μg Pb/g creatinine in 2 of 7 of the children.[30] On the other hand, another study of 15 autistic children given a DMSA challenge reported that urinary mercury levels were elevated in only 1 of the children, and urinary lead levels were elevated in 0 of the 15 autistic children.[31]

Toxic chemicals and ADHD

Hair lead levels have been found to be significantly higher in children with autism and/or ADHD in some,[24,32] but not all studies,[33–34] Many studies have indicated that childhood lead exposure can reduce IQ and attention and cause hyperactivity at levels below the current 10 μg/dL blood lead standard.[35–37] A U.S. study of 97 children with ADHD and 53 control children reported that higher blood lead levels were associated with significantly higher levels of ADHD symptoms.[38] In this study, mean blood lead levels were modest (1.04 μg/dL) and maximum blood lead levels were 3.4 μg/dL.[38] A Chinese case–control study reported that blood mercury levels exceeding 29 nmol/L were associated with a significantly greater risk of ADHD.[39] A study of 4704 U.S. children reported that significantly higher levels of ADHD were found in children exposed to tobacco smoking *in utero*

and in children with higher blood lead concentrations.[40] A Quebec study reported that higher manganese levels in hair and drinking water were associated with significantly higher levels of hyperactive behaviors in schoolchildren.[41] A study of 780 children with high lead levels (20–44 μg/dL) reported that treatment with 1–3 26-day courses of succimmer chelation therapy significantly reduced blood lead levels but did not result in any significant changes in tests of neuropsychologic function, cognition, or behavior.[42]

Impaired detoxification enzymes in autism

Autistic children often have lower levels of detoxification enzymes and antioxidants and may therefore be more susceptible to environmental toxics. Autistic children have significantly lower mean levels of detoxification/antioxidant enzymes such as paroxonase,[43,44] sulphation enzymes,[45] glutathione peroxidase,[46] and superoxide dismutase.[46] Significantly lower levels of methionine, *s*-adenosyl methionine, cysteine, and reduced glutathione were found in a group of 80 autistic children as compared to 73 controls ($p < 0.0001$ in all cases).[47] Another study of 8 autistic children found that reduced blood glutathione levels were significantly below normal in 6 children, blood cysteine levels were below normal in 6 children, and blood sulfate concentrations below normal in 4 patients.[30] A French study reported that urinary levels of coproporphryin and precoproporphryin (markers of lead exposure) were significantly higher in 106 autistic children as compared to 12 controls.[48] On the other hand, a Utah study reported that plasma levels of metallothionein (a metal-detoxifying protein) were similar in 60 autistic children and 50 controls.[49]

Nutritional factors in autism and ADHD

Nutritional deficiencies may also play a major role in autism. Significantly lower levels of nutrients in blood, hair, and other tissues have been seen in autistic children including low levels of magnesium,[50] zinc,[51] selenium,[51] vitamins A, B-complex, D, and E,[51] omega-3 fatty acids,[52,53] and carnitine.[54] A study of 861 autistic children and 123 control children found that feeding infant formulas lacking added docosahexaenoic acid (DHA) and arachidonic acids was associated with a 4.41 increased odds (95% CI 1.24–15.7) of developing autistic spectrum disorder as compared to breastfed infants.[55]

Some studies have reported that nutritional interventions can significantly help many patients with autism and/or ADHD. A double-blind, placebo-controlled study of 20 autistic children reported that use of a broad-based multivitamin and mineral supplement was significantly helpful in reducing sleep and gastrointestinal symptoms, and nonsignificantly helpful in improving behavior and receptive language.[56] A double-blind, placebo-controlled study found that supplementation of L-carnosine in autistic children produced significant improvement in the Gilliam Autism Scale.[57] Other studies have reported some improvement in autistic children supplemented with vitamin B_6,[58] folate,[58] omega-3 fats,[59] and vitamin C.[60] Oral supplementation with magnesium and vitamin B_6 significantly improved social interactions, communications, and intellectual function in the children with autistic-spectrum.[61] Case histories have reported that various nutrients such as cod liver oil,[62] carnitine,[63] and coenzyme Q_{10}[63] appear to help individual autistic patients.

Some studies have reported that ADHD patients have significantly lower levels of omega-3 fatty acids in their blood phospholipids and red blood cell membranes.[64,65] Use of supplements containing omega-3 fatty acids have been helpful to ADHD patients in some but not all studies. An Australian study found that ADHD children given capsules containing 2400 mg fish oil and 600 mg evening primrose oil daily for 15 weeks had significant improvements in many areas of the Conners Parental rating scales relating to hyperactivity and inattention as compared to ADHD children given placebo.[66] However, this study also found no significant changes in any of the Conners Teacher rating scales for either the treatment or placebo group of ADHD children.[66] An Indian study found that daily supplementation with 50 mg of vitamin C and flax oil containing 400 mg of α-linolenic acid daily significantly improved symptoms of inattention, hyperactivity, learning problems, and social problems in 30 children with ADHD.[67] Levels of omega-3 fatty acids in the red blood cells of these children also increased significantly following supplement with flax oil.[67] Several studies have found that evening primrose supplementation significantly improves symptoms of inattention (but not hyperactivity) in children with ADHD.[68,69] An Indiana study compared 4 months' treatment with a supplement containing fish oil and evening primrose oil versus olive oil placebo on 50 children with ADHD.[64] Children receiving the fish/evening primose oil supplement had significant improvements in behavior symptoms on the parental-rated Disruptive Behavior Disorder Rating Scale and in teacher-rated inattention symptoms as compared to children given olive oil placebo.[64] However, no significant improvements in the Conners ADHD scales or in tests of memory and audiovisual processing were seen in the fish/evening primrose oil–treated patients versus placebo.[64] This study also reported that supplementation with fish/evening primrose oil resulted in a significant increase in blood phospholipid and red blood cell levels of omega-3 fatty acids such as DHA and eicosapentaenoic acid.[64]

On the other hand, a Texas study of ADHD children reported that daily supplementation of 345 mg daily of the omega-3 fatty acid DHA did not significantly improve any symptoms of inattention and impulsivity as compared to placebo.[70] Another study involving 18 boys with ADHD reported that use of 4000 mg evening primrose oil capsules produced little improvement in ADHD symptoms as compared to placebo.[71] The only factor in this study to signifi-

cantly improve with administration of evening primrose oil was a significant improvement in teacher rated hyperactivity symptoms.[71]

Double-blind, placebo-controlled studies have reported that supplements of carnitine[72] and zinc[73,74] have been helpful in treating ADHD symptoms. Some studies have found that magnesium and vitamin B_6 supplements significantly reduce excitability and improve concentration in ADHD children.[75,76] However, an Ohio study reported that the use of magnesium and vitamin B_6 supplements was ineffective in treating 10 patients with autistic disorder.[77] Another study found that a dried supplement containing broccoli, cabbage, carrots and other phytonutrients was helpful in reducing ADHD symptoms.[78] Significant improvement in attention and visual/auditory response was noted in 10 ADHD children given a broad range of supplements containing vitamins, minerals, phytonutrients, amino acids, omega-3 fats, and probiotic bacteria.[79]

Blood levels of iron are often low in ADHD patients. A French study reported that serum ferritin levels averaged only 23 ng/mL in 53 children with ADHD but averaged 44 ng/mL in 27 control children ($p < 0.001$).[80] Some studies have reported that supplementation of the diet with metals such as iron, calcium, and zinc can decrease lead absorption in humans and experimental animals.[81] However, a study of 602 lead-exposed Mexican children found that daily supplementation with 30 mg of ferrous fumarate, zinc oxide, or both was not associated with any changes in parent- and teacher-rated symptoms of inattention, hyperactivity, or cognition.[82]

Allergies and food intolerances in autism and ADHD

Allergies and intolerances to food and food additives may also play a role in autism and ADHD. Elimination of potentially allergenic foods such as casein and gluten have been tried on autistic children with mixed results. A Norwegian study found that 10 children with autism on a casein- and gluten-free diet for 1 year improved on autistic traits, cognition, and motor skills to a significantly greater extent than 10 children given a standard diet.[83] On the other hand, a Florida double-blind crossover trial of 13 children with autism found that behavior did not differ significantly between the 6 weeks on a gluten- and casein-free diet versus 6 weeks on the standard diet.[84] Other studies have reported that children with autism have a significantly higher rate of increased intestinal permeability ("leaky gut syndrome") compared to controls.[85] Some researchers have suggested that oral probiotic bacteria supplements may be helpful in treating autism.[63]

The effect of refined sugar and food additives on ADHD patients is controversial, with some, but not all, studies showing that sugar and food additives can trigger worsened ADHD symptoms.[86] A review of 16 studies with ADHD children found that sugar challenges were associated with worsened symptoms of inattention and hyperactivity in 4 studies, little change in 11 studies, and improvement in ADHD symptoms in 1 study.[87]

Diets free of food coloring, food preservatives, and natural salicyclates have been widely used to treat children with ADHD since they were introduced in the 1970s by Dr. Benjamin Feingold.[87] A meta-analysis of 15 double-blind, placebo-controlled studies in patients with ADHD reported that artificial colors such as tartrazine significantly increased ADHD symptoms (overall effect size of 0.283, 95% CI 0.079–0.488).[88] Of the 15 individual studies, 5 showed that food colors were associated with significantly increased ADHD, 8 showed that food colors were associated with nonsignificant increases in ADHD symptoms, and 2 showed that food colors were associated with nonsignificant decreases in ADHD symptoms.[88] Besides food colors, other dietary components that may possibly worsen ADHD symptoms include food preservatives such as benzoate, nitrates, and monosodium glutamate as well as food that naturally contains salicylates (such as almonds, oranges, raspberries, apples, cherries, grapes, peaches, strawberries, cucumbers, plums, and tomatoes).[89]

CONCLUSIONS

Both autism and ADHD appear to involve a broad range of genetic, prenatal, social, developmental, nutritional, and environmental factors, and it is unlikely that only 1 single cause will be found for either disorder.[63,90–93] Multiple treatment modalities are probably needed to treat patients with autism and/or ADHD and may include nutritional, environmental, pharmacologic, and psychosocial interventions. A small pilot study of multiple treatments for 10 patients with autistic spectrum and ADHD has been conducted by us.[17] Larger, well-controlled studies in the future will be needed to determine optimal multimodal treatment plans for patients with autism and/or ADHD.

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