Nutritional Factors in Autism: An Overview of Nutritional Factors in the Etiology and Management of Autism

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Abstract

Autism is thought to have a multifactorial etiology that includes hereditary and environmental triggers accompanied by gastrointestinal disorders, such as chronic duodenitis, gastritis, reflux esophagitis, intestinal lymphoid dysplasia, dysbiosis, excessive intestinal permeability, and yeast overgrowth. Food sensitivity, especially to gluten and casein, is a prominent finding, as are autoimmunity, metabolic disorders, heavy metal toxicity, and nutritional deficiencies or excesses. Accordingly, medical practitioners have used dietary interventions with varying efficacy in autism treatment, including gluten and casein–free diets and use of omega-3 fatty acids, zinc, and carnosine. With most of these interventions, anecdotal reports of favorable responses usually exceed the number of scientifically controlled studies, but several of these studies have suggested efficacy. Researchers have concluded that autism therapy may require concurrent, multiple-agent interventions to counter the disease's multifactorial etiology, which they believe to result in a neurologically toxic body burden.

Bertrand et al estimate that autism is now twice as prevalent as Down syndrome, with an occurrence of at least 40 cases per 10000 children.[1] That number represents a 10-fold increase over the last 2 decades, even when Autism Spectrum Disorder (ASD) and Asperger's syndrome are excluded. Heredity is one causative factor in autism; a 90% concordance rate occurs in identical twins compared to a 30% concordance rate in fraternal twins.[2] Researchers believe that environmental factors during the fetal and neonatal periods and during early childhood trigger the disease's occurrence and that appropriate nutritional interventions prevent or possibly treat it effectively.

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LITERATURE REVIEW

Gastrointestinal Disorders

A prominent feature of autistic children is gastrointestinal (GI) disorders, which seem to occur in approximately one-third of patients. GI symptoms include chronic constipation, diarrhea, and abdominal pain. According to Horvath et al, chronic duodenitis and reflux esophagitis have been diagnosed in up to two-thirds of autistic children.[3] Wakefield et al found a novel form of inflammatory bowel disease, called intestinal lymphoid hyperplasia, in over 90% of autistic children compared to 14% of children who were not autistic.[4] Sandler et al observed decreased autistic behaviors in children with regressive autism (those who develop normally until 1 or 2 years of age and then display autistic symptoms) when they were given vancomycin.[5] Although researchers have not demonstrated scientifically that antifungal medications effectively treat yeast overgrowth, there are anecdotal reports of favorable results. D'Eufemia et al found increased intestinal permeability among 43% of 21 autistic children compared to none among controls.[6] Lucarelli et al found that autism may involve food intolerance or sensitivity as evidenced by 36 autistic children in 1 study who had significantly higher levels of antibodies for food proteins, including lactoglobulin and casein, compared to controls.[7]

Autoimmunity

There is a significantly higher incidence of antibodies to certain parts of the brain among autistic children than among controls. For example, Singh et al found that nearly half of 68 autistic children exhibited serum antibodies to the caudate nucleus compared to none for the controls.[8]

Metabolic Abnormalities

James et al found significantly lower serum levels of nutrients and metabolites—including methionine, cysteine, s-adenosylmethionine, and total glutathione—in autistic children compared to controls.[9] Significantly higher levels of s-adenosylhomocysteine, adenosine, and oxidized methylation and greater oxidative stress also occurred. McGinnis found that elevated nitric oxide and xanthine oxidase and lower antioxidant nutrients and enzymes also indicated increased oxidative stress.[10]

Heavy Metal Toxicity

Numerous studies have suggested that heavy metal toxicity is an etiological factor in autism. For example, Fido and Al-Saad found that 40 autistic boys exhibited significantly

higher hair concentrations of lead, mercury, and uranium compared to 40 normal controls.[11] In contrast, Kern et al[12] found that arsenic, cadmium, and lead levels in hair were significantly lower in 45 autistic children compared to 45 normal controls, leading the authors to conclude that autistic children may be poor detoxifiers and consequently may have higher body burdens of heavy metals that may contribute to autistic symptoms. A study by Yorbik et al supports that study, finding that urine concentrations of cadmium and lead were significantly decreased in 30 autistic children compared with 20 normal controls.[13] Moreover, autistic children may have had a greater exposure to mercury during pregnancy due to maternal dental amalgams. Geier et al found that children whose mothers had 6 or more amalgams were over 3 times more likely to be diagnosed with autism compared to the milder ASD infants whose mothers had fewer than 6 amalgams.[14] Faber et al found that reduced plasma zinc-to-copper ratio is associated with ASD and may be a biomarker of mercury and other heavy metal toxicity.[15] Accordingly, metallothionein formation may be compromised in ASD. Recently, Kinney et al hypothesized that known mutagens, including mercury and cadmium, may contribute to autism by causing de novo mutations.[16]

Vaccines

Mercury is known to be a powerful neurotoxin, yet vaccines given to children until 1999 used thimerosal (ethyl mercury) as a preservative. In their analysis, Geier and Geier associated vaccines containing thimerosal with autism.[17] Subsequent studies have failed to find an association between thimerosal and autism[18]; however, one study was able to associate mercury release into the environment with autism.[19] Kawashima et al (including A. Wakefield) believed that measles immunization might trigger autism in some patients,[20] but no subsequent studies support that study.[21] McGreevy suggested single vaccine programs as an alternative to the triple vaccination.[22]

Hewitson et al from the University of Pittsburgh School of Medicine recently published a relevant animal study.[23] The study was a longitudinal, case-controlled examination of amygdala growth in infant rhesus macaque monkeys to which the researchers administered the complete schedule of US childhood vaccines and then compared with saline-injected controls. Both the vaccine-exposed group and the controls underwent magnetic resonance imaging and positron emission tomography imaging at approximately 4 and 6 months of age, corresponding to the timeframes of the vaccination schedule for human infants. Analysis showed that the vaccine-exposed group failed to undergo the maturational changes in amygdala volume that the researchers saw in the controls. Moreover, for the vaccine-exposed group, the binding capacity of the opioid antagonist [11c] diprenorphine (DPN) remained relatively constant over time, while the controls exhibited a significant decrease in DPN binding. This study lends support to those who question the safety of administration of the complete vaccine schedule that medical practitioners recommended between 1994 and 1999.

It is noteworthy that Sparks et al found that a rapid increase in total brain volume was a consistent finding among children with ASD.[24] Kleinhans et al suggest that an increased brain volume may be the result of the failure of apoptosis in that malfunctioning neural connections are not removed.[25] Failure of this process may occur in autism, especially in regard to the amygdala.[26]

Nutrient Abnormalities

Levels of vitamin B6 were much higher in autistic children than in controls, suggesting that the former cannot effectively convert pyridoxal to pyridoxal-5-phosphate.[27] Large doses of vitamin C in institutionalized autistic children resulted in significant improvement in total autism evaluation scores and worsening of scores when subjects were crossed over to placebo.[28] Autistic children exhibited significantly lower plasma levels of omega-3-polyunsaturated fatty acids than controls.[29] Finally, researchers have made a strong case for vitamin D deficiency in the etiology of autism.[30] Calcitriol (1,25 dihydroxycholecalciferol) downregulates production of inflammatory brain cytokines associated with autism. Autism is more common in dark-skinned persons as is severe vitamin D deficiency.[30] Epidemiologic evidence supports the association of a decrease in solar radiation during winter with an increased risk of autism due to maternal vitamin D deprivation.[31] Meguid et al found that 70 autistic children had significantly decreased circulating levels of serum vitamin D metabolites compared to 42 normal controls in a case-controlled study.[32]

Nutritional Intervention

Medical practitioners have used the gluten-free, casein-free diet extensively in autism treatment. In one controlled, randomized 1-year study of this diet, Newmark matched autistic children in the experimental group (diet group) to other autistic children.[33] The researchers evaluated autistic behaviors under blind conditions. The diet group scored significantly better than the control group. For example, social contact increased in two-thirds of treated group and ritualistic behaviors decreased in 8 of 11. The researchers estimated that evaluation of the diet's efficacy requires 2 months. More recently, a 24-month, randomized, single-blind study of a gluten and casein–free dietary intervention among 72 autistic children reported significant improvements in the elimination diet group.[34] When Whiteley et al gave a polyunsaturated supplement containing 247 mg of docosahexaenoic acid and 40 mg of linoleic acid to 18 autistic children for 3 months, a significant improvement in their language skills occurred.[35] An 8-week, double-blind, placebo-controlled study showed that autistic children benefited from carnosine supplements.[36] Specifically, they exhibited statistically significant improvements on the Gillian Autism Rating Scale and on the Receptive One-Word Picture Vocabulary test.

A decade ago, Megson suggested that children genetically at-risk for autism might benefit from inserting a G-alpha

protein from the pertussis toxin into the diphtheria, pertussis, and tetanus vaccine, separating the protein from retinoid receptors.[37] Administration of vitamin A may reconnect the receptors needed for language processing and attention. A small study by Lonsdale et al found that 8 of 10 children with ASD exhibited clinical improvement when given 50 mg of thiamin tetrahydrofurfuryl disulfide twice daily, even though only 3 of them presented with thiamin deficiency.[38] Adams et al studied oral administration of dimercapto succinic acid in 49 children with ASD using a double-blind protocol.[39] The researchers noted increases in urinary excretion of several heavy metals, especially lead, compared to children given placebo. The treatment normalized low red blood cell–glutathione levels as well as abnormal platelet counts, suggesting a reduction in inflammation.

DISCUSSION

Current evidence indicates that nutritional factors may play an important role in the etiology and management of autism. GI abnormalities affect the majority of autistic children and include duodenitis, ileitis, colitis, excessive gut permeability, dysbiosis, and food sensitivities, especially to gluten and casein. Accordingly, these abnormalities warrant appropriate nutritional interventions including food restrictions and omega-3-fatty acid and antioxidant supplements. A recent study found that micronutrient supplementation was superior to pharmaceutical use in terms of decreased Aberrant Behavior Checklist scores, self-injurious behavior, and greater Clinical Global Impressions.[40] Thus, the participants exhibited less social withdrawal, less anger, less irritability, improved spontaneity, and markedly fewer adverse events.

Because of the severe social, economic, and medical consequences of autism, future protocols for clinical studies should involve interventions with multiple nutritional modalities. For example, at the very least, combinations of gluten and casein restriction should be employed in conjunction with a regimen of omega-3 fatty acids, zinc, and carnosine. Medical practitioners might also recommend supplemental glycine, glutathione, methyl cobalamin, phosphatidyl choline, dipeptidases, and proteases since they collectively address nutritional defects associated with autism.[4] This "shotgun" approach will make it impossible to discern which agent or practice (if any) is effective; however, multiple combinations will give the best possible chance for successful outcomes as opposed to administration of single, double, triple, or limited agents or practices.

Stern[42] recently proposed a hypothesis that maternal hyperinsulinemia during pregnancy may be partly responsible for autism, since there is a two-fold increased incidence in autism in gestational diabetes, which may activate PI3K/Tor pathway due to a genetic mutation. This hypothesis could be tested by use of a restricted carbohydrate diet for autistic children.

The unifying hypothesis of this paper is that autism is a disorder with multiple causative factors that culminate in a neurologically toxic body burden. Because it is difficult, if not impossible, to discern the primary etiological toxins, the authors recommend that medical practitioners concurrently administer multiple agents found to have an ameliorative effect. To summarize, several nutritional therapies for autism are evidence-based[41] and have favorable outcomes.

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