6

Dietary Interventions in Autism

Yasmin Neggers
The University of Alabama, Tuscaloosa, Alabama, United States of America

1. Introduction

The objective of this chapter is to evaluate the research pertinent to the use of dietary interventions to treat autism. A brief description, rationale, any evidence of efficacy and validity of methodology employed for most frequently used inventions in autism follows.

The number of children diagnosed with autism spectrum disorder (ASD) has increased significantly over the last decades in the U.S. and in other countries. Yet to date, there is no clear etiology or cure for autism. In most cases, specific underlying causes cannot be identified (Cubala-Kucharska, 2010). A number of risk factors being investigated include genetic, infectious, metabolic, nutritional and environmental, but less than 10 to 12% of cases have specific causes known (Srinivasan, 2009). Simultaneously the use of alternative treatment approaches in children with autism has increased, but due to significant methodological flaws, the currently available data are inadequate to guide treatment recommendations (Christison and Ivany , 2006).

It has been suggested that nutritional factors play a major role. Significantly lower levels of various nutrients in blood have been observed in autistic children including low levels of zinc, selenium, vitamin D and omega-3 fatty acids (Elder, 2008). In practice, treatment of ASD usually consists of a comprehensive program of educational intervention, speech therapy, behavioral treatment and developmental therapies. Anecdotal reports and parent surveys and a few research studies have indicated some evidence of diminishing the symptoms of autism by use of diets based on food elimination and rotation, as well as through supplementation and alternative treatments based on intestinal healing (Cubala-Kucharska,2010; Srinivasan, 2009). The popularity of these diets indicates a need for more in-depth and rigorous research into their efficacy.

Currently a variety of nutritional interventions are in use, including gluten and casein- free diet (GFCF), ketogenic diet, yeast free diet, restriction of food allergens, probiotics, and dietary supplementation with vitamins A, C, B_6, folic acid , B_{12}, minerals like magnesium and omega-3 fatty acids (Seung et. al, 2007). In most cases, the dietary interventions discussed below were developed for conditions related to autism, e.g., multiple food sensitivity, inflammatory bowel disease, Candida and viral infections. Wide use of complementary and alternative therapies (CAM) by parents and caregivers has been reported (Elder, 2008). The literature currently available suggests that diets removing both gluten and casein show some efficacy and should be studied further.

2. Gluten –Free Casein- Free Diet (GFCF)

One of the most frequently used interventions for ASD is the GFCF diet. Initially focusing on schizophrenia, investigators conducted studies to test the hypothesis that schizophrenia as well as autism was in some way associated with the absorption of "exophrins" contained in gluten and casein (Elder et al., 2006). This diet calls for complete elimination of both gluten and casein, which is found in wheat, rye, barley, and oats, as well as casein, the protein in milk and all milk products.

Rationale: It is hypothesized that some symptoms of autism (e.g., stereotypical and ritualistic behaviors, preservation, excessive activity, speech and language delays) may result from opioid peptides formed from incomplete breakdown of foods containing gluten and casein. It is proposed that increased intestinal permeability, also referred to as "leaky gut syndrome" allows these peptides to cross the intestinal membrane, and cross the blood-brain barrier through entry into the blood stream, thereby affecting the endogenous opiate system and neurotransmission in the nervous system (Cubala-Kucharska , 2010; Milward et al., 2009). This theory is cited to explain why many children with autism have G.I. symptoms, including abdominal pain, diarrhea and gastrointestinal reflex.

Research studies: There have been only a few published studies examining the efficacy of GFCF diets. Most of these studies report some degree of efficacy, yet each has some methodological weakness.

2.1 Uncontrolled trials

A literature search using Pubmed and other search engines was conducted to find studies evaluating the efficacy of the GFCF diet as an intervention to improve behavior, cognitive and social functioning in children with autism. Here some of the methodologically superior studies will be discussed briefly and critiqued.

Reichelt et. al , 1990:

Authors reported the results of an uncontrolled trial with 15 children, ages 3 to 17 years diagnosed with autism. In 8 children, gluten was eliminated and milk reduced; in three children milk was eliminated and gluten reduced; and in four children, both gluten and milk was eliminated. The children were followed for one year. Behavioral assessment was done by a clinical questionnaire at the beginning and the end of the treatment year. This was compared with the pretreatment year retrospectively. Results showed that at least half of the children improved during the treatment year. This study suffers from several methodological flaws. The subject pool was small and diagnostically heterogeneous. No information was provided about dietary compliance. Also no control group was used.

Lucarelli et al., 1995

In an uncontrolled study, 36 children, 8 to 13 years, with a diagnosis of autism were placed on individualized elimination diets for 8 weeks. Cow proteins were eliminated from all diets. In addition, each child received allergen testing, and any food allergen that tested positive was also removed from the diet. At base line and after 8 weeks children were evaluated with the Behavior Summarized Evaluation (BSE). A statistically significant reduction in group scores on 5 of the 7 BSE subscales after 8 weeks on the diet was reported. A lack of controls and relatively short intervention affect the validity of results of this study.

Cade et al., 2000

Seventy children with a diagnosis of autism on the GFCF elimination diet for one year were studied. There was no control group of children. Ten children with autism were matched for age, cognitive level and symptom severity. A statistically greater improvement was observed in the diet group on multiple domains of autism symptoms. Problems with the study include uncontrolled design and the outcomes measurement by an invalidated instrument.

2.2 Controlled clinical trials

Knivensberg et al., 2002:

A single blind study evaluated the effect of the GFCF diet on a group of 20 children with a diagnosis of autism and urinary peptide abnormalities. The authors were testing the hypothesis that products from incomplete digestion of proteins could cause synthesis of caseomorphines and glutomorphines. These compounds could have opioid-like effects when absorbed through a permeable intestine. Evaluation tests conducted before and after a treatment of one year in the areas of communications, language, and motor skills showed significant improvement in the group of children following a GFCF diet (Table 1). Improvements were also noted in social connections, willingness to learn and other areas. The children following the diet had fewer autistic traits after this one year intervention. However, the benefit of using matched controls was diminished by not blinding parents, teachers and subjects to treatment conditions.

Elder et al. 2006

A trial of the GFCF diet in 13 children with autism was carried out by Elders et al., 2006. Individual child preferences were taken into account and the participants were provided all meals and snacks from the metabolic kitchen. They evaluated the effect of the GFCF diet on autistic symptoms as measured by the (a) Childhood Autism Rating Scale (b) Urinary peptide levels on gluten free diet. Analysis indicated no significant differences in the behavior of autistic children as measured by emotional expression, body use, peculiarities in object use, resistance to change, activity level and intellectual ability. Also, there was no change in the urinary peptide levels in children on GFCF diet (Table 1).

Milward et al., 2009 (Cochrane Review,)

In this comprehensive review an extensive search was carried out to identify any randomized controlled trials (RCT) of gluten and/or casein free diets as intervention to improve behavior, cognitive and social functioning in individuals with autism . Only three papers reporting on three randomized trials were identified which met the rigorous criteria set by the investigators (Table 2). These trials were not mentioned above and are briefly discussed here.

1. Whitely et al., 2010: (The ScanBrit Randomized Single Blind Trial): This NIH funded study conducted a two stage, 24 month randomized controlled trial in 72 Danish children assigned to diet (A) or non-diet (B) to evaluate core autism behaviors. Results suggested that GFCF had a significant beneficial group effect at 8, 12 and 24 months of intervention on core autistic and related behaviors of children diagnosed with ASD. Due to the absence of a placebo group, this study was unable to eliminate potential effects derived from interventions outside of dietary changes. (Table 2).

2. Diet and Behavior in Young Children with Autism (Clinical trial No NCT00090428 Ongoing): This ongoing double blind randomized clinical trial is following children on a gluten free and casein free diet for 18 weeks. This long term rigorous trial with adequate sample size may clarify the issues involved with determining the efficacy of GFCF diets (Table 2).
3. Study to Assess the Role of a Gluten Free-dairy Free (GFCF) Diet in the Dietary Management of Autism Associated Gastrointestinal Disorders (ClinicalTrial .gov.Identifier: NCT0116388) (Ongoing, expected completion date April 2011) This ongoing randomized, double blind trial will asses the effect of a GFCG diet on GI symptoms associated with ASD in thirty activities- including physicals, blood samples and allergy testing. Also, an amino acid based supplement drink will be provided at no cost at the MGHFC in Boston, or at the Newton Wellesley Hospital in Newton, or at LADDERS in Lexington MA.

The results of the first trial indicated that a combined gluten and casein free diet reduced the autistic symptoms. The second trial showed no significant difference in outcome measures between the treatment and the control group. The results of the third trial have not yet been published. None of these trials reported an adverse outcome . It is hoped that as these rigorously conducted randomized clinical trials are completed, their results will further clarify the efficacy of GFCF diets in treatment of autism. However, on the basis of limited data available, the current knowledge about the efficacy of GFCF at this time does not merit a recommendation of their use as a standard treatment for autism..

Investigators	Type of Intervention and Participants	Intervention and duration of study	Outcomes Measured
Elder, 2006	Randomized, double blind crossover trial. 15 children with autism spectrum disorders (ASDs), ages 2-16.	Gluten and casein free diet adapted to the individual child's food preference vs. matched diet but with gluten and casein 12 weeks	-Childhood Autism Rating Scale (CARS) -Urinary Peptide Levels (UPL) -Ecological Communication Orientation (ECO) - In-home observation of child's behavior
Knivsberg, 2002	Single-blind, randomized trial. 20 children with ASDs and abnormal urinary peptide pattern Ages 62-120 months	Gluten free vs. normal diet 12 months	Autistic traits Cognitive skills (Leiter International performance Scale), Linguistic ability, Motor ability (Movement Assessment Battery for Children)

Table 1. Characteristics of Studies Which Met the Cochrane Review Criteria

Investigators	Type of Study and Participants	Intervention and duration of study	Primary Outcomes
ScanBrit Dietary Intervention in Autism (under the remit of a Scandinavian- British collaborative research group) NCT00614198	Single-blind, randomized-controlled, matched pair adaptive trial. 72 Danish children ages 4-11 years formally diagnosed for PDD. Exclusion criteria: co-morbid diagnosis for epilepsy, tuberous sclerosis or developmental age < 24 months.	Gluten-and casein – free diet. April 2006-October 2008.	Outcomes: Autism Diagnostic Observation Schedule (ADOS), Gilliam Autism rating scale (GARS), Vineland Adaptive Behavior Scale (VABS) Changes in appearance of multiple compounds in urine
Diet and Behavior in Young Children with Autism. National Institutes of Health, Clinical trial No. NCT00090428	Randomized, Double Blind Placebo Control. 30 children, at the University of Rochester Medical Center, Rochester, New York, ages 30-54 months	Gluten-and casein-free diet Vs. Placebo. They will also receive uniform educational and behavioral services through their provider. Controlled diet Phase I August 2004- Estimated completion Feb 2009	Safety and efficacy of the gluten free casein free diet, measured at weeks 18 and 30.
A Study to Assess the Role of a Gluten Free-dairy Free (GFCF) Diet in the Dietary Management of Autism Associated Gastrointestinal Disorders. Massachusetts General Hospital. ClinicalTrials .govIdentifier: NCT0116388	Randomized , double blind Trial Crossover Assignment. Estimated enrollment: 30, ages 2-17 years	Gluten free-Casein-free diet. Study started April 2010. Estimated completion date: April 2011.	To assess if improvements in GI symptoms result in improvements in autistic behavior when using a GFCF diet and dietary management of GI symptoms associated with ASD. To determine the nutritional management of a GFCF restrictive diet. To assess the role of food allergies in the maintenance of GI symptoms.

Table 2. Characteristics of Recently Completed and Ongoing Randomized Controlled Trials which Met the Cochrane Review Criteria.

3. Ketogenic diets

The ketogenic diet was first introduced as a therapeutic method to reduce the number and intensity of epileptic seizures. But it has been reported that in addition, the ketogenic diet is beneficial for mental behavior and hyperactivity. In the classic ketogenic diet, also known as the long-chain triglyceride diet, fat provides the majority of energy, protein is based on minimum daily requirements, and carbohydrates are severely restricted (Kossoff and Zupec-Kana, 2009; Evangeliou et al., 2003).

Rationale

It is hypothesized that autistic behavior is associated with a disturbance in glucose metabolism, particularly, mitochondrial energy production, leading to an excess of reduced nicotinamide adenine dinucleotide (NADH) or a lack of nicotinamide dinucleotide (NAD). It is thought that application of a ketogenic diet would produce an improved mitochondrial function by sparing NAD, which will be consumed in the oxidation of glycolytic substrates (Evangeliou et al., 2003; Carroll and Koenigsberger, 1998).

In the past decade, there have been four major meta-analyses of the efficacy of the ketogenic diet. All of these reviews concluded that there is some evidence of seizure reduction and other benefits in children with epilepsy despite the lack of blinded, controlled trials at the time of publications (Keen, 2006; Yeou-Mei et. al, 2003). However, the ketogenic diet has not been shown to be efficacious specifically when used to treat children diagnosed with autism. Also, to our knowledge no randomized clinical trials have been conducted to evaluate the effect of the ketogenic diet for treatment of symptoms of autism.

Research Studies: There is a paucity of data in evaluating the efficacy of the ketogenic diet as a dietary intervention in autism. In a pilot study, Evangeliou et al, 2003 examined the efficacy of the ketogenic diet in autism. Thirty children were put on a ketogenic diet for 6 months .Of the 60% of the patients who adhered to the diet improvement was recorded in several parameters in accordance with the Childhood Autism Rating Scale. These data are very preliminary and better designed clinical trials are needed to test the efficacy of ketogenic diets in the treatment of autism.

4. Feingold diet

This diet is based on the benefit of a food-restriction diet for attention deficit and hyperactivity disorder. Scientifically undocumented behavioral improvements after elimination of food colors and flavors have been reported. According to Dr. Feingold's hypothesis elimination of food additives resulted in some cases in dramatic decline in hyperactive symptoms (Feingold, 1985). At this time no rigorous randomized trials have been conducted to evaluate the efficacy of the Feingold diet for easing the symptoms of ASD.

5. Antioxidant diets

Antioxidant diets have gained the attention of some investigators who are concerned about oxidative stress in autism and related conditions. Commonly recommended foods are fresh fruits and vegetables, cooked legumes, and whole grains (Jeep et al., 2008). The super foods recommended on this type of diet are broccoli, Brussels sprouts, berries like blueberries and Goji berries. Moderate servings of animal products such as lean meat are allowed. This dietary pattern is part of a healthy diet recommended for the general population but it has not been tested for reducing symptoms of ASD.

6. Conclusions

Among the dietary interventions currently in use for treatment of ASD, the gluten-free-casein free diet shows the most promise of efficacy. However, this diet is not without cost in terms of inconvenience and limitation on foods of choice for the affected individual. Due to the potential for nutritional deficiency as a result of long-term dietary exclusion, appropriate clinical and dietetic support should be considered during any attempt to make such dietary changes. The American Dietetic Associations position at this time is that more research is needed to determine the efficacy of dietary therapy approaches (Marcason, 2009).The lack of long term data, preferably life-span data on health risk associated with nutrient limiting diets such as GFCF require further safety study. At present, two double blind, placebo controlled trials are being conducted and results of these trials are likely to provide valid information pertaining to the efficacy of GFCF diet in treatment of autism.

7. References

A Study to Assess the Role of a Gluten Free-Dairy Free (GFCF) Diet in the Dietary Management of Autism Associated Gastrointestinal Disorders.Massachusetts General Hospital. ClinicalTrials.govIdentifier: NCT0116388.

Cade R, Privette M, Fregly M. Autism and schizophrenia: intestinal disorders. Nutr. Neurosci. 2000; 3:57-72.

Carroll J, Koenigsberger D. The ketogenic diet: A practical guide for caregivers. J Am Diet Assoc. 1998; 98 (3): 316-321.

Christison GW, Ivany K. Elimination Diets in Autism Spectrum Disorders: Any wheat amidst the chaff? Dev Behav Padiar. 2006; 27 (2): S162-S169

Cubala-Kucharska M. The review of most frequently occurring medical disorders related to aetiology of autism and the methods of treatment. Acta Neurobiol Exp. 2010; 70:141-146.

Diet and Behavior in Young Children with Autism. National Institutes of Health, Clinical trial No. NCT00090428. Clinical trial registry. Diet and behavior in young children with autism. ClinicalTrial.gov.

Elder JH, Shanker M, Shuster J, Douglas T, Burns S, Sherill L. The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. J Autism Dev Disorders. 2006;36(3): 413-420.

Elder JH. The gluten –free,casein-free diet in autism: An overview with clinical implications. Nutr. Clin Pract. 2008; 23 (6):583-588

Evangeliou A, Valchonikolis I, Mihailidou H. et al. Application of a ketogenic diet in children with autistic behavior: Pilot study. J Child Neurol. 2003; 18: 113-118.

Feingold B. Why your child is hyperactive. New York, NY. Random House; 1985.

Jeep R, Couey R, Pittman ES. The super antioxidant diet and nutrition guide. Charlottesville, VA. Hampton Roads Publishing Company; 2008.

Keen DL. A systematic review of the use of ketogenic diet in childhood epilepsy. Pediatr Neurol.2006; 35:1-5.

Knivsberg A, Reichelt KL, Hoten I. A randomized controlled study of dietary intervention in autistic syndrome. Nutr Neurosci. 2002; 5: 251-261

Kossoff EH , Zupec-Kana BA. Ketogenic diets; an update for child neurologists. J Child Neurol. 2009; 24 (8):979-88.

Lucarelli S, Fredianai T, Zingoni AM. Food allergy and infantile autism. Pan Minerva Med. 1995; 37:137-141.

Marcason W. What is the current status of research concerning use of a gluten-free, casein-free diet for children diagnosed with autism? J Am Diet Assoc. 2009; 109.

Milward C, Ferrier M, Calver SJ, Connell-J GG.. Gluten-and casein-free diets for autistic spectrum disorder. Cochrane database of Systematic reviews. 2009 (2): 1-27.CD003498.

Reichelt KL, Ekrem J, Scott H. Gluten, milk protein, and autism: dietary intervention effects on behavior and peptide secretion. J Appl Nutr. 1990; 42:1-11.

Seung HK, Rogalski Y, Shankar M, Elder J. The gluten-and casein- free diet and autism: Communication outcomes from a preliminary double blind clinical trial. J Med Speech-Language Path. 2007; 15(4): 337-345.

Srinivasan P. A review of dietary interventions in autism. Ann Clin Psychiatry. 2009; 21 (4): 237-47

Whitely P, Haracopos D, Knivsberg AM Reichelt KR, Parlar S, Jacobsen J, Seim A, Pedersen L, Schondel M, Shattock M.. The Scan Brit randomized controlled, single blind study of a gluten and casein free dietary intervention for children with autism spectrum disorders. Nutr Neuroscience. 2010; 13 (2): 87-100.

Yeou-Mei CL, Williams S, Basualdo-Hammond C, et al. . A prospective study: Growth and nutrition status of children treated with the ketogenic diet. J Am Diet Assoc. 2003; 103: 707-712.