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J Child Neurol 2010; 25; 114 originally published online Jun 29, 2009;
DOI: 10.1177/0883073809336127

Special Article

Journal of Child Neurology
Volume 25 Number 1
January 2010 114-119
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10.1177/0883073809336127
http://jcn.sagepub.com

Celiac Disease Presenting as Autism

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Gluten-restricted diets have become increasingly popular among parents seeking treatment for children diagnosed with autism. Some of the reported response to celiac diets in children with autism may be related to amelioration of nutritional deficiency resulting from undiagnosed gluten sensitivity and consequent malabsorption. A case is presented of a 5-year-old boy diagnosed with severe autism at a specialty clinic for autistic spectrum disorders. After initial investigation suggested underlying celiac disease and varied nutrient deficiencies, a gluten-free diet was instituted along with dietary and supplemental measures to secure nutritional sufficiency. The patient's gastrointestinal symptoms rapidly resolved, and signs and symptoms suggestive of autism progressively abated. This case is an example of a common malabsorption syndrome associated with central nervous system dysfunction and suggests that in some contexts, nutritional deficiency may be a determinant of developmental delay. It is recommended that all children with neurodevelopmental problems be assessed for nutritional deficiency and malabsorption syndromes.

Keywords: autism; autistic spectrum disorder; gluten sensitivity; celiac disease; nutrition; malabsorption

In a seminal paper published in 1943 titled "Autistic Disturbances of Affective Contact," Leo Kanner first described a series of children with the neuropsychiatric condition currently known as autism.[1] According to the latest revision of the *Diagnostic and Statistical Manual of Mental Disorders* (fourth Edition, Text Revision),[2] autism is a disorder of impaired social interaction and communication, limited activities and interests, as well as stereotyped behaviors—difficulties that are usually evident by 3 years of age. Concomitant with isolative behavior, children with autistic disorders frequently manifest significant aggression, tendencies toward self-injury and self-harm, irritability, as well as hyperactive and erratic behavior. Diagnosis is made using a number of different measures and screening tools, many based on observation by a team of health professionals. The prognosis is generally unfavorable with chronic impairment for the affected individual and a sustained impact on loved ones and caregivers. In this article, we present the case of a child diagnosed with autism whose illness resolved after underlying celiac disease and assorted nutritional deficiencies were addressed.

Over the past few decades, autism has been recognized as the most severe form of affliction in a spectrum of pervasive developmental disorders referred to as autistic spectrum disorders. Population-based studies in America and the United Kingdom have demonstrated that the prevalence of autism is increasing significantly and that this disorder has become a serious public health issue.[3-6] From an incidence as low as 1:2500 in the mid-1980s, the reported rate of autism rose to about 1:300 in 1996[6] and has continued the climb to an unprecedented rate of 1:150 in 2002.[5] The increasing incidence and prevalence of this condition has generally been thought to result from expanding definitions of autism, as well as earlier diagnosis and an increased inclination for parents of disabled children to seek care.[7-9] Recent study, however, has demonstrated that only a small portion of increased autism rates can be accounted for by these factors.[10] The authors of this recent report speculate that changes in the environment might be a significant determinant of autistic spectrum disorder. Ongoing research is investigating many possible determinants including genetic influences, pre- and post-natal development, environmental factors, nutritional compromise, and immune deficiencies.[11]

Celiac disease is an immune-mediated malabsorption syndrome triggered by gluten-containing grains (wheat, rye, barley, and oats). Some patients with this condition present with gastrointestinal symptoms including diarrhea, bloating, fatigue, weight loss, and nutrient deficiencies, but there is increasing evidence that celiac

Received February 20, 2009. Accepted for publication March 13, 2009.

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The authors have no conflicts of interest to disclose with regard to this article.

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Genuis SJ, Bouchard TP. Celiac disease presenting as autism. *J Child Neurol.* 2010;25:114-119.

disease can present with a variety of clinical symptoms that are not apparently gastrointestinal in nature. Serological diagnosis is made with antiendomysial antibodies and antitissue transglutaminase antibodies, which have a high specificity and sensitivity for celiac disease.[12] A definitive diagnosis can be made by tissue biopsy of the intestinal tract. The symptoms are generally ameliorated with avoidance of triggers that contain gluten.

The association between celiac disease and central nervous system dysfunction has been known for several decades,[13] especially in relation to neuropathy, ataxia, migraine, and epilepsy.[14] In fact, many new cases of celiac disease are detected following an initial presentation of neurological complaints.[15] A recent clinical case report discussed in the *Journal of Internal Medicine*, for example, confirms that signs and symptoms of schizophrenia may be a presentation of celiac disease—a clinical problem that may resolve after institution of a gluten-free diet.[16] A pediatric case study suggesting a direct link between celiac disease and symptoms characteristic of autistic spectrum disorder is presented here for consideration.

Case Report

A 5-year-old boy diagnosed with autistic disorder presented for evaluation to a physician trained in environmental medicine. The family was upset that the child was diagnosed with a chronic debilitating psychiatric condition. With no family history of illness or autistic spectrum disorder, they were looking for an explanation about the origins of his health problem. The mother, a health care worker, was concerned that perhaps an environmental exposure may be a determinant in the child's condition and wished to explore the possibility of accrued toxicants. A detailed history and environmental assessment were undertaken by the physician, a physical examination was performed, and laboratory investigations were carried out.

The history revealed that at 3 years of age, the patient was referred by a pediatrician to the Preschool Assessment Service at a specialized Autism Spectrum Clinic in a major medical centre in Alberta, Canada. After a 3-day assessment by a pediatric consultant, a speech-language pathologist, a psychologist, and a social worker, the child was diagnosed with a "severe communication disorder," with social interaction difficulties and sensory processing delay. A magnetic resonance imaging (MRI), electroencephalography (EEG), optometry assessment, blood work, and genetic testing were undertaken as well as the *Communication and Symbolic Behavior Skills Assessment*[17] and the *Bayley Scales of Infant Development-Second Edition*.[18] A pediatric neurology consultation was also arranged.

After 10 months, a composite follow-up of all previous assessments and investigations was undertaken. Blood work was normal other than low hemoglobin [normal amino acids, organic acids, thyroid-stimulating hormone (TSH), mean corpuscular volume (MCV), and ferritin]. Genetic testing was unremarkable (normal karyotype, negative for fragile X) and the MRI and EEG were also normal. Two evaluation instruments for autism were administered—the *Autism Diagnostic Interview—Revised*[19] and the *Autism Diagnostic Observation Schedule*,[19] along with neuropsychological testing and assessment for communication disorders. At the conclusion of this composite assessment, the boy was given a primary diagnosis of autistic spectrum disorder with significant findings of language disorder, scattered language development, and social communication impairment. The parents recall they were explicitly told the condition was severe.

A plan was instituted including speech-language therapy, intensive individualized educational programming, and contact was encouraged with the Autism Society. The parents were told that this was a chronic disorder, that there was no evidence for a relationship between vaccinations and autism, and that there was no research to prove that any alternative therapies would be of assistance. They subsequently spent considerable time and resources consulting various complementary and alternative medicine practitioners to explore the potential etiology of their son's affliction and to seek help addressing his health problems, all to no avail. The parents were very discouraged; after consulting a chiropractor, a naturopathic doctor, as well as undergoing numerous ancillary tests by complementary and alternative medicine practitioners and trying numerous supplements, they presented to a specialist in environmental medicine.

Upon direct questioning at initial presentation, the 5-year-old child was reported by the parents to have unexplained fatigue, confusion, and an inability to tolerate bright lights in addition to his developmental delay. Gastrointestinal symptoms included bloating, belching, and abdominal pain as well as frequent nausea, vomiting, and diarrhea. He had generalized pruritus as well as rectal itching. The parents indicated the boy also experienced frequent tinnitus and that he commonly put his fingers in his ears. Along with recurrent upper respiratory tract infections and congestion, he had difficulty sleeping and often experienced nightmares. Psychiatric symptoms included a frequently depressed mood, disproportionate anger, and emotional lability. There was no obvious history of toxicant exposure at home, but he had been intermittently cared for in a daycare from age 30 months onward. The boy had received all of his vaccinations—but the parents did not correlate any change in demeanor, symptoms, or behavior prior to or after immunizations.

On exploring his history, the child was born at-term weighing 4230 g with an Apgar score of 8 at 1 minute and 9 at 5 minutes after an uneventful pregnancy and delivery. No concerns were evident in the neonatal period. Development in the first 18 months of life appeared fine

according to the parents—his motor skills seemed to progress normally and he achieved expected milestones. After 2 years of age, however, his language skills slowly began to regress and he developed frequent echolalia. He also demonstrated a change in temperament as he started to whine repeatedly and to scream without provocation. He became an increasingly picky eater and would reject food on the basis of taste, smell, or appearance. Not infrequently, the boy experienced loose stools but there was no obvious abdominal pain prior to age 3. There was no history of seizures, major illness, or trauma.

Physical examination revealed a slim boy who was uncommunicative, restless, and somewhat agitated. General examination was unremarkable other than dark rings around the eyes. There were no dysmorphic features evident. He had difficulty maintaining eye contact, and he appeared disinterested in what was taking place. No abnormality was found on abdominal assessment.

Nutritional biochemistry assessment was undertaken as well as screening for selected toxicants. Investigations revealed inadequate levels of fat-soluble vitamins, including notable deficiencies of vitamins A, D, and E as well as low coenzyme Q10 and folate. Plasma levels of ω-3 fatty acids including α-linolenic acid and docosahexanoic acid were also very low. In addition, polyunsaturated ω-6 fatty acids including linoleic acid and γ-linolenic acid were noted to be markedly deficient. These findings along with low saturated fat status (despite regular consumption of saturated fats in his diet) were suggestive of difficulty with fat absorption. Amino acid status and mineral status were unremarkable other than a low zinc level. Given the evidence for fat malabsorption, testing for antiendomysial antibodies and antitissue transglutaminase antibodies was done to explore a potential cause for the disordered nutritional profile. Antiendomysial antibodies levels were 3+ and antitissue transglutaminase antibodies levels were 1835 U (normal < 4). Antinuclear antibody and antithyroid peroxidase antibody levels were normal. The complete blood count was normal, but ferritin was low. No evidence of accrued toxicants was found in the child.

An assessment of the patient's diet revealed frequent consumption of wheat. Given the positive screen for celiac disease (positive antiendomysial antibodies and extremely high antitissue transglutaminase antibodies), dietary intervention was immediately commenced. All gluten was eliminated from the boy's diet, and a concerted effort to replenish deficient nutrients was undertaken. Fruits and vegetables were juiced to make the nutrients easier to absorb, and fat-soluble vitamins, ω-3 fatty acids (in the form of distilled cod liver oil), ω-6 fatty acids, and folic acid were given as supplements.

Within 1 month, the boy's gastrointestinal symptoms were relieved and his behavior had changed dramatically. The mother excitedly reported that for the first time, her 5-year-old boy became progressively more communicative and told her that he loved her. Within 3 months, his functioning had improved so much that he no longer required an individualized learning program and was able to enter a normal classroom with no aide.

The parents consulted a gastrointestinal specialist to discuss celiac disease, and he suggested there was no longer any evidence of autism. The physician discussed small intestinal biopsy as the means to a definitive diagnosis of celiac disease but indicated that with the serological results and the clinical history, he was satisfied; after discussion, the parents decided not to proceed with a biopsy. He did suggest, however, that they return to the Autism Clinic to have the diagnosis re-evaluated. The family indicated that the assessment at the Autism Clinic had been "intense," and the child was adamant he wanted no part of going back. With the feeling that returning to the clinic would provide no benefit to the child, they decidedly refused to go back. Follow-up biochemical nutritional testing was declined because of expense. The child has continued on the gluten-free diet and has progressed well and remained healthy over the following 2½ years. In discussion with the mother at the time of submitting this paper, she commented "he is doing incredibly well and is so very happy."

Literature Review and Discussion

Autism is usually a lifelong diagnosis where most afflicted individuals fail to reach normal functioning—about 85% of patients maintain unfavorable outcomes.[20] Moreover, although extensive educational interventions have been helpful to achieve some measure of daily functioning,[21] there is currently no cure or approved therapy for the disorder.[22] Adequate guidelines for identifying the illness have been delineated,[23] but the etiology of the condition remains unclear in most cases. Because autistic spectrum disorder is a syndromic diagnosis based on a constellation of neuropsychiatric signs and symptoms, there may be different paths leading to behavioral manifestations that meet the criteria for this condition. This case study indicates that a vigorous search for etiology and biochemical dysregulation may prove rewarding in some children with autism.

There has been discussion in the literature as to whether gluten- and casein-restricted diets can improve symptoms in children with autism.[24] Proponents of the idea that gluten and casein are triggers for neurodevelopmental dysfunction have advanced various theories as to the proposed pathophysiologic mechanisms by which these incitants may provoke central nervous system illness. The opiate hypothesis suggests that both gluten and casein are broken down to form metabolites with opiate agonist properties, which leak from the gut and pass into the central nervous system where they disrupt opioid

activity in the brain.[25] A second proposed mechanism suggests that gluten and casein can trigger inflammation in the gut leading to autoimmune illness or cross-reactivity with other potential central nervous system antigens.[26] Another consideration is that gut inflammation in celiac patients can precipitate underlying malabsorption of essential nutrients required for normal central nervous system function.

For patients with celiac disease, impaired breakdown of foodstuffs and digestion may result from inflammation in the upper intestinal tract, altered pH in the gut, as well as a disturbed digestive enzyme milieu required for proper food breakdown. Inflammation in the upper intestine may also induce dysregulation of absorptive processes and impair normal uptake of specific nutrients in the gut—potentially leading to nutritional insufficiency. As a consequence, nutrient inadequacy may lead to deficient essential substrate required for normal central nervous system functioning. Disordered brain biochemistry and physiology may in turn manifest in signs and symptoms of a pervasive developmental disorder such as autism. The gluten elimination diet may allow for cessation of inflammation, improved digestion and absorption, and the uptake of required nutrients for proper brain physiology. Just as vitamin C deficiency can result in scurvy, thiamine insufficiency can cause beriberi, and vitamin D inadequacy can lead to rickets, deficiency of certain essential nutrients can result in brain malfunction, potentially manifesting as a developmental disorder.

This is not the first case report of an association between autism and celiac; cases have been reported as early as 1971.[27] In a case-control study, no autism was found in 120 patients with celiac disease, and no celiac disease was found in 11 patients with autism.[28] These findings, however, could be related to the small sample size of the study. Looking retrospectively at a larger population (N = 150) of randomly selected patients with pervasive developmental disorders, Barcia and colleagues[29] recently found an increased incidence of intestinal biopsy-confirmed celiac disease in their patients with pervasive developmental disorders (3.3%) compared to the normal population (0.9%). These patients underwent a gluten-free diet for 6 months and had relief of their gastrointestinal symptoms but not of their behavioral symptoms (possibly because nutrient status was not assessed and corrected along with the restriction diet). The authors of this recent study recommend screening for celiac disease in all children with autism, even if no gastrointestinal symptoms are present. This is in contrast to a recent review, which suggested that only children with autism and symptomatic gastrointestinal complaints should be screened.[30] In summary, the literature to date suggests a possible association between autism and celiac in a subgroup of patients. The case history in this article is the first explicit report in the literature (to the authors' knowledge) of resolution of both gastrointestinal and neuropsychiatric symptomatology by identifying underlying celiac disease in a child diagnosed with autism, followed by a gluten-restricted diet and correction of specific nutritional deficiencies.

There have been other cases of children with autism reported in the literature who have significantly improved using nutritional interventions such as folate,[31] ω-3 fatty acids,[32] cod liver oil,[33] and coenzyme Q10.[34] Patel and Curtis[35] report on the use of nutritional therapy along with the combination of environmental trigger avoidance, detoxification of heavy metals, and behavioral therapy to treat autism and attention-deficit hyperactivity disorder (ADHD). Although the sample size in the study was small (n = 10), they report enormous success and call for more study. All 10 children showed significant improvement in many areas of social interaction, concentration, writing, language, and behavior.[35] The authors of this pilot research also reviewed other findings related to nutritional and environmental factors at play in autism and ADHD.[36] Notably, they allege that nutritional deficiencies are commonly found in children with autism, including fat-soluble vitamins A, D, E as well as ω-3 fatty acids —just as was found in the case history presented in this article. In addition, iodine deficiency and other environmental causes of hypothyroxinemia have also been postulated as a cause of autism.[37] It is acknowledged, however, that in the case report presented in this article, that (*a*) the specific etiological pathway to illness and subsequent improvement remains undetermined, and (*b*) if nutritional deficiency is a major etiological determinant, it also remains unclear which specific deficiency or deficiencies led to the problem and which interventions led to resolution of disease.

Based on preliminary observation, some have advocated for the use of certain dietary measures in all patients with autism. A recent review exploring the role of gluten and casein elimination diets found, however, that most reported research had significant limitations in study design.[24] In 1 single-blind clinical trial, nonetheless, matched pairs of patients with autism were randomly assigned to a gluten- and casein-free diet or no diet; the diet group showed significantly greater improvement than the control group in many areas of autistic spectrum disorder-specific impairments.[38] The authors of that report recommended that further double-blind, placebo-controlled trials be completed to determine benefit of elimination diets in children with autistic spectrum disorder.

Concluding Thoughts

The brain is a biological organ that requires complex interaction of numerous biochemical nutrients to carry out physiological processes. Emerging evidence confirms that deficiency of assorted nutrients such as folate,[39] vitamin D,[40] or essential fatty acids[41] may impair various

biological processes required for normal metabolic and neurological functioning. Just like digestion and respiration, moods and thoughts have biochemical substrates[42]; deficiency of nutrients required to carry out biological functions in the brain may result in neuropsychiatric syndromes like autism, characterized by disordered moods, thoughts, and behaviors.

The medical profession, however, has sometimes remained lethargic in accepting dietary compromise or nutritional deficiency as a major determinant of health status. Furthermore, nutritional assessment and nutrient interventions are sometimes considered to be outside the mainstream of conventional medicine.[43] With abundant evidence in the literature that nutrients are fundamental building blocks of individual biochemistry and that deficient nutrition is a well-recognized common cause of illness, this attitude needs to be revisited. As the pathway to neuropsychiatric dysfunction may be multifactorial, however, it is not being suggested that all cases of autism are related to nutritional compromise. In each clinical case, it is important to assess nutritional status to rule out biochemical nutrient deficiency as a potential source of brain malfunction.

There has been much recent press regarding the alleged success of assorted complementary and alternative medicine therapies including myriad supplements and assorted other interventions in the treatment of autistic spectrum disorder. As a result, many desperate families having children with autism pursue these types of therapies in an effort to ameliorate the neuropsychiatric condition.[44] A "shot-gun" approach to treatment by trying successive supplements or assorted unproven remedies without identifying the nutritional status of the individual is not optimal: it does not target specific biochemical deficiencies and can fail to identify or address etiologic abnormalities potentially responsible for the central nervous system dysfunction. A scientific biochemical approach to laboratory nutrient assessment is in order.[45]

Based on emerging information that micronutrient deficiency may be a determinant of central nervous system dysfunction, 3 recommendations are presented for consideration:

1. All children with developmental, behavioral, and inexplicable central nervous system disorders should be routinely screened for celiac disease.
2. Considering the escalating public health problem with pervasive developmental disorders, further study into the correlation between micronutrient deficiency and neuropsychiatric problems is in the public interest and should be undertaken.
3. Recognizing that neuropsychiatric dysfunction exacts an enormous cost both financially and personally, micronutrient screening is recommended for all children with significant central nervous system dysfunction. Such screening should include plasma amino acid status, serum screen for coenzyme Q10 and fat-soluble vitamins, red blood cell mineral status, serum folate, plasma fatty acid profile, and urine organic acids to assess functionality of nutrient physiology.[43]

Autism is a devastating neuropsychiatric disorder, which appears to have rapidly increased in incidence over the past two decades. With a current incidence of 1 in 150, this chronic disorder has become a serious public health challenge. Extensive research continues to explore potential determinants of this illness as well as reasons to account for the epidemiological rise of pervasive developmental disorders. It is possible that some of the response to gluten-free diets found in gluten-elimination studies can be related to attenuation of nutritional compromise initially resulting from malabsorptive difficulties as a consequence of undiagnosed sensitivity to gluten. The investigative and management approach in this case is presented not as a solution to all autistic patients' impairments but to raise awareness that nutritional status could play a central role in central nervous system function. It is relevant to investigate for nutritional deficiencies in children with autism and preferable to treat according to deficiencies, rather than to blindly prescribe diets and supplements to a broad population base which, despite sharing a common diagnosis of autism, do not share the same etiologic factors. As emerging research regarding determinants related to autism continues to unfold, a comprehensive scientific etiologic assessment including environmental and nutritional factors could be useful in each child presenting with central nervous system dysfunction including autism.

References

1. Kanner L. Autistic disturbances of affective contact. *Nerv Child*. 1943;2:217-250.
2. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR: 4th ed., Text Revision Edition*. Washington, DC: American Psychiatric Association; 2000.
3. Baird G, Simonoff E, Pickles A, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet*. 2006;368(9531):210-215.
4. Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. *JAMA*. 2003;289(1):49-55.
5. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—autism and developmental disabilities monitoring network, 14 sites, United States, 2002. *MMWR Surveill Summ*. 2007; 56(1):12-28.
6. Geier MR, Geier DA. Thimerosal in childhood vaccines, neurodevelopment disorders, and heart disease in the United States. *J Am Phys Surg*. 2003;8(1):6-11.
7. Fombonne E. The prevalence of autism. *JAMA*. 2003; 289(1):87-89.

8. Fombonne E. Epidemiology of autistic disorder and other pervasive developmental disorders. *J Clin Psychiatry*. 2005;66 (suppl 10):3-8.
9. Newschaffer CJ, Croen LA, Daniels J, et al. The epidemiology of autism spectrum disorders. *Annu Rev Public Health*. 2007; 28:235-258.
10. Hertz-Picciotto I, Delwiche L. The rise in autism and the role of age at diagnosis. *Epidemiology*. 2009;20(1):84-91.
11. Hertz-Picciotto I, Croen LA, Hansen R, Jones CR, van de Water J, Pessah IN. The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism. *Environ Health Perspect*. 2006;114(7):1119-1125.
12. Rostom A, Dube C, Cranney A, et al. The diagnostic accuracy of serologic tests for celiac disease: a systematic review. *Gastroenterology*. 2005;128(4 suppl 1):S38-S46.
13. Cooke WT, Smith WT. Neurological disorders associated with adult coeliac disease. *Brain*. 1966;89(4):683-722.
14. Bushara KO. Neurologic presentation of celiac disease. *Gastroenterology*. 2005;128((4 suppl 1):S92-S97.
15. Luostarinen L, Pirttila T, Collin P. Coeliac disease presenting with neurological disorders. *Eur Neurol*. 1999;42(3):132-135.
16. De Santis A, Addolorato G, Romito A, et al. Schizophrenic symptoms and SPECT abnormalities in a coeliac patient: regression after a gluten-free diet. *J Intern Med*. 1997;242(5):421-423.
17. Wetherby AM, Allen L, Cleary J, Kublin K, Goldstein H. Validity and reliability of the communication and symbolic behavior scales developmental profile with very young children. *J Speech Lang Hear Res*. 2002;45(6):1202-1218.
18. Bayley N. *Bayley Scale of Infant Development: Manual*. San Antonio, TX: The Psychological Corporation; 1993.
19. Papanikolaou K, Paliokosta E, Houliaras G, et al. Using the autism diagnostic interview-revised and the autism diagnostic observation schedule-generic for the diagnosis of autism spectrum disorders in a greek sample with a wide range of intellectual abilities. *J Autism Dev Disord*. 2009;39(3):414-420.
20. Seltzer MM, Shattuck P, Abbeduto L, Greenberg JS. Trajectory of development in adolescents and adults with autism. *Ment Retard Dev Disabil Res Rev*. 2004;10(4):234-247.
21. Myers SM, Johnson CP. Management of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1162-1182.
22. Broadstock M, Doughty C, Eggleston M. Systematic review of the effectiveness of pharmacological treatments for adolescents and adults with autism spectrum disorder. *Autism*. 2007; 11(4):335-348.
23. Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1183-1215.
24. Christison GW, Ivany K. Elimination diets in autism spectrum disorders: any wheat amidst the chaff? *J Dev Behav Pediatr*. 2006;27(2 suppl):S162-S171.
25. Shattock P, Whiteley P. Biochemical aspects in autism spectrum disorders: updating the opioid-excess theory and presenting new opportunities for biomedical intervention. *Expert Opin Ther Targets*. 2002;6(2):175-183.
26. Vojdani A, O'Bryan T, Green JA, et al. Immune response to dietary proteins, gliadin and cerebellar peptides in children with autism. *Nutr Neurosci*. 2004;7(3):151-161.
27. Goodwin MS, Cowen MA, Goodwin TC. Malabsorption and cerebral dysfunction: a multivariate and comparative study of autistic children. *J Autism Child Schizophr*. 1971;1(1):48-62.
28. Pavone L, Fiumara A, Bottaro G, Mazzone D, Coleman M. Autism and celiac disease: failure to validate the hypothesis that a link might exist. *Biol Psychiatry*. 1997;42(1):72-75.
29. Barcia G, Posar A, Santucci M, Parmeggiani A. Autism and coeliac disease. *J Autism Dev Disord*. 2008;38(2):407-408.
30. Erickson CA, Stigler KA, Corkins MR, Posey DJ, Fitzgerald JF, McDougle CJ. Gastrointestinal factors in autistic disorder: a critical review. *J Autism Dev Disord*. 2005;35(6):713-727.
31. Rimland B. Controversies in the treatment of autistic children: vitamin and drug therapy. *J Child Neurol*. 1988;3(suppl):S68-S72.
32. Amminger GP, Berger GE, Schafer MR, Klier C, Friedrich MH, Feucht M. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. *Biol Psychiatry*. 2007;61(4):551-553.
33. Megson MN. Is autism a G-alpha protein defect reversible with natural vitamin A? *Med Hypotheses*. 2000;54(6):979-983.
34. Kidd PM. Autism, an extreme challenge to integrative medicine. Part 2: medical management. *Altern Med Rev*. 2002;7(6): 472-499.
35. Patel K, Curtis LT. A comprehensive approach to treating autism and attention-deficit hyperactivity disorder: a prepilot study. *J Altern Complement Med*. 2007;13(10):1091-1097.
36. Curtis LT, Patel K. Nutritional and environmental approaches to preventing and treating autism and attention deficit hyperactivity disorder (ADHD): a review. *J Altern Complement Med*. 2008;14(1):79-85.
37. Roman GC. Autism: transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. *J Neurol Sci*. 2007;262(1-2):15-26.
38. Knivsberg AM, Reichelt KL, Hoien T, Nodland M. A randomised, controlled study of dietary intervention in autistic syndromes. *Nutr Neurosci*. 2002;5(4):251-261.
39. Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: clinical applications. *JAMA*. 2002; 287(23): 3127-3129.
40. Genuis SJ, Schwalfenberg GK, Hiltz MN, Vaselenak SA. Vitamin D status of clinical practice populations at higher latitudes: analysis and applications. *Int J Environ Res Public Health*. 2009;6(1):151-173.
41. Genuis SJ, Schwalfenberg G. Time for an oil check: the role of essential omega 3 fatty acids in maternal and pediatric health. *J Perinatol*. 2006;26(6):359-365.
42. Genuis SJ. Toxic causes of mental illness are overlooked. *Neurotoxicology*. 2008;29(6):1147-1149.
43. Lo C. Integrating nutrition as a theme throughout the medical school curriculum. *Am J Clin Nutr*. 2000;72(3 suppl):882S-889S.
44. Wong HH, Smith RG. Patterns of complementary and alternative medical therapy use in children diagnosed with autism spectrum disorders. *J Autism Dev Disord*. 2006;36(7):901-909.
45. Bralley JA, Lord RS. *Laboratory Evaluations in Molecular Medicine: Nutrients, Toxicants, and Cell Regulators*. Norcross, GA: The Institute for Advances in Molecular Medicine; 2005.