

Gluten- and Casein-Free Diet as an Intervention for Autism Spectrum Disorders: a Review

Dieta Isenta em Glúten e Caseína Como Terapêutica para Desordens do Espectro Autista: Artigo de Revisão

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ABSTRACT

The hypothesis that the symptoms of autism spectrum disorders can be affected by excluding foods containing gluten and casein has generated considerable interest among researchers. A review of the literature describing the results of gluten- and casein-free diet as a therapeutic intervention was performed. Based on an analysis of PubMed® citations using the search terms ["casein" OR "gluten" AND "autism"], 64 articles were listed, 7 of which met our inclusion criteria. All, but one, of the papers supported a positive effect for a gluten- and casein-free diet for cases of autism, where symptoms were duly mitigated. Only a few studies have experimentally assessed the potential effectiveness of a gluten- and casein-free diet for cases of autism and the existing studies are based on small sample sizes and on short term treatment duration. Further controlled studies are required to clarify the role of a gluten- and casein-free diet for cases of autism spectrum disorders.

KEYWORDS: Autism; Gluten- and casein-free diet

RESUMO

A hipótese de que as doenças do espectro autista podem ser afectadas pela exclusão de alimentos que contenham glúten e caseína tem gerado considerável interesse entre os pesquisadores. Neste sentido foi realizada uma revisão da literatura que descreve os resultados da utilização de uma dieta isenta em glúten e caseína como terapêutica. Com base nos resultados da pesquisa na PubMed®, utilizando os termos de busca ["caseína" OU "glúten" E "autismo"], 64 artigos foram identificados, dos quais 7 preencheram os critérios de inclusão. Todos, excepto um dos estudos, suportaram o efeito positivo da utilização desta intervenção na atenuação dos sintomas associados ao autismo. Apenas alguns estudos constataram experimentalmente a eficácia da dieta isenta de glúten e caseína e mesmo esses estudos baseiam-se em amostras de pequenas dimensões, bem como em curtos períodos de intervenção. Assim, a realização de mais estudos é necessária para esclarecer o papel da dieta isenta de glúten e caseína como terapêutica para casos de doenças do espectro autista.

PALAVRAS-CHAVE: Autismo; Dieta isenta de glúten e caseína

INTRODUCTION

Autism Spectrum Disorders

Autism spectrum disorders (ASD) is the most commonly studied spectrum of developmental disorders believed to have a neurobiological etiology (1). There is growing evidence that autism is a complex multifactorial disorder involving the brain and the body, as a result of the interaction between genetic vulnerabilities and environmental factors, such as heavy metals and pesticides (2). According to the American centers for Disease Control, studies in Asia, Europe and North America have identified individuals with an ASD with an approximate prevalence of 0.6% to over 1%. Based on the Autism and Developmental Disabilities Monitoring Network, the United States Department of Health and Human Services estimated the prevalence of ASD as steadily growing over the past years (3). In 2008, approximately one in 54 boys and one in 252 girls living in the Autism and Developmental Disabilities Monitoring Network communities were identified as having ASD. Comparison of 2008 findings with those for earlier surveillance years indicated an increase in estimated ASD prevalence of 23% when the 2008 data were compared with the data for 2006 and an estimated increase of 78% when the 2008 data were compared with the data for 2002. Because the Autism and Developmental

Disabilities Monitoring Network sites do not make up a nationally representative sample, these combined prevalence estimates should not be generalized to the US as a whole (4). Currently there are several types of psychological interventions and therapies to assist in the relief and improvement of ASD symptoms. These strategies primarily aim to help participants to be as independent as possible in all areas of their daily life. Therapeutics for children with ASD aim to provide an improvement of their skills, making them more socially skilled to adapt to the environment, promoting a more structured support to orientation, assimilation and accommodation of the information, enabling a growing social inclusion. Therapies need to be maintained throughout life and should be structured according to the patient's stage of life. One of the most popular nutritional therapies used is the gluten- and casein-free diet, regarding the behavior changes in children with ASD that practice this diet. One of the reasons why this diet is unattractive is because it is a very strict diet that excludes all foods containing gluten, such as all derived from wheat, rye, barley and oats, as well as food containing casein (5).

Central Effects of Autism

Autism is a serious developmental disorder

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characterized by a restricted, repetitive and stereotyped pattern of behavior; interests and activities are a core part of symptom presentation. The diagnosis of autism is usually conferred when the child is 2 to 3 years old, after extensive evaluation according to the criteria of the Diagnostic Statistical Manual IV. The children either exhibits a failure to advance from birth or, after a period of apparently normal growth, suffer a loss of newly acquired skills (6). Suffering of ASD also places a person at elevated risk for various comorbidities such as eczema, allergies, asthma, ear and respiratory infections, severe headaches, migraines, seizures and gastrointestinal problems, including abdominal pain, constipation or diarrhea and bloating (7).

Intestinal Effects of Autism

Some authors reported that ASD symptoms may be improved with a gluten and casein free-diet because the autistic child's digestive tract works sub-optimally (8, 9). According to this theory, gliadomorphins and casomorphins (exorphins released from the partial luminal digestion of dietary gliadin and casein, respectively) are absorbed through a leaky gut, enter into the central nervous system and interfere with normal brain function (10, 11). During digestion, opiate type compounds from gluten and casein in the diet are activated because of an incomplete breakdown of proteins. These exorphins are then absorbed into the circulation where they exert an opioid-type action on the brain (8, 9). They can directly regulate transmission in all the main neurotransmission systems or, alternatively, form peptidase enzyme ligands inhibiting the hydrolysis of natural opioid peptides (9). The peptides' transport across the gut epithelium lumen is thought to occur due to its 'leaky' nature in autistic individuals (12). Tight junction proteins associated with a series of peripheral junctional proteins form the predominant barrier within the paracellular pathway, performing important gate and fence functions. The intestinal hyperpermeability can essentially be translated into a two-fold consequence: on the one hand, the presence of biologically active peptide species derived from dietary proteins, and on the other the presence of an abnormally permeable gut, will result in the transport of biologically active peptides and other compounds across the gastrointestinal tract and/or blood-brain-barrier to exert an effect in ASD (13). Recent research indicates that there is a pathological inflammation of the intestinal mucosa in autism, that could explain the gut hyperpermeability observed, although there is no evidence to support the statement that gluten or casein may cause the inflammation (14-17). Moreover recent evidence indicates that immune dysfunction and neuro-inflammation could also explain the alteration of blood-brain-barrier integrity. Brain mast cell activation due to allergic, environmental and/or stress triggers could lead to focal disruption of the blood-brain barrier and neuro-inflammation, thus contributing to the development of autistic symptoms (18).

Gluten- and Casein-Free Diet

Gut hyperpermeability has been reported in approximately a quarter to a third of children with ASD, and there are indications of a reduction of gastrointestinal permeability in those cases where a gluten- and casein-free diet has been implemented (19).

De Magistris et al. observed a high percentage of abnormal intestinal permeability values among patients with autism (36.7%) and their relatives (21.2%) compared with normal subjects (4.8%). They also showed that patients with autism practicing a gluten- and casein-free diet had significantly lower intestinal permeability values compared with those who were on an unrestricted diet (20). In addition to the relationship with autism, increased intestinal permeability is also a symptom of other pathologies, such as Crohn's disease, celiac disease, food allergy, acute pancreatitis, non-alcoholic fatty liver disease and alcoholic liver (21).

The intestinal permeability question is contradictory, being supported by the abovementioned De Magistris et al. (20) study as well as by D' Eufemia et al. (22) study's, where 43% of the children with ASD without evident gastrointestinal symptoms had increased intestinal permeability as compared with all of the 40 controls, but refuted by Robertson et al. (23), who developed a controlled pilot study and did not detect differences in the intestinal permeability measurement.

In order to summarize the studies that describe the implementation of this therapy in autistic patients we conducted a systematic review. Studies used in this systematic review were identified from Pubmed® database. Combination of Medical subject headings (MeSH) terms used was ["casein" OR "gluten") AND "autism"]. For the purpose of this analysis, inclusion criteria were studies in which children with ASD were the target population and that focused on the gluten- and casein-free diet. Studies published in other languages than English, French, Portuguese and Spanish were excluded. If an author was included in more than one selected paper and the sample was the same, the most recent paper was selected, and earlier versions were rejected. Though this search retrieved 64 articles we only selected 7 for analysis. Selected papers were published between 2002 and 2013 and participants' ages ranged from 2 to 16 years. Selected papers were analyzed. Data was systematized in (a) Author; Year, (b) Country, (c) Type of study, (d) n, (e) Interventions, (f) Main results and (g) Main limitations (Table 1).

CRITICAL ANALYSIS

Six of the seven studies selected indicate positive results from the application of this diet, particularly in what concerns the development of cognitive skills and improvement of gastrointestinal symptoms. The same number of studies pointed out small sample size, and three are based on parental reports, which could be considered limitations for the studies, however the inclusion of case reports due to the existence of a few studies. In addition, two of the seven studies use additional therapies that could also be considered

as confounding factors when interpreting the results.

All studies selected described the application of a gluten- and casein-free diet and the comparison of the ASD related symptoms before and after application of the diet. As stated above, the majority of them found positive results and are quite different with regard to the geographical location, which demonstrates the broad spectrum of interest in the subject (8, 24-29).

Some articles (8, 25, 26) did not refer the method used to assess adherence and compliance to the diet, so it becomes difficult to evaluate the veracity of the facts, since in some cases eating disorder symptoms can occur in these children, such as stealing food, which is justified because these children do not understand why they cannot eat everything.

Regarding the safety of this diet, Cornish concludes that children with ASD on a gluten- and casein-free diet are receiving approximately the same nutritional value as children with autism without elimination diets (30). However, given the frequency of the disease, it is difficult to gather an appropriate sample size and homogeneous in nature, to measure the real impact of diet on growth and development of children.

Researchers are unanimous in agreeing that a greater insight into the underlying biological mechanisms is needed, namely because the positive effects may happen only in subgroups of autistic patients. Furthermore, only few studies have experimentally assessed the potential effectiveness of a gluten- and casein-free diet for cases of autism and the existing studies are based on small sample sizes and on short term intervention duration.

In addition, the food alternatives are increasingly available, particularly as a result of pressure from associations of celiac patients, but are significantly more expensive (in the case of gluten-free products), however this disadvantage can be minimized by giving preference to the consumption of natural or home-made food. At least in some cases, nutritional supplementation could be indispensable (31, 32).

Certainly, these interventions must be oriented by multidisciplinary teams, including nutritionists, which need to be prepared to discuss the pros and cons of the gluten- and casein-free diet with parents and to monitor the compliance to diet.

CONCLUSIONS

The growing interest in the ASD, as well as the current evidence, encourages the development of studies, eventually multicenter studies seeking the sample size optimization that clarifies the role of this diet in improving the symptoms of ASD. Further controlled studies are required to clarify the role of a gluten- and casein-free diet for cases of ASD.

TABLE 1: Summary results of the studies selected describing the implementation of a gluten and casein free diet as therapy in autistic patients. Consider (a) Author; Year, (b) Country, (c) Type of study, (d) n, (e) Interventions, (f) Main results and (g) Main limitations

Auhor; Year	Country	Type of study	N	Intervention	Main results	Main limitations
Hsu C.L. et al. 2009	Taiwan	Case report	1 child with ASD	GFCF diet for 11 month	Objective measurements revealed relative increment in developmental age levels. In addition, improved nutrition status based on improvement in gastrointestinal symptoms resulted in noticeable advances in growth development. The therapy may be more feasible in Taiwan because of cultural factors such as dietary preference and product availability.	A double-blind behavioral report from other observers before and after intervention was not initiated. Biochemical studies such as concentration of gluten/casein derivatives in the blood and urine were not obtained. Prospective studies with larger sample size are needed.
Whiteley P. et al. 2010	Denmark	Randomized, controlled, single blind study	72 children with ASD	GFCF diet for 12 months	Dietary intervention may positively affect developmental outcome for some children diagnosed with ASD. Additional investigations are required including appropriate clinical and dietetic support during dietary changes.	Reduced participant sample for the second phase (first stage during 12 months and second stage during 24 months) of the study. The lack of a placebo condition group for comparison.
Elder, J.H. et al. 2007	USA	Double-blind, controlled trial	15 children with ASD	GFCF diet for 12 weeks	The number of verbal responses, in order to evaluate the number of different words and total utterances produced was not statistically significant between intervention and control group.	Small sample size and a large heterogeneity among participants. Secondary analysis of pre-existing data. Short duration of the dietary intervention.
Knivsberg, A. M. et al.; 2002	Norway	Trial	20 children with ASD	GFCF diet for 12 months	Pre-post-test showed improvements in the DIPAB of the intervention group better than the controls, and significant changes in the other standardized assessments.	Losses during the intervention. Bad night's sleep and uncontrollable influences.
Pennesi, C.; Klein, L. 2012	USA	Parental report	387 children with ASD	GFCF diet for 5 months	The GFCF dietary intervention may positively affect some children diagnosed with ASD; however, the subsets of children which could potentially benefit from the dietary intervention remain undetermined.	Children with ASD use various other therapies in conjunction with the GFCF diet. These additional therapies must be considered as confounders.
Harris, C.; Card, B. 2012	USA	Cross-sectional study	13 children with ASD	An online survey to collect data on general health, demographics, gastrointestinal symptoms and behavior patterns, and a food frequency questionnaire. Gastrointestinal symptoms were evaluated using the GSRS, and behavior patterns were evaluated using the CARS.	GSRS and CARS scores did not differ significantly according to diet but parents of all the children on a GFCF diet reported improved GI symptoms and behavior patterns. The compliance with a GFCF diet must be a concern among studies that aim to explore the relationship between diet and ASD outcomes.	Small sample size, the subjective nature of the questionnaires, and the uncertainty of parents to accurately quantify the severity of their children's symptoms.
Herbert, M.; Buckley, J. 2013	USA	Case report	1 child with ASD	GFCF diet for 7 years	Marked improvement in autistic and medical symptoms; decreasing of the CARS score from 49 to 17. It is also suggested that addition of medium-chain triglycerides to a healthy gluten-free casein-free diet may significantly improve symptoms of a ASD.	Small sample size. From 5 to 6 years old, multivitamin supplementation was prescribed. Drugs were prescribed to control inflammatory bowel disease and to reduce anxiety. These therapies should be considered as confounders.

ASD – autism spectrum disorders; CARS – Childhood Autism Rating Scale; DIPAB – Diagnosis of Psychotic Behavior in Children; GFCF – gluten-free and casein-free; GSRS - Gastrointestinal Symptoms Rating Scale

REFERENCES

- Iwata K, Matsuzaki H, Miyachi T, et al. Investigation of the serum levels of anterior pituitary hormones in male children with autism. *Molecular Autism* 2011; 19:2-16.
- Srinivasan P. A review of dietary interventions in autism. *Annals of Clinical Psychiatry* 2009; 21(4):237-47.
- Centers for disease control and prevention. Summary of Autism/ ASD Prevalence Studies. Available at: <http://www.cdc.gov/ncbddd/autism/data.html>. Accessed February 25, 2014.
- Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators; Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report Surveillance Summaries*. 2012; 61(3):1-19.
- Reynolds K. Autism spectrum disorders in childhood: a clinical update. *Community Practitioner: the journal of the Community Practitioners' & Health Visitors'* 2011; 84(7):36-8, 6 Reichelt KL, Knivsberg A. The possibility and probability of gut-to-brain connection in autism. *Annals of Clinical Psychiatry* 2009; 21(4):205-211.
- Compert P, Laake D. *The Kid-Friendly ADHD & Autism Cookbook – The Ultimate Guide to the Gluten-free, Casein-free diet*. Beverly: Fair Winds 2009; 17-25.
- Kohane IS, McMurry A, Weber G, et al. The Co-Morbidity Burden of Children and Young Adults with Autism Spectrum Disorders. *PLoS ONE* 2012; 7(4): e33224.
- Hsu C, Lyn C, Chen C. The Effects of a Gluten and Casein-free Diet in Children with Autism: A Case Report. *Chang Gung medical journal* 2009; 32(4):459-65.
- Shattock P, Whiteley P. Biochemical aspects in autism spectrum disorders: updating the opioid-excess theory and presenting new opportunities for biomedical intervention.

- Expert opinion on therapeutic targets 2002; 6(2):175-83.
10. Reichelt KL, Ekrein J, Scott H. Gluten, milk proteins and autism: dietary intervention effects on behavior and peptide secretion. *Journal of Applied Nutrition* 1990; 42:1-11.
11. Zioudrou C, Streaty RA, Klee WA. Opioid peptides derived from food proteins. The exorphins. *Journal of Biological Chemistry* 1979; 254:2446-49 in White J. *Intestinal Pathophysiology in Autism*. *Experimental Biology and Medicine* 2003; 228:639-49.
12. Elder J. The gluten-free, casein-free diet in autism: an overview with clinical implications. *Nutrition in clinical practice* 2009; 23(6):583-8.
13. Whiteley P, Shattock P, Carr K, et al. How Could a Gluten- and Casein-Free Diet Ameliorate Symptoms Associated with Autism Spectrum Conditions? *Autism Insights* 2010; 2: 39-53.
14. Wakefield A, Murch S, Anthony A, Linnell J, Casson D, Malik M, Berelowitz M, Dillon A, Thompson M, Harvey P, Valentine A, Davies S, Walker-Smith J. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. 1998; 35: 637-641.
15. Wakefield A, Anthony A, Murch S, Thomson M, Montgomery S, Davies S, O'Leary J, Berelowitz M, Walker-Smith J. Enterocolitis in children with developmental disorders. 2000; *Am J Gastroenterol* 95: 2285-2295.
16. Sabra A, Bellanti J, Colon A. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. 1998; 35: 234-235.
17. Horvath K, Papadimitriou J, Rabsztyan A, Drachenberg C, Tildon J. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr* 1999; 135:559-563.
18. Theoharides T, Zhang B. Neuro-inflammation, blood-brain barrier, seizures and autism. *Journal of Neuroinflammation* 2011; 8:168.
19. Whiteley P, Shattock P, Knivsberg AM, et al. Gluten- and casein-free dietary intervention for autism spectrum conditions. *Frontiers in Human Neuroscience* 2013; 6:344.
20. De Magistris L, Familiari V, Pascotto A, et al. Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. *Journal of pediatric gastroenterology and nutrition* 2010; 51(4):418-24.
21. DeMeo MT, Mutlu EA, Keshavarzian A, Tobin MC. Intestinal permeation and gastrointestinal disease. *Journal of Clinical Gastroenterology* 2002; 34:385-96.
22. D'Eufemia P, Celli M, Finocchiaro R, et al. Abnormal intestinal permeability in children with autism. *Acta Paediatrica* 1996; 85(9):1076-9.
23. Robertson MA, Sigalet DL, Holst JJ, et al. Intestinal permeability and glucagon-like peptide-2 in children with autism: a controlled pilot study. *Journal of Autism and Developmental Disorders* 2003; 38(6):1066-71.
24. Whiteley P, Haracopos D, Knivsberg AM, et al. The ScanBrit randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders. *Nutritional neurosciences* 2010; 13(2):87-100.
25. Elder J, Sankar M, Shuster J. The gluten free, casein-free diet in autism results of a preliminary double blind clinical trial. *Journal of autism and developmental disorders* 2006; 36(3):413-20.
26. Knivsberg A, Reichelt K, Hoien T, et al. A randomised, controlled study of dietary intervention in autistic syndromes. *Nutritional neuroscience* 2002; 5(4):251-61.
27. Pennesi C, Klein L. Effectiveness of the gluten-free, casein-free diet for children diagnosed with autism spectrum disorder: Based on parental report. *Nutritional neuroscience* 2012.
28. Harris C, Card B. A pilot study to evaluate nutritional influences on gastrointestinal symptoms and behavior patterns in children with Autism Spectrum Disorder. *Complementary Therapies in Medicine* 2012; 20:437-40.
29. Herbert M, Buckley J. Autism and Dietary Therapy: Case Report and Review of the Literature. *Journal of Child Neurology* 2013; 00(0):1-8.
30. Cornish E. Gluten and casein free diets in autism: a study of effects on food choice and nutrition. *Journal of human nutrition and dietetics* 2006; 15(4):261.
31. Lerner A. New therapeutic strategies for celiac disease. *Autoimmunity Reviews* 2010; 9(3):144-7.
32. The British Dietetic Association. Gluten and Casein Free Diet for Autism Spectrum Disorder. Food fact Sheet 2012.