

FOOD ALLERGY INVESTIGATIONS AND ITS SIGNIFICANCE IN AUTISM SPECTRUM DISORDERS.**ANANTH N RAO*, MINAKSHI KOCH, SABYASACHI GHOSH AND SURESH KUMAR.V**

Metabolic Diseases and Research, Apollo Hospitals, Bangalore.

Corresponding author* ananthnrao@yahoo.co.in / drananth_n@apollohospitals.comABSTRACT**

Autism is a developmental disorder with sensitivity to dietary and environmental antigens. Children with typical forms of autism to attention deficits frequently have sensitivities to certain foods. A food allergy is an IgE or IgG mediated reaction which shows symptoms within hours of having ingested the food. In the Department of Metabolic Diseases and Research, Apollo Hospital, serum samples of children, clinically diagnosed with Autism Spectrum Disorders (ASD) using DSM IV criteria, were tested for food allergy (IgE) on commonly used foods / food stuffs in a typical Indian cooking or form a part of the diet. We, in this study have attempted to demonstrate that the immediate or IgE mediated food allergy pattern is easily recognizable and anti-gliadin IgG in ASD studies is valuable. Improvement is seen with foods free from allergens recognized on the IgG/ IgE based investigation leading to speculation about a high prevalence of food allergy in ASD children.

KEYWORDS

Food allergy, autism, IgG, IgE, GF/CF diet

INTRODUCTION

A food allergy is an adverse immune response to a food protein^{1, 2}. Food allergy is distinct from other adverse responses to food, such as food intolerance, pharmacologic reactions, and toxin-mediated reactions³. A food allergy is an IgE mediated reaction which leads to symptoms within hours of having ingested the food⁴. The food allergic population may react to as little as 100mg of food, possibly less. The dose causing a reaction and the severity of reaction cannot be predicted⁵. Classic immunoglobulin-E (IgE)-mediated food allergies are classified as type-I immediate hypersensitivity reactions. These allergic

reactions have an acute onset (from seconds to one hour) and may include⁶:

- (1) Angioedema
- (2) Urticaria
- (3) Itching of the mouth, throat, eyes, skin
- (4) Nausea, vomiting, diarrhea, stomach cramps, and/or abdominal pain. This group of symptoms is termed gastrointestinal hypersensitivity or anaphylaxis.
- (5) Rhinorrhea, nasal congestion
- (6) Wheezing, scratchy throat, shortness of breath, or difficulty swallowing

(7) Anaphylaxis: a severe, whole-body allergic reaction that can result in death⁷.

Food intolerance should be one of the suspects when someone is suffering from sleep disorders. It has been suggested that symptoms of tension and jitteriness, common to food-sensitive individuals, are apt to manifest in restlessness and inattentiveness by day and insomnia by night. Insomnia, as well as tossing about or crying out at night, are very frequent manifestations of food intolerance⁸.

Some people may also experience allergy symptoms since conserved plant allergens can cause IgE antibodies to cross react with allergens from plant derived food or other non-food allergens⁷. There is overwhelming scientific evidence for the usefulness of evaluation of food allergy testing in ADHD, autism, and other psychiatric disorders which are not yielding to conventional diagnosis or

therapeutic interventions. The second is that the only reasonable way for this testing to be done is with a laboratory which has a well documented quality control process in place, both proactively – from the ground up – and manifesting in ongoing monitoring and sampling of the results⁹.

A food allergy (IgE reaction) is an immediate immune response that includes symptoms such as a rash, hives, sneezing, or anaphylaxis. Food sensitivity (IgG) is a delayed immune response that includes chronic symptoms in the areas of inflammation/ pain, digestion, and energy/ mood such as headaches, GI inflammation, gut pain, diarrhea, constipation, hyperactivity, or anxiety. Because the reactions are very subtle and delayed for hours, or a day or more, IgG mediated food allergies are very difficult to recognize¹⁰.

Table 1

The key differences between IgE and IgG mediated allergies/ sensitivities are summarized below

IgE-Mediated Allergies	IgG-Mediated Allergies
Immediate onset (within minutes)	Delayed onset (4-72 hours)
Circulating half-life of 1-2 days	Circulating half-life of 21 days
Permanent allergies (life-long)	Temporary allergies
Includes foods, inhalants & moulds and activates complement	Includes foods, herbs & spices

FOOD ALLERGY AND AUTISM

The Autism spectrum disorders are more common in the pediatric population than are some better known disorders such as diabetes, spinal bifida, or Down syndrome. The Centre for Disease Control and Prevention has recently estimated the prevalence of ASDs in the United States at approximately 5.6 per 1000 (1 of 155 to 1 of 160) children¹¹.

In recent years, various studies mostly in the alternative medicine literature have suggested that food allergies play a role in causing or worsening autism. It's been suggested that autism could result from a loss of regulation of

the immune system, causing an increase in inflammatory-causing chemical signals from white blood cells. It is felt that these chemicals (cytokines) may be responsible for the neurological abnormalities seen in children with autism. Recent studies suggest that children with autism may respond to certain foods, particularly gluten- and casein-containing foods, by producing more of these inflammatory cytokines. The cytokines from the autistic children were much higher than those from non-autistic children after being exposed to gluten or casein. This increase may help

predict when an autistic child would benefit from dietary avoidance of these proteins¹²⁻¹⁷.

Some of the health risks which are posed due to intolerance towards gluten are anaemia, asthma, auto-immune conditions (eg. lupus, rheumatoid arthritis, bursitis, Addison's disease, Crohn's disease), back pain, behavioural problems in children, cancer, celiac disease, chronic fatigue, dehydration, depression, dermatitis, diabetes, eczema, failure to thrive (in children), gastro-intestinal distress, hyperthyroidism, infertility, irritable bowel syndrome, learning difficulties, liver disease (eg. Jaundice), low iron, malabsorption problems, malnutrition (from poor absorption of nutrients), migraines, mineral deficiency, miscarriage, mood swings, neurological conditions (eg. multiple sclerosis, motor neuron disease, epilepsy, memory loss), obesity, osteoporosis, overweight, psoriasis, psychological problems, respiratory problems, sinusitis, sperm abnormalities, ulcerative colitis, vasculitis, weight fluctuation. Intolerance towards casein causes anaemia, dehydration, dermatitis, gastro-intestinal distress, irritable bowel syndrome, low iron, malabsorption problems, malnutrition, migraines, mineral deficiency, Osteoporosis, respiratory problems and skin problems⁽¹⁸⁻²⁴⁾.

The 'opioid-excess' theory of autism²⁵ suggests that autism is the consequence of the action of peptides of exogenous origin affecting neurotransmission within the central nervous system (CNS). Peptides, formed through the incomplete breakdown of foods containing gluten (found in cereal produce) and casein (derived from dairy produce), exhibit direct opioid activity or form ligands for the peptidase enzymes which break down endogenous endorphins and enkephalins. The passage of elevated levels of peptides through to the CNS is further aided by gastrointestinal conditions indicative of an abnormally porous intestinal membrane²⁶. The resultant presence of intensified opioids activity disrupts a variety of systems within the CNS.

PATIENT HISTORY

In the Department of Metabolic Diseases and Research, Apollo Hospital, serum samples of 118 children were collected. Of these 57.7% were clinically tested with Autism Spectrum Disorder (ASD), 17.30% for Pervasive Developmental Disorder- Not specified (PDD-NOS) and 25% for Attention Deficit Hyperactivity Disorder (ADHD). Presently, some researchers believe that there is a correlation between ASD and ADHD. It is estimated that ADHD affects approximately 4.5 million children in the US. The main characteristics that define ADHD include inattention, hyperactivity and impulsivity²⁷. In India, while there are no reliable figures available, the number of ADHD cases are said to be mounting.

The Male: Female ratio in this study was found to be 4:1. The prevalence of ASD is about 2 per 1,000 people, with about four times more often in boys (usually the first-born) and occurs around the world in all races and social backgrounds²⁸.

Sleep problems are frequently reported in autism with prevalence estimates of 44-83% for sleep disorders. Amongst this study group 32.82 % were seen to be having sleep related disorders.

Thirty two percent (32 %) children in the study group were seen to be suffering from constipation. Many children on the autism spectrum have a history of recurrent otitis media. Some also have thrush, vaginal yeast infections and other symptoms of systemic yeast related problems²⁹. 8.41% mothers of patients in the study group had a history of Urinary Tract Infection (UTI). Fried foods and non-vegetarian foods have also been identified as common causes of allergies in India³⁰. In our studies 85 children were vegetarians while only 33 of them were non-vegetarians.

MATERIALS AND METHODS

The serum samples were collected within 2 hrs after a meal for the testing of food allergy (IgE). Patient samples to be investigated can

generally be stored at +2 °C to +8 °C. The tests included kit method using EUROLINE Food India (Lot Numbers A080807AB and A090721AB) for antibodies of class IgE against food allergens.

The test kit contains test strips coated with parallel lines of different allergen extracts. If samples are positive, specific antibodies of class IgE bind to the allergens. The test strips include allergens for milk, hen's egg yolk, milk powder, wheat flour, rice, soya bean, peanut, coconut, apple, grape, potato, spinach, onion, cucumber, chicken, mustard, coffee, ginger, crab and prawn.

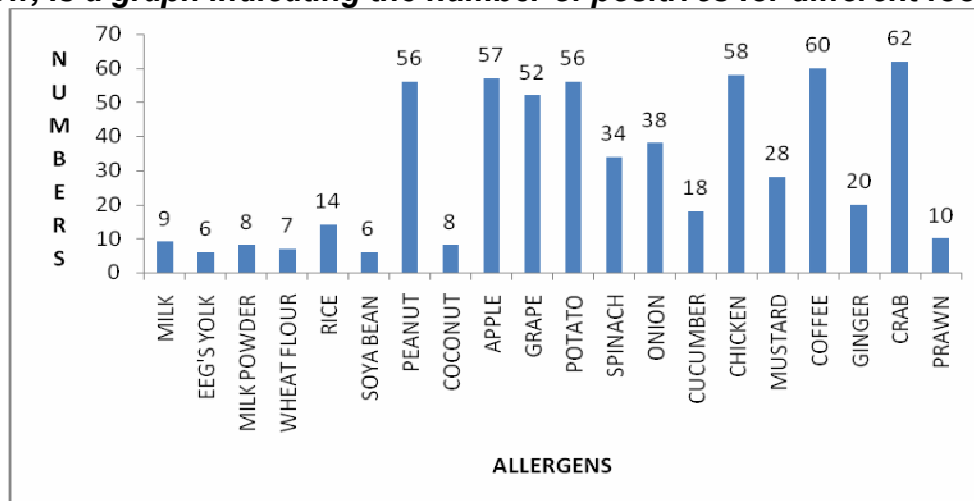
From the same study population, 94 serum samples of patients were tested for IgG.

Patient samples to be investigated can be generally stored between +2°C- +8° C. It is not to be frozen. The tests included kit method using EUROIMMUN Anti-Gliadin (GAF-3X) ELISA (IgG) (Lot no. E090603AX). The ELISA test kit provides a semi quantitative *in vitro* assay for human antibodies of the IgG class against (GAF-3X) in serum or plasma. In the first reaction step, diluted patient samples are incubated in the wells. In the case of positive samples, specific IgG antibodies (also IgA and IgM) will bind to the antigens. To detect the bound antibodies, a second incubation is carried out using an enzyme labeled anti-human IgG (enzyme conjugate) catalyzing a colour reaction.

RESULTS

Graph 1

Given below, is a graph indicating the number of positives for different food allergens.



Graph indicating number of positives for different allergens (n=118).

The graph given above shows that maximum allergy is seen for peanut, potato, apple, grape, onion, chicken, coffee and crab. Coffee allergy was seen in 50.84%. Potato and onion formed 47.45% and 32.20% of the allergens respectively. In fruits apple and grape showed 48.30% and 44.06% allergenicity. Cucumber allergy was seen in 15.24% individuals.

Egg, milk, wheat, peanuts, and buckwheat are the most common food allergens. However, in

our studies egg showed 5.08 %, milk showed 7.62% and wheat flour showed 5.93% incidence. Peanut allergy was seen in 47.45% of the subjects. Chicken and crab allergies arouse in 49.15% and 52.54% study subjects respectively. Prawn allergy was seen in 8.47 % individuals only.

Rice allergy is stated to be commonly seen in the Indian population. However, in our studies rice allergy occurred in only 11.86%.

However, sometimes allergies are also seen due to cross-reactivity between airborne and food allergens. Some examples of cross-

reactivity between airborne and food allergens are as given below:

Table 2

Examples of cross-reactivity between airborne and food allergens ^{(31, 32).}

ALLERGEN	ASSOCIATED FOOD ALLERGY
Grass	Tomato, Potato, Carrot, Celery, Garlic, Onion, Wheat, Rice, Green Pea, Peanut, Apple, Peach, Orange, Watermelon, Melon, Kiwi
Birch	Hazelnut, Walnut, Apple, Pear, Carrot, Celery, Potato, Orange, Kiwi
Mugwort	Celery, Carrot, Spices, Green Bean, Mustard, Hazelnut
Ragweed	Watermelon, Melon, Cucumber, Banana
Plantain	Melon
Latex	Avocado, Potato, Banana, Tomato, Chestnut, Kiwi
House Dust Mite, Cockroach, Chironomid (fish food)	Prawn, Crab, Shellfish, Lobster, Shrimp
Chicken feathers (Pillows, arts and crafts), Feather dust, Chicken droppings, house dust, egg yolk, Oats.	Chicken

For Anti-gliadin IgG assay, only 3.14% tested positive i.e. indicating sensitivity towards gliadin.

DISCUSSION AND CONCLUSION

Recently some authors have suggested that food peptides might be able to determine toxic effects at the level of the central nervous system by interacting with neurotransmitters. In fact a worsening of neurological symptoms has been reported in autistic patients after the consumption of milk and wheat ³³. Apart from behavioral symptoms, certain medical conditions (eg. Gastrointestinal (GI) symptoms) are present in many but not all ASD children. The presence of co-morbidities also affects the behavioral symptoms. Because of the high prevalence of GI symptoms and the apparent clinical improvement by dietary intervention frequently reported by parents, a link between GI abnormalities and the onset and

development of ASD's has been posited. Improvement of behavioral symptoms is most commonly reported with a dairy and wheat free diet (the so-called gluten-free, casein-free [GF / CF] diet, leading to speculation about a high prevalence of food allergy (FA) in ASD children³⁴.

Gluten is a protein common to many cereal grains, including wheat, rye, oats and barley, while casein is the protein product in dairy foods. Dairy foods have been found to be the cause of many related health problems such as eczema, asthma, constipation, diarrhea, and reflux, in addition to the behavior and learning problems³⁵.

When following a GF/CF diet, people commonly over- substitute corn and soy in the place of gluten and casein. Soy and corn are also very common food sensitivities, and removal of these foods, as well, can make a remarkable difference on health, behavior, and attention for certain individuals. Soy is inflammatory to the gut (the digestive tract); it's known to inhibit thyroid function, contains strong estrogen compounds, and decreases absorption of calcium, magnesium, zinc and other minerals. For milk, (depending on the diet and food restrictions) one can use rice milk, potato milk, coconut milk, hemp milk, almond milk, hazelnut milk, and homemade nut/ seed milk blends. For yogurt, there is homemade nut/seed milk yogurt and homemade and commercial coconut yogurt³⁶.

Studies are currently underway to examine the effectiveness of the GF-CF diet, which has not gained widespread acceptance in the U.S. medical community. One recent study found behavioral improvements in kids on a GF-CF diet, while another study found no significant effects from the diet. Though the results of one small trial adds weight to the existing anecdotal evidence for a gluten and/or casein free diet for autism, there is not yet sufficient evidence for clinicians to advise the use of such diets in

cases of autistic spectrum disorder³⁷. Only 3.14 % of the study population showed sensitivity towards gliadin which means that the Indian population might still not consider a GF-CF diet as a major remedy for fighting autism. However, it also means that these studies need to be continued in a larger population.

Constipation is a frequent finding in children with gastrointestinal symptoms and autism³⁸. As constipation and feeding issues/ food selectivity often have a behavioral etiology, data suggest that a neurobehavioral rather than a primary organic gastrointestinal etiology may account for the higher incidence of these gastrointestinal symptoms with autism³⁹.

As sleep disorders are common in both ASD and ADHD further research on clinical characteristics and sleep architecture using well characterized and better-selected patient populations are warranted for both ASD and ADHD. Longitudinal study of sleep disorders and the treatment effects will provide a better understanding of the relationship between sleep disorders and the developmental disorders⁴⁰. Avoidance of food allergens, food chemicals, and chelation therapy may also provide some relief to autism/ ADHD patients⁴¹.

REFERENCES

1. Sampson H. Update on food allergy. *J Allergy Clin Immunol*, 113 (5): 805–819, (2004).
2. Sicherer S, Sampson H. Food allergy. *J Allergy Clin Immunol*, 117 (2), 470–5, (2006).
3. Janeway CA, Travers P, Hunt S, Walport M. Host defense against infection. In: *Immunobiology: the immune system in health and disease*, 3rd ed. London: Current Biology Publications; 1997. p. 9.1-9.52. Chandra RK. Food allergy and nutrition in early life: Implications for later health. *Proc Nutr Soc*, 59: 273-277, (2000).
4. Pirson F. Food allergy: a challenge for the clinician. *Acta Gastroenterol Belg*, 69: 38-42, (2006).
5. Eigenmann PA. Are specific immunoglobulin E titers reliable for prediction of food allergy? *Clin Exp Allergy*, 35:247-249, (2005).
6. Lack G. Clinical practice. Food allergy. *N Engl J Med*, 359: 1252-1260, (2008).
7. Bock SA, Munoz- Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*, 107: 191-193, (2001).
8. Goldberg B, Trivieri L, Anderson J W. *Alternative medicine: the definitive guide*. 2nd Edn, Celestial Arts, 598: 50–51, (2002).
9. Carter, Urbanowicz, et al. Effects of a few food diet in attention deficit disorder.

- Archives of Diseases in Childhood, 69: 564-568, (1993)
10. Dixon HS. Treatment of delayed food allergy based on specific immunoglobulin G RAST testing. *Otolaryngol Head Surg*, 123: 48-54, (2000).
 11. <http://www.cdc.gov>. Accessed on 03.01.2010.
 12. Croen LA, Grether JK, Yoshida CK, et al. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders. *Arch Pediatr Adolesc Med*, 159: 151-7, (2005).
 13. Knivsberg AM, Reichelt KL, Nodland M. Reports on dietary intervention in autistic disorders. *Nutr Neurosci*, 4(1): 25-37, (2001).
 14. Kidd PM. Autism, an extreme challenge to integrative medicine. *Alternative medicine review*, 7(6): 472-99, (2002).
 15. Sun S, Itokazu N, Le HT, et al. Innate immune responses and cytokine production against dietary proteins in children with autism spectrum disorder and those with dietary protein intolerances. *J Allergy Clin Immunol*, 109: 222, (2002).
 16. Jyonouchi H., Sun S, Le HT, et al. Cytokine production against common dietary proteins in patients with autism spectrum disorder and developmental regression in comparison with patients with dietary protein intolerance. *J Allergy Clin Immunol*, 109: 221, (2002).
 17. Practice Parameters for Allergy Diagnostic Testing. *Ann Allergy Asthma Immunol*, 75(6): 543-625, (1995).
 18. Eaton SB, Konner M, Shostak M.: Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. *Am J Med*, 84(4):739-49, (1988).
 19. Hoggan R. Considering wheat, rye, and barley proteins as aids to carcinogens. *Med Hypotheses*, 49(3):285-8, (1997).
 20. Connor TM, Cronin CC, Loane JF, Meara NM, et al. Type 1 diabetes mellitus, coeliac disease, and lymphoma: a report of four cases. *Diabet*, 16(7):614-7, (1999).
 21. Potocki P, Hozyasz K. Psychiatric symptoms and coeliac disease. *Psychiatr Pol*, 36(4):567-78, (2002).
 22. Goldstein R, Braverman D, Stankiewicz H. Carbohydrate malabsorption and the effect of dietary restriction on symptoms of irritable bowel syndrome and functional bowel complaints. *Israel Medical Association Journal*, Vol 2(8): 583-587, (2000).
 23. Sher K, Jayanthi V, Probert CSJ, et al. Infertility, obstetric and gynaecological problems in coeliac disease. *Dig Dis*, 12:186-190, (1994).
 24. Wurtman RJ.: Nutrients that modify brain function. *Sci Am*, 246:50-9, (1982).
 25. Panksepp J. A neurochemical theory of autism. *Trends in neurosciences*, 2: 174-7, (1979).
 26. Waring and Ngong JM. Sulphate metabolism in allergy-induced autism: Relevance to the disease aetiology. *Biological perspectives in Autism*, 25-33, (1993).
 27. Kidd PM. Attention deficit/ hyperactivity disorder (ADHD) in children: rationale for its disorders integrative management. *Altern Med Rev*, 5(5): 402-28, (2000).
 28. Newschaffer CJ, Croen LA, Daniels J et al. The epidemiology of autism spectrum disorders". *Annu Rev Public Health*, 28: 235-58, (2007).
 29. Shaw W. Increased urinary excretion of analogs of Krebs cycle metabolism in arabinose in two brothers with autistic features. *Clin Chem*, 41 (8): 1094-1104, (1995).
 30. Food allergies common in India. 2009. http://prod.bolohealth.com/featurearticle/top_features/35-food-allergies-common-in-india?page=2. Accessed on 03.01.2010
 31. Ferreira F, Hawranek T, Gruber P, Wopfner N, Mari A. Allergic cross-reactivity: from gene to clinic. *Allergy*, 59:243-267, (2004).
 32. Quirce S, Maranon F, Umpierrez A, de las Heras M, Fernandez-Caldas E, Sastre J. Chicken serum albumin (Gal d 5*) is a partially heat-labile inhalant and food allergen implicated in the bird-egg syndrome. *Allergy*, 56(8):754-62, (2001).
 33. Lucarelli S, Frediani T, Zingoni AM., Ferruzzi F, Giardini O, Quintieri F, et al.

- Food allergy and infantile autism. *Panminerva Med*, 37 (3): 137, (1995).
34. Jyonouchi H. Food allergy and autism spectrum disorders: Is there a link? *Current allergy and asthma reports*, 9(3): 194-201, (2009).
 35. Oski F. *Don't drink your milk*. Syracuse: Mollica Press, (1983).
 36. Mathews J. Diet for Autism. *Food Allergens, Sensitivities, & Substitutes*. *Clin Exp Allergy*, 39(2):261-70, (2009).
 37. Millward C et al. Gluten- and casein-free diets for autistic spectrum disorder (Review). *Nutritional Neuroscience*, Volume 5(4): 251 – 261, (2002).
 38. Afzal N, Murch S, Thirrupathy K, Berger L, Fagbemi A, Heuschkel R. Constipation with acquired megarectum in children with autism. *Pediatrics*, 112(4): 939-42, (2003).
 39. Ibrahim SH, Voigt RG, Katusic SK, Weaver AL, Barbaresi WJ. Incidence of gastrointestinal symptoms in children with autism: a population study. *Pediatrics*, 124(2): 680-6, (2009).
 40. Ming X, Walters AS. Autism spectrum disorders, attention deficit/hyperactivity disorder, and sleep disorders. *Curr Opin Pulm Med*, 15 (6): 578-584, (2009).
 41. Curtis LT, Patel KJ. Nutritional and environmental approaches to preventing and treating autism and attention deficit hyperactivity disorder (ADHD): a review. *Altern Complement*, 14(1):79-85, (2008).