Cambridge Nutritional Sciences

FOOD INTOLERANCE
(Food IgG Antibodies)

Theory, Facts & Fallacies

Dr. Nigel Abraham PhD, FIBMS
Scientific Director CNS

FOODPRINT®

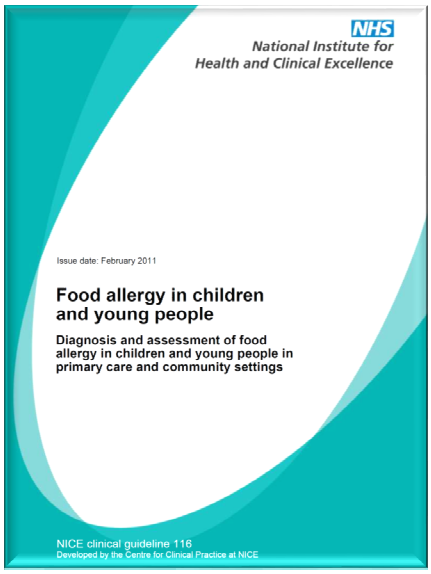
FoodDetective™

INTRODUCTION

Food 'allergy' in the UK: 500% increase in hospital admissions seen since 1990.

In the past we tended to see the immediate type of reaction, but now we are seeing much more of serious delayed reactions.

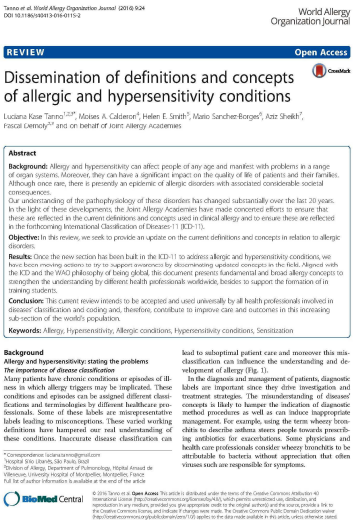
Why has there been such an increase?



ADVERSE FOOD REACTIONS

Tanno LK, Calderon MA, Smith HE, Sanchez-Borges M, Sheikh A, Demoly P; Joint Allergy Academies. World Allergy Organ J. 2016 Aug 9;9:24. doi: 10.1186/s40413-016-0115-2. eCollection 2016.

- Allergy and hypersensitivity, previously perceived as simple and rare disorders, are now common and increasingly a major global public health problem.
- Numerous reports over the last 20 years have been indicating that the world is dealing with an allergy epidemic.
- They are complex conditions able to be expressed in many different organs and in any age, having a significant impact on the quality of life of patients and their families.
- All health care professionals, in whatever role may thus encounter patients with allergic conditions.



Tanno et al. World Allergy Organization Journal (2016) 9:24
DOI 10.1186/s40413-016-0115-2

World Allergy Organization Journal

REVIEW Open Access

Dissemination of definitions and concepts of allergic and hypersensitivity conditions

Luciana Kase Tanno[1,2,3*], Moises A. Calderon[4], Helen E. Smith[5], Mario Sanchez-Borges[6], Aziz Sheikh[7], Pascal Demoly[8,9] and on behalf of Joint Allergy Academies

Abstract

Background: Allergy and hypersensitivity can affect people of any age and manifest with problems in a range of organ systems. Moreover, they can have a significant impact on the quality of life of patients and their families. Although once rare, there is presently an epidemic of allergic disorders with associated considerable societal consequences.

Our understanding of the pathophysiology of these disorders has changed substantially over the last 20 years. In the light of these developments, the Joint Allergy Academies have made concerted efforts to ensure that these are reflected in the current definitions and concepts used in clinical allergy and to ensure these are reflected in the forthcoming International Classification of Diseases-11 (ICD-11).

Objective: In this review, we seek to provide an update on the current definitions and concepts in relation to allergic disorders.

Results: Since the new section has been built in the ICD-11 to address allergic and hypersensitivity conditions, we have been moving actions to try to support awareness by disseminating updated concepts in the field. Aligned with the ICD and the WHO philosophy of being global, this document presents fundamental and broad allergy concepts to strengthen the understanding by different health professionals worldwide, besides to support the formation of in training students.

Conclusion: This current review intends to be accepted and used universally by all health professionals involved in diseases' classification and coding and, therefore, contribute to improve care and outcomes in this increasing sub-section of the world's population.

Keywords: Allergy, Hypersensitivity, Allergic conditions, Hypersensitivity conditions, Sensitization

Background

Allergy and hypersensitivity: stating the problems

The importance of disease classification

Many patients have chronic conditions or episodes of illness in which allergy triggers may be implicated. These conditions and episodes can be assigned different classifications and terminologies by different healthcare professionals. Some of these labels are misrepresentative labels leading to misconceptions. These varied working definitions have hampered our real understanding of these conditions. Inaccurate disease classification can lead to suboptimal patient care and moreover this misclassification can influence the understanding and development of allergy (Fig. 1).

In the diagnosis and management of patients, diagnostic labels are important since they drive investigation and treatment strategies. The misunderstanding of diseases' concepts is likely to hamper the indication of diagnostic method procedures as well as can induce inappropriate management. For example, using the term wheezy bronchitis to describe asthma steers people towards prescribing antibiotics for exacerbations. Some physicians and health care professionals consider wheezy bronchitis to be attributable to bacteria without appreciation that often viruses such are responsible for symptoms.

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Diseases
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ADVERSE FOOD REACTIONS

- The prevalence of migraine, asthma, dermatitis and irritable bowel syndrome has been continuously increasing
- Etiological studies suggest that these diseases may be related to adverse food reactions (food hypersensitivity)
- Numerous studies have found that the levels of food-specific IgG's and IgG subclasses in serum are significantly higher in individuals with food hypersensitivity
- **IgG-mediated immunologic responses play an important role in the pathogenesis of adverse food reactions**

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IgG GUIDED DIET

Geoffrey Hardman, Gillian Hart. Nutrition & Food Science Vol. 37 No. 1, 2007 pp. 16-23

- Survey commissioned by Allergy UK – 5286 participants
- Assay performed using CNS ELISA test
- Questionnaire 3 months after IgG food test
- 76% reported a significant improvement in their condition
- 68% noticed a benefit within 3 weeks
- Those with more than 1 condition more likely to report noticeable improvement
- 92% reported a return of symptoms on reintroduction of offending foods

NFS 37,1

16

Dietary advice based on food-specific IgG results

Geoffrey Hardman
Centre for Health Economics, University of York, Heslington, York, UK, and
Gillian Hart
YorkTest Laboratories Ltd, York Science Park, York, UK

Abstract

Purpose – To provide evidence that elimination diet based on food-specific IgG test results is an effective, reliable and valid aid to the management of chronic medical conditions.

Design/methodology/approach – A postal survey, commissioned by Allergy UK, was carried out with 5,286 subjects reporting a wide range of chronic medical conditions, who had taken a food-specific IgG enzyme-linked immunosorbant assay blood test. Questionnaires, issued three months after the results, were analysed to investigate the effect of eliminating the foods identified by the test. To check for response bias, a separate group of patients who had not responded were interviewed by telephone. The analysis and reporting of the data was carried out at the University of York.

Findings – Of patients who rigorously followed the diet 73.8 per cent had a noticeable improvement in their condition. Of patients who benefited from following the recommendations 68.2 per cent felt the benefit within three weeks. Those who reported more than one condition were more likely to report noticeable improvement. 81.5 per cent of those that dieted rigorously and reported three or more co-morbidities showed noticeable improvement in their condition. For those who dieted rigorously and reported high benefit, 92.3 per cent noticed a return of symptoms on reintroduction of the offending foods.

Originality/value – These data provide evidence for the use of elimination diet based on food-specific IgG blood test results as an aid to management of the symptoms of a range of chronic medical conditions.

Keywords Food products, Diet
Paper type Research paper

Introduction

A role for food-specific IgG antibodies in the underlying mechanism of food intolerance (non-IgE mediated food allergy) has been proposed, as has the measurement of food-specific antibodies as a strategy for identifying foods to which a patient may be sensitive (Marinkovich, 1996). It is proposed that the presence of food-specific IgG indicates a potential sensitivity to that particular food and that the patient may achieve benefit by eliminating the food(s) from their diet. Recent study showed a consistent increase in IgG_4 antibody titres across the three Irritable Bowel Syndrome (IBS) subgroups compared to controls for wheat, beef, pork, lamb, and soya bean (Zar *et al.*, 2005), and a clinically significant improvement in symptoms has been observed in IBS patients eliminating foods identified by such a method (Atkinson *et al.*, 2004). However, the exact role of IgG antibodies as markers of food intolerance in general is not clear. IgG antibodies to food antigens are often present in healthy individuals and are generally considered to be part of the normal immune response to food allergens (Barnes, 1995).

Food intolerance has been associated with a myriad of chronic symptoms including headaches (Rees *et al.*, 2005), intestinal and skin symptoms (Sampson and McCaskill, 1985), behavioural changes and respiratory disorders (Pelikan, 1988). Currently, the best accepted method for diagnosing and confirming food intolerance is empirical, by elimination diet and subsequent challenge (Radcliffe, 2002). Using this method patients

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SURVEY RESULTS – ALLERGY UK 2007 MAIN MEDICAL CONDITION REPORTED		% WHO REPORTED MODERATE TO HIGH BENEFIT
Gastrointestinal	IBS, Crohn's Disease	80%
Respiratory	Asthma, breathing difficulties	78%
Neurological	Migraine, Headaches	72%
Dermatological	Eczema, Acne, Psoriasis	76%
Musculo-skeletal	Arthritis, Rheumatoid Arthritis	64%
Psychological	Depression, ADHD, Panic Attacks	81%
Other	Bloating, Lethargy, general feeling of Malaise	79%

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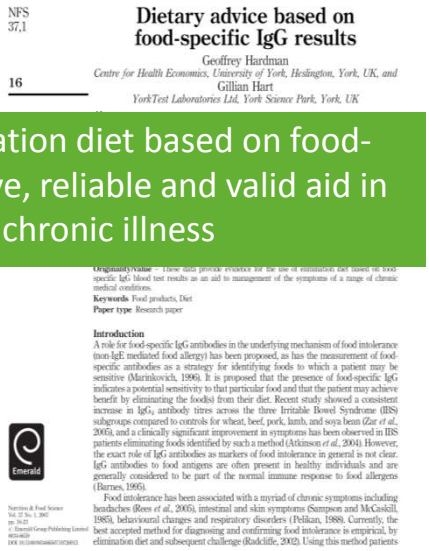

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Emerald

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Provided evidence that elimination diet based on food-specific IgG testing is an effective, reliable and valid aid in the management of chronic illness

Q How do we define food allergy and intolerance?

STANDARD CLASSIFICATION

ADVERSE REACTION TO FOOD

IMMUNE MEDIATED

NON–IMMUNE MEDIATED

IgE
Type I Allergy

IgG
Type III Allergy
Sensitivity

Enzyme Deficiency (Lactose, Histamine)
Pharmacological Effect (Biogenic amines)
Chemical Effect

Classic 'Allergic' Reaction

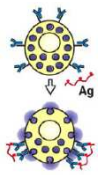
Food Allergy ⟷ Food Intolerance

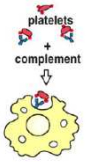
COMMON TERMINOLOGY

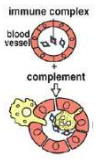
CLASSIFICATION OF ALLERGIC REACTIONS

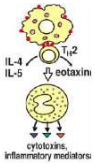
Classified in four groups as defined by Gell and Coombs in 1963

TYPE I - IgE	TYPE II-IgG/IgM	TYPE III - IgG	TYPE IV – T CELLS
Mast Cell activation	FcR-dependent Cell destruction	Immune Complex deposition	Eosinophilic inflammation Monocyte activation









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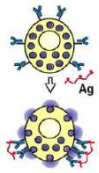

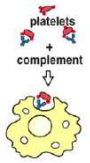

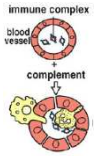

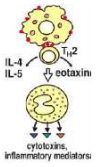

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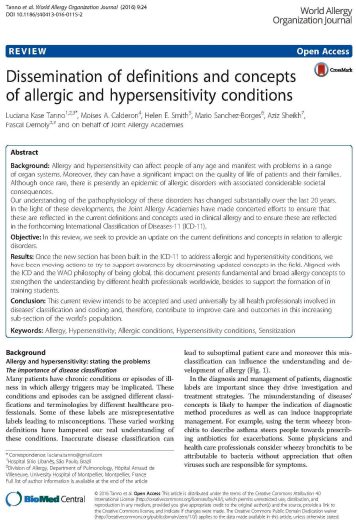
- Concepts in medicine and the new knowledge generated in the last few years have substantially changed our view of the immune system and its interaction with the environment and external agents.
- Such developments in pathophysiology, pharmacology and clinical practice necessitate reviewing current definitions and terminologies.



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World Allergy Organization Journal

REVIEW Open Access

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Our understanding of the pathophysiology of these disorders has changed substantially over the last 20 years. In the light of these developments, the Joint Allergy Academies have made concerted efforts to ensure that these are reflected in the current definitions and concepts used in clinical allergy and to ensure these are reflected in the forthcoming International Classification of Diseases-11 (ICD-11).
Objective: In this review, we seek to provide an update on the current definitions and concepts in relation to allergic disorders.
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BioMed Central

FOOD INTOLERANCE (IgG)

Allergy UK

"45% of the population suffer from a food intolerance"

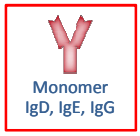
- Non-specific / multiple symptoms
- Most people are undiagnosed
- **Many clients will be affected**

Q

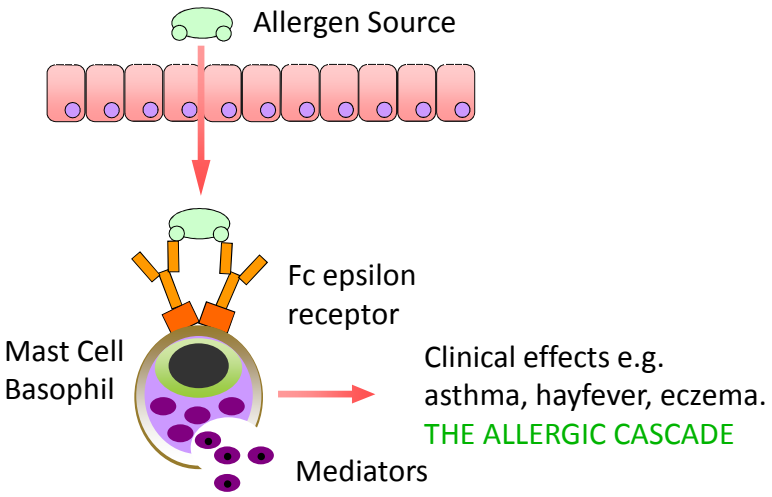
What are IgG antibodies & what is their significance ?

ANTIBODY CLASSIFICATION

Name	Types	Description
IgA	2	Found in gut, respiratory tract, urogenital tract, saliva, tears and breast milk. First line immune defense system against invading pathogens
IgD	1	Antigen receptor on B cells that haven't been exposed to antigens. Can produce immune response via mast cells and basophils
IgE	1	Binds antigens and triggers histamine response from mast cells and basophils. Type I hypersensitivity
IgG	4	Provides the majority of antibody-based immunity against pathogens. Can cross placenta to give passive immunity to fetus.
IgM	1	Expressed at the surface of B cells. Use in early stages of B cell immunity before there is sufficient IgG



ANTIBODY PRODUCTION – PROVOCATION IgE ALLERGY



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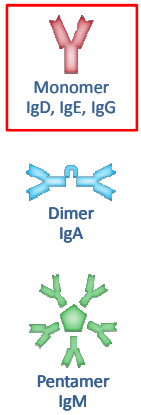

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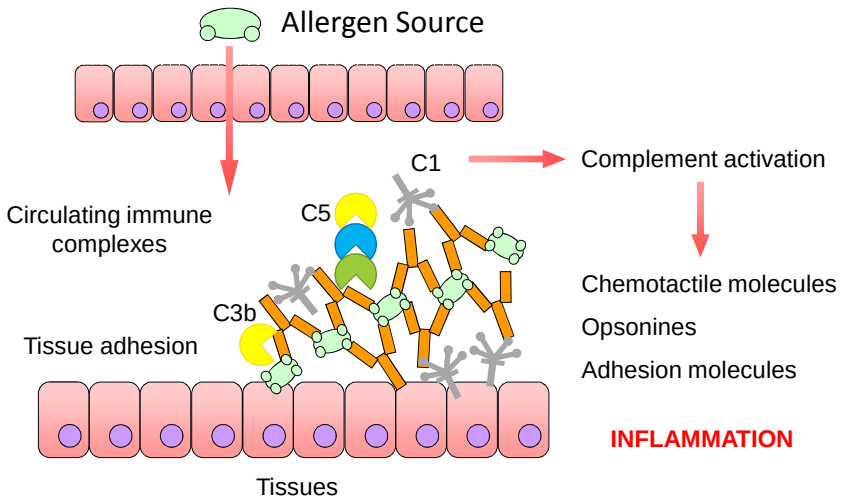
ANTIBODY PRODUCTION – CIRCULATING IMMUNE COMPLEXES (CIC)



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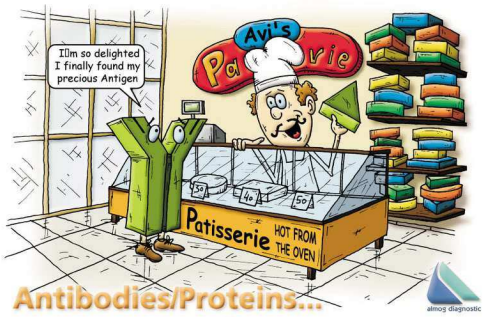
WHAT DOES THE PRESENCE OF IgG ANTIBODIES MEAN?

Whilst it is a normal physiological phenomenon to produce IgG antibodies to foods, we have to remember that the presence of such antibodies in the serum constitutes an immunological defence reaction against the food



Oral tolerance is the normal state and it is not a normal reaction to develop high levels of antibodies to all foods that are consumed regularly.

Q

What about IgG_4 antibodies & their significance ?

IgG SUBCLASS PROPERTIES

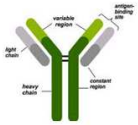
PROPERTY	IgG1	IgG2	IgG3	IgG4
Neutralisation	++	++	++	++
Activation of complement pathway	++	+	+++	
Opsonisation	+++	+	++	
Binding to macrophages	++	+	+++	++
Binding to neutrophils	+		+	

IgG1 and IgG3 have strong **pro-inflammatory** properties

IgG4 has protective, **anti-inflammatory** properties

IgG4 deficiency seen in 10 to 15% of healthy patients

IgG4 FUNCTION



- Acts as a 'blocking agent' against the actions of IgE
- Catches and neutralises the (food) antigen before IgE can bind to it
- IgG4 acts to prevent acute allergic reactions (Type I allergy) occurring
- No complement activation and no opsonising capacities
- **No involvement with Type III (IgG-mediated) food intolerance**
- **Invalid measurement, to detect 'delayed-onset' food intolerance**

THE BOTTOM LINE FOR ALLERGY DIAGNOSIS

R. C. Aalberse, S. O. Stapel, J. Schuurman and T. Rispens.
Clinical & Experimental Allergy, 39, 469–477

- IgG4 by itself is unlikely to be a cause of allergic symptoms. In general, the presence of allergen-specific IgG4 indicates that anti-inflammatory, tolerance-inducing mechanisms have been activated.
- The existence of the IgG4 subclass, its up-regulation by anti-inflammatory factors and its own anti-inflammatory characteristics may help the immune system to dampen inappropriate inflammatory reactions.


REVIEW

Immunoglobulin G4: an odd antibody

Clinical & Experimental Allergy

Summary

Introduction

(EAACI) Task Force Report. 2008

European Academy of Allergy & Clinical Immunology (EAACI) Task Force Report. 2008

- Testing of IgG to foods is considered irrelevant for the laboratory work-up of food allergy or intolerance.
- Testing for IgG4 against foods is not recommended as a diagnostic tool.
- Due to lack of any controlled studies on the diagnostic value of IgG testing in food allergy, it should not be performed in the case of food-related complaints. (Papers cited 1982 – 2006)

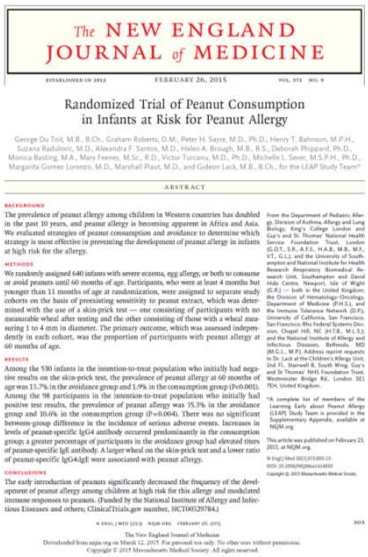

Position paper

Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report*

IgG & FOOD ALLERGY – LEAP STUDY

LEAP Study team N Engl J Med 2015;372:803-13

- Conclusions: The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.
- Increases in levels of peanut-specific IgG antibody occurred predominantly in the consumption group.
- Observations indicate that IgG is associated with a protective role against the development of allergy.



The NEW ENGLAND JOURNAL of MEDICINE

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

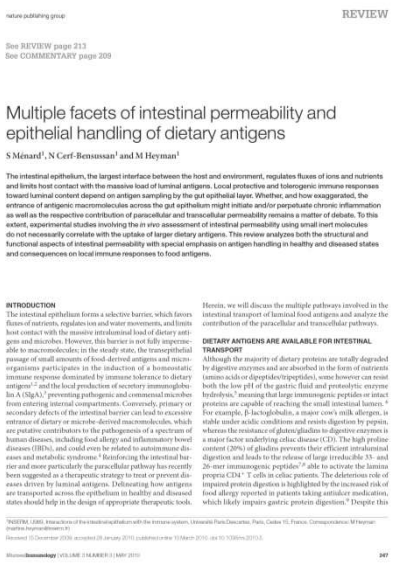
ABSTRACT

Q What are the mechanisms of IgG mediated food intolerance ?

INTESTINAL PERMEABILITY

Ménard S, Cerf-Bensussan N, Heyman M. Mucosal Immunol. 2010 May;3(3):247-59. doi: 10.1038/mi.2010.5. Epub 2010 Mar 10. PMID: 20404811

- In intestinal diseases, increased permeability to large molecules mostly (food antigens, microbial fragments) can have a role in exacerbating inappropriate immune responses



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Multiple facets of intestinal permeability and epithelial handling of dietary antigens

S Ménard[1], N Cerf-Bensussan[1] and M Heyman[1]

The intestinal epithelium, the largest interface between the host and environment, regulates fluxes of ions and nutrients and limits host contact with the massive load of luminal antigens. Local protective and tolerogenic immune responses toward luminal content depend on antigen sampling by the gut epithelial layer. Whether, and how exaggerated, the entrance of antigenic macromolecules across the gut epithelium might initiate and/or perpetuate chronic inflammation as well as the respective contribution of paracellular and transcellular permeability remains a matter of debate. To this extent, experimental studies involving the *in vivo* assessment of intestinal permeability using small inert molecules do not necessarily correlate with the uptake of larger dietary antigens. This review analyzes both the structural and functional aspects of intestinal permeability with special emphasis on antigen handling in healthy and diseased states and consequences on local immune responses to food antigens.

INTRODUCTION

The intestinal epithelium forms a selective barrier, which favors fluxes of nutrients, regulates ion and water movements, and limits host contact with the massive intraluminal load of dietary antigens and microbes. However, this barrier is not fully impermeable to macromolecules; in the steady state, the transepithelial passage of small amounts of food-derived antigens and microorganisms participates in the induction of a homeostatic immune response dominated by immune tolerance to dietary antigens[1,2] and the local production of secretory immunoglobulin A (SIgA),[3] preventing pathogenic and commensal microbes from entering internal compartments. Conversely, primary or secondary defects of the intestinal barrier can lead to excessive entrance of dietary or microbe-derived macromolecules, which are putative contributors to the pathogenesis of a spectrum of human diseases, including food allergy and inflammatory bowel diseases (IBDs), and could even be related to autoimmune diseases and metabolic syndrome.[4] Reinforcing the intestinal barrier and more particularly the paracellular pathway has recently been suggested as a therapeutic strategy to treat or prevent diseases driven by luminal antigens. Delineating how antigens are transported across the epithelium in healthy and diseased states should help in the design of appropriate therapeutic tools.

Herein, we will discuss the multiple pathways involved in the intestinal transport of luminal food antigens and analyze the contribution of the paracellular and transcellular pathways.

DIETARY ANTIGENS ARE AVAILABLE FOR INTESTINAL TRANSPORT

Although the majority of dietary proteins are totally degraded by digestive enzymes and are absorbed in the form of nutrients (amino acids or dipeptides/tripeptides), some however can resist both the low pH of the gastric fluid and proteolytic enzyme hydrolysis,[5] meaning that large immunogenic peptides or intact proteins are capable of reaching the small intestinal lumen.[6] For example, β-lactoglobulin, a major cow's milk allergen, is stable under acidic conditions and resists digestion by pepsin, whereas the resistance of gluten/gliadins to digestive enzymes is a major factor underlying celiac disease (CD). The high proline content (20%) of gliadins prevents their efficient intraluminal digestion and leads to the release of large (reducible 33- and 26-mer immunogenic peptides[7,8] able to activate the lamina propria CD4$^+$ T cells in celiac patients. The deleterious role of impaired protein digestion is highlighted by the increased risk of food allergy reported in patients taking antiulcer medication, which likely impairs gastric protein digestion.[9] Despite this

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IgG AND THE GUT MICROBIOME

Hippe B, Remely M, Bartosiewicz N, Riedel M, Nichterl C, Schatz L, Pummer S, Haslberger A
Endocr Metab Immune Disord Drug Targets. 2014 Mar;14(1):67-75.

- Pilot study analysed interactions of gastrointestinal microbiota, gut permeability, nutrition, IgG levels, and their impact or correlation on food intolerances and well-being.
- Anti-inflammatory effects of *Faecalibacterium prausnitzii* or *Lactobacilli* and gut barrier functions of *Akkermansia* may have a key role in food intolerances.

Endocrine, Metabolic & Immune Disorders - Drug Targets, 2014, 14, 67-75 67

Abundance and Diversity of GI Microbiota Rather than IgG$_4$ Levels Correlate with Abdominal Inconvenience and Gut Permeability in Consumers Claiming Food Intolerances

Berit Hippe[1], Marlene Remely[1], Natalie Bartosiewicz[2], Monika Riedel[2], Claudia Nichterl[2], Lulit Schatz[2], Sandra Pummer[2] and Alexander Haslberger[1,*]

adverse reactions to food [1]. They are a rapidly increasing problem in the western world and according to the World Allergy Organization (WAO) 220-250 million people are effected. The trend continues to rise, especially in children [2]. In Europe, 2-5% of people suffer from a food allergy, while intolerances are estimated at 20% [3]. Genetic aspects such as single nucleotide polymorphisms [4], environmental influences such as the discussed "hygiene hypothesis" [5], and stress from the social environment [6, 7] have been linked to intolerances. Recently aspects of gut macrobiota and gut permeability are in discussion for their role in food intolerance [7].

An inappropriate tolerance to food antigen has been associated with mechanisms of apoptosis [8] or paralysis of T-cells [9] and failure in the production of regulatory T-cells

intolerance are well described [16]. In contrast many aspects [17] in the area of non IgE- mediated intolerances remain poorly understood [18-20]. Various food components, and also a number of natural and artificial food additives have been discussed for non-IgE mediated adverse reactions [21, 22]. Furthermore, the role of IgG antibodies in these intolerances remains highly controversial. IgG1s formed as the initial response after contact with a new food antigen. With further exposure to the antigen, a change in the formation of IgG$_4$ antibodies seems to take place [23]. Following this change the amount of IgG$_4$ rises from 3% up to 50%. High IgG$_4$ concentrations may indicate an intense conflict of the immune system with food antigens. The synthesized IgG$_4$ antibodies are suspected to sensitise cells, but may also block the IgE mediated allergic response [24]. Actual untreated allergies show increased IgG$_4$ levels in 50% of cases. However, the identification of the triggering food is difficult as the symptoms often stop after hours or days. In many of these IgG$_4$ mediated immune responses a disturbed intestinal permeability, leading to a constant

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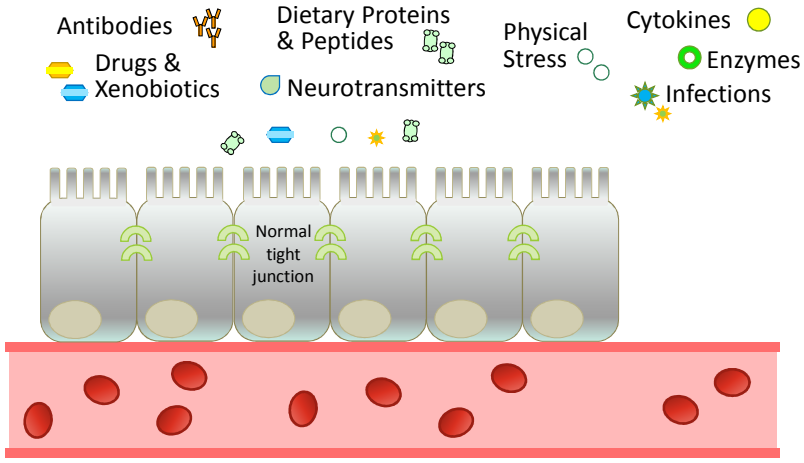
IgG AND THE GUT MICROBIOME

Hippe B, Remely M, Bartosiewicz N, Riedel M, Nichterl C, Schatz L, Pummer S, Haslberger A
Endocr Metab Immune Disord Drug Targets. 2014 Mar;14(1):67-75.

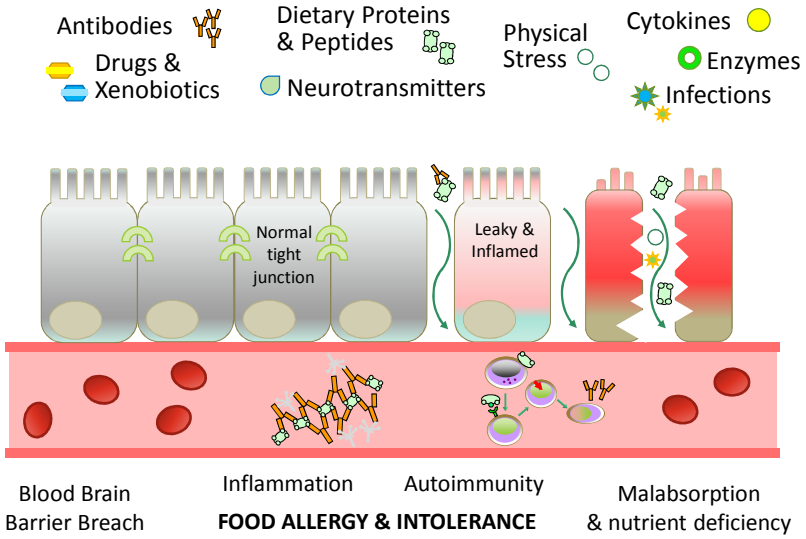
Abundance and Diversity of GI Microbiota Rather than IgG_4 Levels Correlate with Abdominal Inconvenience and Gut Permeability in Consumers Claiming Food Intolerances

- Even in absence of diagnosed milk intolerance, discomfort increased, if the IgG levels were high or Lactobacilli and Bifidobacteria levels were low.
- The analytical strategy to include the analysis of major commensal gastrointestinal microbiota groups in addition to food intolerances, IgG levels, resulted in significant correlations.

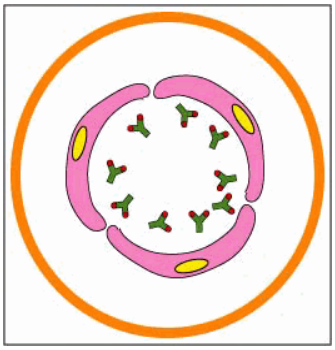
'LEAKY GUT' SYNDROME



'LEAKY GUT' SYNDROME



IMMUNE COMPETENCY AND 'TOTAL LOAD



- With an efficient immune response, the half-life of a complex may be a few minutes which may **NOT** elicit symptoms
- An overload of antigen or poor immunity, will lead to deposition of large complexes in the tissues and probable symptoms.

FOOD IMMUNE COMPLEXES

R. PAGANELLI, R. J. LEVINSKY & D. J. ATHERTON Department of Immunology, The Institute of Child Health, London.
Clin. exp. Immunol. (1981) 46, 44-53..

- The formation of an antigen-antibody complex in the circulation is a normal physiological method of antigen elimination.
- However, there is a great deal of evidence suggesting that increased levels of circulating immune complexes are associated with a variety of diseases in which the complexes, once deposited in the tissues, cause damage by activating complement and other effector mechanisms.

Clin. exp. Immunol. (1981) 46, 44-53.

Detection of specific antigen within circulating immune complexes: validation of the assay and its application to food antigen–antibody complexes formed in healthy and food-allergic subjects

R. PAGANELLI, R. J. LEVINSKY & D. J. ATHERTON *Department of Immunology, The Institute of Child Health, London*

(Accepted for publication 17 April 1981)

SUMMARY

A simple two-step method for the detection of specific antigen within immune complexes is described. The immune complexes are precipitated from serum by polyethylene glycol, dissociated by incubation in acid pH buffer and adsorbed onto the surface of polystyrene tubes. The antigen is detected by the binding of a radiolabelled affinity-purified specific antibody. The assay can detect the antigen within both antigen- and antibody-excess immune complexes of any immunoglobulin class, and can also allow semiquantitative comparison of different samples. Immune complexes containing food protein antigens after eating have been found in the serum of both normal subjects and atopic patients; the latter group showed higher mean levels of antigen-specific immune complexes. The method can be adopted for large-scale screening of clinical samples for suspected antigens if suitable antisera are available.

INTRODUCTION

Circulating soluble immune complexes (IC) are thought to play a role in a variety of diseases (WHO, 1977). These include systemic lupus erythematosus, certain forms of glomerulonephritis, rheumatoid arthritis, chronic inflammatory bowel disease, certain malignancies as well as parasitic infections. They have also been described in healthy subjects and in physiological conditions such as pregnancy (Masson, Delire & Cambiaso, 1977). The fact that immune complexes are found in such diverse clinical conditions indicates their heterogeneity and indeed such differences in immunoglobulin class, complement-binding capacity as well as size have been described in different diseases (Levinsky & Soothill, 1979). The great variety of methods used for the detection of immune complexes depend on these different physicochemical or biological properties. Hence, some characterization of immune complexes in disease can be achieved by using several methods in combination, but to date none of these have reliably been able to detect the antigen within the immune complex. Recently we have become interested not only in the immune response to antigens entering the host through the gastrointestinal mucosal surface but also in the mechanisms whereby food antigen entry fails to elicit damaging reactions in normal individuals. It is well recognized that the gut mucosa is not completely impermeable to macromolecules (Walker & Isselbacher, 1974) and that the amounts absorbed are sufficient to immunize (Peterson & Good, 1963) since low levels of antibodies to food antigens may be detected in most healthy subjects (May *et al.*, 1977). The

Correspondence: Dr R. J. Levinsky, Department of Immunology, The Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

0009-9104/81/1000-0044$02.00 © Blackwell Scientific Publications

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IMMUNE COMPLEX FORMATION

Severance EG, Gressitt KL, Halling M, Stallings CR, Origoni AE, Vaughan C, Khushalani S, Alaedini A, Dupont D, Dickerson FB, Yolken RH. Neurobiol Dis. 2012 Dec;48(3):447-53. doi: 10.1016/j.nbd.2012.07.005. Epub 2012 Jul 16.

- In conclusion, a significant portion of C1q activation in non-recent onset schizophrenia can be attributed to the formation of immune complexes with the food antigens, milk caseins and wheat glutens.
- Our data provide a starting point to examine if perinatal exposure to food antigens in susceptible individuals represents a plausible means by which C1 activation could ultimately result in symptoms and behaviour characteristic of schizophrenia.

Contents lists available at SciVerse ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Complement C1q formation of immune complexes with milk caseins and wheat glutens in schizophrenia

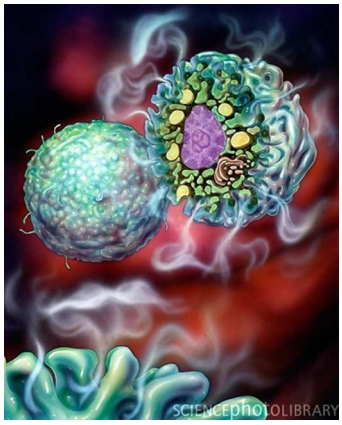
Emily G. Severance [a,b], Kristin L. Gressitt [a], Meredith Halling [a], Cassie R. Stallings [b], Andrea E. Origoni [b], Crystal Vaughan [b], Sunil Khushalani [b], Armin Alaedini [c], Didier Dupont [d], Faith B. Dickerson [b], Robert H. Yolken [a]

ARTICLE INFO

ABSTRACT

Introduction

IgG & MAST CELL ACTIVATION?



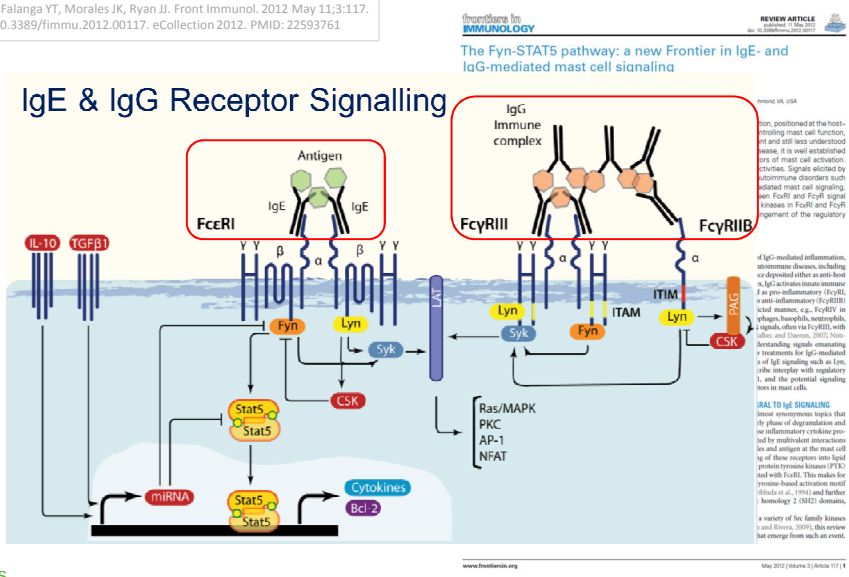
Mast cells are found in connective tissue and basophils are a type of white blood cell.

They contain histamine and other mediators, used for fighting infection

Introduction
Definitions
Antibodies
Significance
IgG vs IgG4
Mechanisms 6
Inflammation
Diseases
Developments
Conclusion

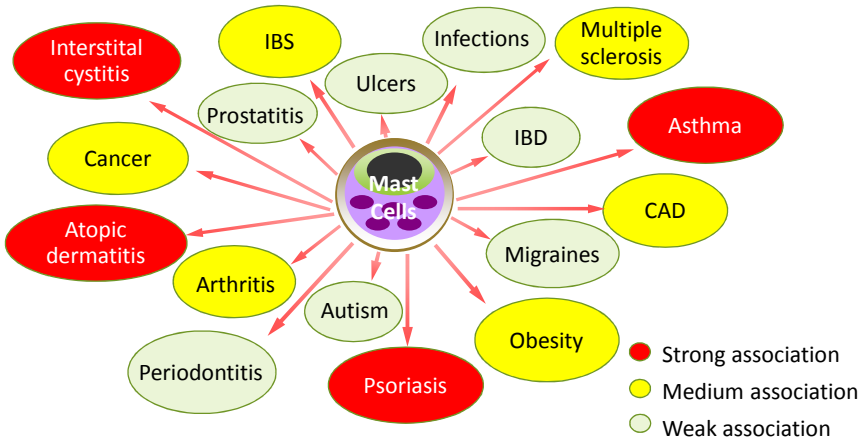
IgG & MAST CELL ACTIVATION?

Pullen NA, Falanga YT, Morales JK, Ryan JJ. Front Immunol. 2012 May 11;3:117. doi: 10.3389/fimmu.2012.00117. eCollection 2012. PMID: 22593761



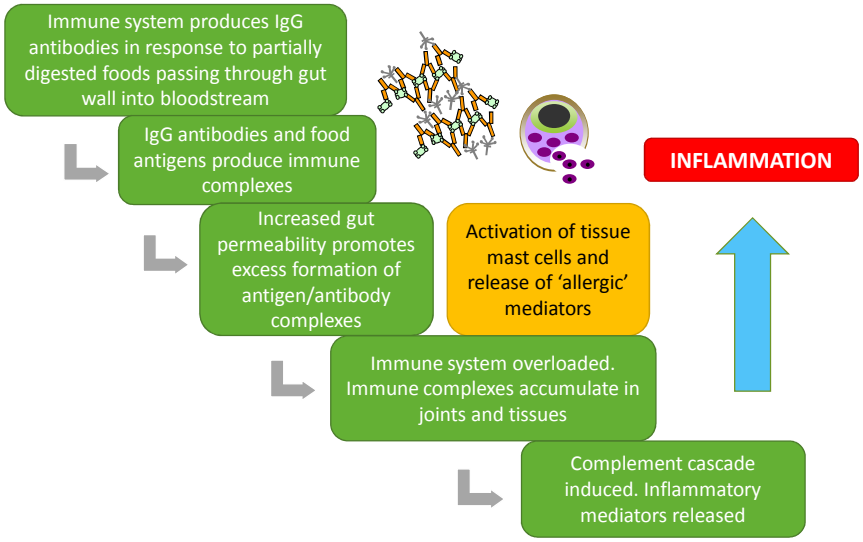
Cambridge Nutritional Sciences

MAST CELL INVOLVEMENT IN INFLAMMATORY DISEASE



Biochim Biophys Acta. 2012 January ; 1822(1): 21–33.

MECHANISM OF IgG FOOD INTOLERANCE



What diseases and conditions have been associated with raised levels of food IgG antibodies?

INFLAMMATION & OBESITY

Wilders-Truschnig M, Mangge H, Lieners C, Gruber H, Mayer C, März W. Exp Clin Endocrinol Diabetes. 2008 Apr;116(4):241-5. Epub 2007 Dec 10. PMID: 18072008

- Obese children have significantly higher IgG antibody values directed against food antigens than normal weight children.
- Anti-food IgG antibodies are tightly associated with low grade systemic inflammation.
- These findings raise the possibility, that anti-food IgG are pathogenically involved in the development of obesity and atherosclerosis.

Article

IgG Antibodies Against Food Antigens are Correlated with Inflammation and Intima Media Thickness in Obese Juveniles

FOODPRINT AND INFLAMMATION STUDY

Average Drop 53.3 %

Patient ID	Received Date	Result mg/L	Grade	Received Date	Result mg/L	Grade	% Drop
55195	09/11/2015	1.2	2	08/02/2016	1.2	2	4.5
55196	09/11/2015	3.3	4	29/02/2016	0.4	1	87.1
55197	09/11/2015	4.7	4	10/02/2016	0.5	2	88.7
55202	09/11/2015	1.5	3	10/02/2016	1.1	2	24.4
55205	09/11/2015	3.6	4	22/02/2016	1.0	2	70.7
55206	09/11/2015	1.8	3	22/02/2016	0.8	2	58.3
55210	09/11/2015	7.6	4	16/03/2016	6.1	4	19.8
55355	16/11/2015	5.1	4	10/02/2016	4.8	4	5.7
55482	23/11/2015	3.6	4	14/03/2016	2.0	3	45.7
55483	23/11/2015	2.8	3	08/02/2016	0.7	2	74.6
55490	23/11/2015	1.0	2	22/02/2016	0.6	2	41.2
57101	22/02/2016	1.5	3	22/02/2016	0.4	1	73.9
57479	09/03/2016	2.1	3	23/05/2016	0.5	1	73.8
57486	09/03/2016	3.7	4	25/05/2016	2.1	3	42.5
57558	14/03/2016	7.8	4	23/05/2016	0.9	2	88.5
57397	07/03/2016	9.3	4	23/05/2016	0.5	1	94.8
57478	09/02/2016	5.2	4	25/05/2016	1.7	3	66.7
*56504	23/03/2016	3.7	4	25/05/2016	4.1	4	+10.9
57900	04/04/2016	3.7	4	GP Result	2.6	3	30.5

	GRADE	RISK
Grade	1 / 2	Low Risk
Grade	3	Moderate Risk
Grade	4	High Risk

INFLAMMATION & OBESITY

Wilders-Truschnig M, Mangge H, Lieners C, Gruber H, Mayer C, März W. Exp Clin Endocrinol Diabetes. 2008 Apr;116(4):241-5. Epub 2007 Dec 10. PMID: 18072008

IgG Antibodies Against Food Antigens are Correlated with Inflammation and Intima Media Thickness in Obese Juveniles

atherosclerosis. Especially, as described for the IBS above, a dietary elimination therapy based on the presence of IgG antibodies to food components may be indicated. Such a dietary therapy may be effective in reducing low grade inflammation and thereby preventing clinical consequences like type 2 diabetes and atherogenesis.

Food Intolerances in Athletes – Understanding the Performance Impact

http://www.runtothefinish.com/2014/09/food-intolerances-in-athletes.html

Impacts on the athlete:

- Increased inflammation results in muscle soreness and slows down recovery time
- Increases stress on the body leading to fatigue as the body needs more rest
- Prevents nutrients from being fully absorbed
- Weakens the immune system.
- Causes weight gain
- Can impact breathing by inflaming the air ways

IgG WEIGHT and Quality of Life

Lewis, Woolger, Melillo, Alonso et al. Obesity & Weight loss Therapy 2012 2:1

- 120 subjects with a mean age of 45.5 and BMI of 20> avoided positive foods for 90 days
- Body composition, blood pressure & quality of life measured at baseline 30,60 and 90 day follow up.
- On average participants lost 1lb a week and 3 inches from the waist Reduction in weight, BMI, waist and hip circumferences, blood pressure
- Improvements in all indicators of quality of life including mental quality.


Obesity & Weight loss Therapy

Eliminating Immunologically-Reactive Foods from the Diet and its Effect on Body Composition and Quality of Life in Overweight Persons

Cambridge Nutritional Sciences

Research Papers

- Delayed food allergy
- Irritable Bowel Syndrome (IBS)
- Inflammation, obesity & arthritis
- Migraine
- Asthma / respiratory diseases
- Crohn's disease
- Behaviour problems (schizophrenia & autism)

Hindawi Publishing Corporation
BioMed Research International
Volume 2013, Article ID 729349, 11 pages
http://dx.doi.org/10.1155/2013/729349

Hindawi

Research Article

Antibodies against Food Antigens in Patients with Autistic Spectrum Disorders

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Academic Editor: David Bernardo

Purpose. Immune system of some autistic patients could be abnormally triggered by gluten/casein assumption. The prevalence of antibodies to gliadin and milk proteins in autistic children with paired/impaired intestinal permeability and under dietary regimen either regular or restricted is reported. *Methods.* 162 ASDs and 44 healthy children were investigated for intestinal permeability, tissue-transglutaminase (tTG), anti-endomysium antibodies (EMA)-IgA, and total mucosal IgA to exclude celiac disease; HLA-DQ2/-DQ8 haplotypes; total systemic antibodies (IgA, IgG, and IgE); specific systemic antibodies: α-gliadin (AGA-IgA and IgG), deamidated–gliadin-peptide (DGP-IgA and IgG), total specific gliadin IgG (all fractions: α, β, γ, and ω), β-lactoglobulin IgG, α-lactalbumin IgG, casein IgG; and milk IgE, casein IgE, gluten IgE, -lactoglobulin IgE, and α-lactalbumin IgE. *Results.* AGA-IgG and DPG-IgG titers resulted to be higher in ASDs compared to controls and are only partially influenced by diet regimen. Casein IgG titers resulted to be more frequently and significantly higher in ASDs than in controls. Intestinal permeability was increased in 25.6% of ASDs compared to 2.3% of healthy children. Systemic antibodies production was not influenced by paired/impaired intestinal permeability. *Conclusions.* Immune system of a subgroup of ASDs is triggered by gluten and casein; this could be related either to AGA, DPG, and Casein IgG elevated production or to impaired intestinal barrier function.

Introduction
Definitions
Antibodies
Significance
IgG vs IgG4
Mechanisms
Inflammation
Diseases 8
Developments
Conclusion

DELAYED ALLERGY

Dixon HS. Otolaryngol Head Neck Surg. 2000 Jul;123(1 Pt 1):48-54.
PMID: 10889481

- Elimination of IgG positive foods is successful in significantly decreasing symptoms
- In all 80 patients studied 71% achieved a 75% or greater improvement level

Treatment of delayed food allergy based on specific immunoglobulin G RAST testing

HAMILTON S. DIXON, MD, Rome, Georgia

This preliminary, descriptive study after extensive clinical experience demonstrates specific IgG food RASTs done in 114 consecutive patients with strong positive histories for delayed food allergy. Elimination of the positive foods was the sole means of treatment. The symptoms leading to the test are detailed, and the method of workup is reviewed. The overall results demonstrated a 71% success rate for all symptoms achieving at least a 75% improvement level. Of particular interest was the group of patients with chronic, disabling symptoms, unresponsive to other intensive treatments. Whereas 70% obtained 75% or more improvement, 20% of these patients obtained 100% relief. (Otolaryngol Head Neck Surg 2000;123:48-54.)

Food allergy has remained a very controversial subject, especially with pediatricians and traditional allergists. Whereas IgE was not discovered until 1969, thereby explaining immediate hypersensitivity, the exact mechanisms for delayed hypersensitivity remain in part theoretical.[1] The exact role of immune complexes, complement, and IgG in type III delayed hypersensitivity has not lent itself to a single reliable test for easy diagnosis. Furthermore, the prevalence of cyclic or delayed food allergy has never been well established in the literature.

From the clinical standpoint, delayed food allergy has no cause-and-effect relationship. Therefore the symptoms go unsuspected by both patient and physician. History, elimination diets, reintroduction of foods, and other conservative measures are usually not helpful.

For many years, traditional allergists have used scratch tests and now prick tests for foods, along with inhalant testing. Many false-positive and false-negative results have made these tests unreliable, frequently only 20% accurate.[2]

Challenge feeding tests have been the gold standard for delayed food allergy and are accurate in trained hands.[3] Even more difficult is the double-blind placebo-controlled food challenge. Unless exact rules are followed, reproducibility at challenge is low,[4] and its impracticality has led to infrequent use in clinical practice.

Cytotoxic food testing has been shown to be accurate only in well-controlled laboratories with highly trained technicians. Results have often been equivocal, especially in office laboratories. The next generation test, the ALCAT, may hold more promise, but it is still not in general use.

Provocation-neutralization testing has also been shown to be efficacious in 6 published double-blind studies, with 75% to 80% accuracy demonstrated.[5,6] I completed another double-blind study using videostroboscopy of vocal folds and provocation-neutralization testing in patients with allergic dysphonia.[7] Internal medicine–pediatric allergists have been reluctant to accept this test because it is not immediately reproducible due to the nature of type III hypersensitivity. This time-consuming test is used by only a small number of otolaryngic allergists. Patient compliance in my practice has been poor because patients must make multiple visits and travel long distances to complete the necessary battery of skin tests. This problem has left many patients with incomplete workups and a continuation of troubling symptoms.

Thus there is currently no standardized, accepted test for delayed food allergy. Furthermore, the prevalence of delayed food allergy as a significant cause of illness has not been well reported.[8] Even many traditional allergists are unaware of its importance, referring to this problem as food intolerance, which is regarded as nonallergic and is usually thought to be associated with chemical sensitivities caused by additives and food colors.

Specific IgG testing for foods has been controversial for several reasons: (1) IgG reflects exposure to the food; (2) IgG levels occur in the normal population[9]; (3) IgG is a protective antibody; (4) IgG_4 is thought by some to be more specific for clinical food allergy than total specific IgG[10,11]; (5) some food reactions are nonimmunologic; (6) there is little correlation between RAST classes (titers) and severity of symptoms; (7)

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0194-5998/2000/$12.00 + 0 23/1/106402
doi:10.1067/mhn.2000.106402

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DELAYED ALLERGY

Di… 3-54.

Table 3. Order of symptom improvement in 80 atopic patients after elimination of positive foods by specific IgG tests

Symptom	No. reported	≥75% improvement	100% improvement
Diarrhea	20	90%	45%
Cramps	13	84%	38%
Cough	22	77%	36%
Cervical headache	15	73%	20%
Nausea	17	70%	24%
Burping	13	69%	15%
Hoarseness	20	65%	15%
Throat clearing	29	65%	28%
Nasal drainage	36	63%	17%
Fullness in ears	17	64%	29%
Nasal congestion	40	62%	20%
Asthma	13	61%	15%
Sinus headache	33	60%	24%
Gas	26	57%	12%
Itchy eyes	19	57%	26%
Sneezing	20	55%	20%
Ear popping	11	54%	27%
Watery eyes	15	53%	6%
Fatigue after meals	31	51%	23%
Dizziness	24	50%	21%
Ringing in ears	18	50%	5%
Skin rash	12	50%	8%
Chronic fatigue	25	48%	0%
Migraine headache	19	47%	16%
Itchy skin	14	35%	7%

Symptom not included if reported fewer than 10 times.

Treatment of delayed food allergy based on specific immunoglobulin G RAST testing

HAMILTON S. DIXON, MD, Rome, Georgia

This preliminary, descriptive study after extensive clinical experience demonstrates specific IgG food RASTs done in 114 consecutive patients with strong positive histories for delayed food allergy. Elimination of the positive foods was the sole means of treatment. The symptoms leading to the test are detailed, and the method of workup is reviewed. The overall results demonstrated a 71% success rate for all symptoms achieving at least a 75% improvement level. Of particular interest was the group of patients with chronic, disabling symptoms, unresponsive to other intensive treatments. Whereas 70% obtained 75% or more improvement, 20% of these patients obtained 100% relief. (Otolaryngol Head Neck Surg 2000;123:48-54.)

Food allergy has remained a very controversial subject, especially with pediatricians and traditional allergists. Whereas IgE was not discovered until 1969, thereby explaining immediate hypersensitivity, the exact mechanisms for delayed hypersensitivity remain in part theoretical.[1] The exact role of immune complexes, complement, and IgG in type III delayed hypersensitivity has not lent itself to a single reliable test for easy diagnosis. Furthermore, the prevalence of cyclic or delayed food allergy has never been well established in the literature.

From the clinical standpoint, delayed food allergy has no cause-and-effect relationship. Therefore the symptoms go unsuspected by both patient and physician. History, elimination diets, reintroduction of foods, and other conservative measures are usually not helpful.

For many years, traditional allergists have used scratch tests and now prick tests for foods, along with inhalant testing. Many false-positive and false-negative results have made these tests unreliable, frequently only 20% accurate.[2]

Challenge feeding tests have been the gold standard for delayed food allergy and are accurate in trained hands.[3] Even more difficult is the double-blind placebo-controlled food challenge. Unless exact rules are followed, reproducibility at challenge is low,[4] and its impracticality has led to infrequent use in clinical practice.

Cytotoxic food testing has been shown to be accurate only in well-controlled laboratories with highly trained technicians. Results have often been equivocal, especially in office laboratories. The next generation test, the ALCAT, may hold more promise, but it is still not in general use.

Provocation-neutralization testing has also been shown to be efficacious in 6 published double-blind studies, with 75% to 80% accuracy demonstrated.[5,6] I completed another double-blind study using videostroboscopy of vocal folds and provocation-neutralization testing in patients with allergic dysphonia.[7] Internal medicine–pediatric allergists have been reluctant to accept this test because it is not immediately reproducible due to the nature of type III hypersensitivity. This time-consuming test is used by only a small number of otolaryngic allergists. Patient compliance in my practice has been poor because patients must make multiple visits and travel long distances to complete the necessary battery of skin tests. This problem has left many patients with incomplete workups and a continuation of troubling symptoms.

Thus there is currently no standardized, accepted test for delayed food allergy. Furthermore, the prevalence of delayed food allergy as a significant cause of illness has not been well reported.[8] Even many traditional allergists are unaware of its importance, referring to this problem as food intolerance, which is regarded as nonallergic and is usually thought to be associated with chemical sensitivities caused by additives and food colors.

Specific IgG testing for foods has been controversial for several reasons: (1) IgG reflects exposure to the food; (2) IgG levels occur in the normal population[9]; (3) IgG is a protective antibody; (4) IgG_4 is thought by some to be more specific for clinical food allergy than total specific IgG[10,11]; (5) some food reactions are nonimmunologic; (6) there is little correlation between RAST classes (titers) and severity of symptoms; (7)

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MIGRAINE – IgG-MEDIATED?

Julio Pascual and Agustı´n Oterino. Cephalalgia 0(00) 1–3.
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- Increased IgG antibodies and cytokines would lead to an inflammation response, which seems to play an important role in the pathophysiology of migraine attacks.
- Supporting this hypothesis, a recent study has shown that anti-food IgG antibodies in obese juveniles are associated with systemic inflammation
- These data are interesting, as obesity seems to be a risk factor in the development of chronic migraine.

Editorial
Cephalalgia

IgG-mediated allergy: A new mechanism for migraine attacks?

Julio Pascual and Agustin Oterino

Despite recent advances offered by modern neuroimaging and genetic techniques, the pathophysiology of migraine has not been fully clarified. As pointed out by Selby and Lance 50 years ago, a relevant proportion of patients report that their migraine attacks are usually precipitated by dietary items (1). In a survey analysing the prevalence of dietary migraine in 500 new migraine patients, Peatfield et al. found in 1984 that 19.2% of migraine patients reported sensitivity to cheese, 18.2% to chocolate and 11.1% to citrus fruit (2). The same year, Monro et al. published a paper in the *Lancet* with the categorical title 'Migraine Is a Food-Allergic Disease', describing the treatment of just nine patients with severe refractory migraine with either sodium cromoglycate or placebo after the patients ate foods previously identified as provocants (3). Sodium cromoglycate exerted a protective effect, which made the authors conclude that a food-allergy reaction is the cause of migraine, at least in this group of patients with dietary precipitants. Definite proof that this is a reproducible fact, however, has proved elusive. In other studies objective evidence of hypersensitivity was found in very few cases, and those reporting a reduction in migraine during formal diets not only include a low number of patients, but mostly make no serious attempt to conceal the dietary strategy from the patients, pay insufficient attention to placebo effect and include an incredible prevalence of atopic diseases in migraine patients.

One of the obstacles to acceptance of the dietary hypothesis is the lack of a clear scientific explanation of the mechanisms implicated in the development of migraine attacks supposedly precipitated by food. The first obvious proposed mechanism was an allergy mediated by IgE antibodies. Theoretically, the interaction of a food constituent with a specific IgE antibody would produce a response by activation of complement or degranulation of mast cells. Several independent studies have failed to find elevated IgE levels or complement activation during migraine attacks, even in patients with a history of food-precipitated headaches (4,5).

These results, together with the finding that diet-sensitive patients are usually sensitive to several and different foods, led to the next proposal for a common pathogenic mechanism: antigenic similarities between these disparate foods seemed less likely than sharing a common chemical constituent (2). Investigators tried to confirm the so-called 'amine hypothesis' first by clinical challenge tests with substances like tyramine or β-phenylethylamine. As elegantly reviewed by Peatfield (5), the results of these studies can be interpreted as inconsistent. The next step was to investigate the amines' metabolic routes. Could the elimination pathways of such amines be deficient in dietary migraine patients? There are two major breakdown pathways for these substances in humans: oxidation by monoamine oxidase (MAO) to parahydroxyphenylacetic acid and sulphation by phenosulphotransferase to water-soluble conjugates. MAO, a mitochondrial enzyme, exists in two forms in humans, with different substrate specificities. MAO A predominates in gut mucosa and liver and preferentially inactivates catecholamines and serotonin. The human platelet contains only MAO B, which metabolises phenylethylamine, benzylamine and methylhistamine. Tyramine and dopamine are substrates for both forms (6). The easy availability of platelets led to MAO B being the only form to be studied in migraine patients. Most studies have found a low platelet MAO B activity but only during migraine attacks, both in dietary and non-dietary patients (5). The significance of these findings remains uncertain. The sulphation route has also been explored in migraine patients. A reduced urinary output of sulphated tyramine metabolites after an oral tyramine load in subjects with food-sensitive migraine

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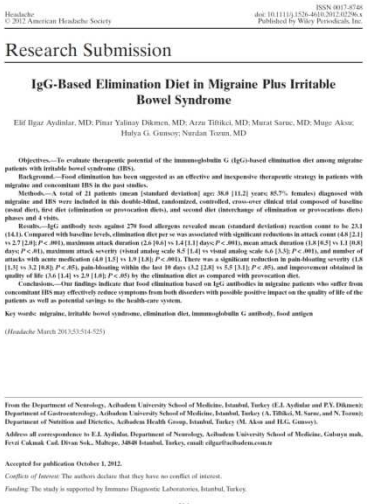
IBS AND MIGRAINE

Aydinlar EI, Dikmen PY, Tiftikci A, Saruc M, Aksu M, Gunsoy HG, Tozun N. Headache. 2013 Mar;53(3):514-25. Epub 2012 Dec 6. PMID: 23216231

- **Conclusions:** Our findings indicate that food elimination based on IgG antibodies in migraine patients who suffer from concomitant IBS may effectively reduce symptoms from both disorders with possible positive impact on the quality of life of the patients as well as potential savings to the health-care system.



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Research Submission

IgG-Based Elimination Diet in Migraine Plus Irritable Bowel Syndrome

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Objectives.—To evaluate therapeutic potential of the immunoglobulin G (IgG)-based elimination diet among migraine patients with irritable bowel syndrome (IBS).

Background.—Food elimination has been suggested as an effective and inexpensive therapeutic strategy in patients with migraine and concomitant IBS in the past studies.

Methods.—A total of 21 patients (mean [standard deviation] age: 38.8 [11.2] years; 85.7% females) diagnosed with migraine and IBS were included in this double-blind, randomized, controlled, cross-over clinical trial composed of baseline (usual diet), first diet (elimination or provocation diets), and second diet (interchange of elimination or provocation diets) phases and 4 visits.

Results.—IgG antibody tests against 270 food allergens revealed mean (standard deviation) reaction count to be 23.1 (14.1). Compared with baseline levels, elimination diet per se was associated with significant reductions in attack count (4.8 [2.1] vs 2.7 [2.0]; $P < .001$), maximum attack duration (2.6 [0.6] vs 1.4 [1.1] days; $P < .001$), mean attack duration (1.8 [0.5] vs 1.1 [0.8] days; $P < .01$), maximum attack severity (visual analog scale 8.5 [1.4] vs visual analog scale 6.6 [3.5]; $P < .001$), and number of attacks with acute medication (4.0 [1.5] vs 1.9 [1.8]; $P < .001$). There was a significant reduction in pain-bloating severity (1.8 [1.3] vs 3.2 [0.8]; $P < .05$), pain-bloating within the last 10 days (3.2 [2.0] vs 5.5 [3.1]; $P < .05$), and improvement obtained in quality of life (3.6 [1.4] vs 2.9 [1.6]; $P < .05$) by the elimination diet as compared with provocation diet.

Conclusions.—Our findings indicate that food elimination based on IgG antibodies in migraine patients who suffer from concomitant IBS may effectively reduce symptoms from both disorders with possible positive impact on the quality of life of the patients as well as potential savings to the health-care system.

Key words: migraine, irritable bowel syndrome, elimination diet, immunoglobulin G antibody, food antigen

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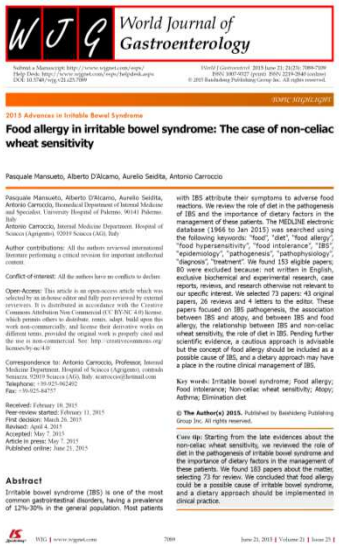
What is the current medical opinion about IgG ?

IBS: A ROLE FOR IgG

Mansueto P, D'Alcamo A, Seidita A, Carroccio A. World J Gastroenterol. 2015 Jun 21;21(23):7089-109. Review. PMID: 26109796

- Irritable bowel syndrome (IBS) is one of the most common GI disorders, having a prevalence of 12%-30%.
- Most patients with IBS attribute their symptoms to adverse food reactions.
- Review of publications (1966 to 2015)
- Studies reported that serum IgG levels are higher in patients with IBS and food allergy history, perhaps related to an inflamed or "leaky" gut.
- Hypersensitivity reactions may play a role in causing IBS symptoms in a subset of patients.


World Journal of Gastroenterology

Food allergy in irritable bowel syndrome: The case of non-celiac wheat sensitivity

Pasquale Mansueto, Alberto D'Alcamo, Aurelio Seidita, Antonio Carroccio

Abstract

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IBS: A ROLE FOR IgG

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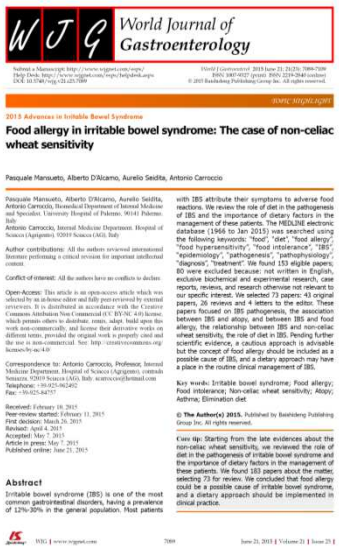
- Patients might have selective gut permeability to food allergens. The increase of food-specific IgG titers could be a specific reaction, rather than a non-specific response to increased gut mucosal permeability.
- Pending further scientific evidence, a cautious approach is advisable but the concept of food allergy should be included as a possible cause of IBS, and a dietary approach may have a place in the routine clinical management of IBS.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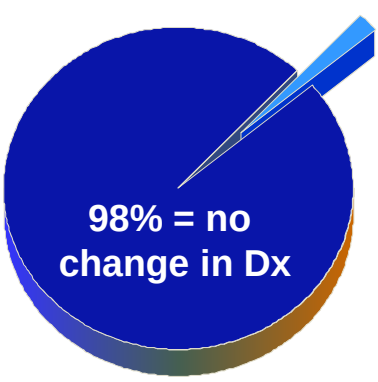
Pasquale Mansueto, Alberto D'Alcamo, Aurelio Seidita, Antonio Carroccio

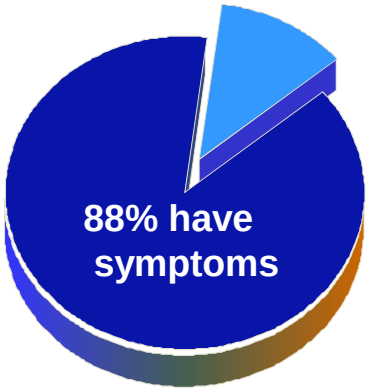
Abstract

IBS PROGNOSIS

Heaton, Thompson. Irritable Bowel Syndrome. 1999 Health Press, Oxford



n=398
median 7 years



n=5952
1-8 years

IgG EVALUATION

Mullin GE, Swift KM, Lipski L, Turnbull LK, Rampertab SD. Nutr Clin Pract. 2010 Apr;25(2):192-8. Review. PMID: 20413700

- Literature review (2010) evaluating the validity of tests used to assess food reactions
- Food hypersensitivity, food allergy, food sensitivity, food intolerance testing and adverse food reactions
- IgG–based testing showed promise, with clinically meaningful results
- Proven useful as a guide for elimination diets
- Further investigation into the clinical application is required

Techniques, Materials, Devices

Testing for Food Reactions: The Good, the Bad, and the Ugly

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An increasing number of commercial tests for food allergies are marketed to consumers and healthcare practitioners with tenuous claims. The aim of this article is to provide an evidence-based review of the tests and procedures that currently are used for patients with suspected food allergy. A systematic review of the literature evaluating the validity of tests and procedures used in food reactions was performed using conventional search engines (eg, PubMed, Ovid) as well as consumer sites (eg, Google, Bing). The National Library of Medicine Medical Subject Headings (MeSH) term *food hypersensitivity* was used along with *food allergy testing*, *food sensitivity testing*, *food intolerance testing*, and *adverse food reactions*. Of the results obtained, testing for immunoglobulin E (IgE)–mediated food allergy was best represented in PubMed. IgE-based testing continues to be the gold standard for suspected food allergies. Among modalities used by many conventional and alternative practitioners, immunoglobulin G (IgG)–based testing showed promise, with clinically meaningful results. It has been proven useful as a guide for elimination diets, with clinical impact for a variety of diseases. Mediator release testing and antigen leukocyte cellular antibody testing were only represented on consumer sites. Further investigation into the validity and the clinical application of these tests and procedures is required. Disclosing the basis for food reactions continues to present a diagnostic challenge, and testing for food allergies in the context of an appropriate clinical history is paramount to making the correct diagnosis. (*Nutr Clin Pract.* 2010;25:192-198)

Keywords: food sensitivity; food hypersensitivity; allergy and immunology; immunoglobulin E; immunoglobulin G; skin tests

More than 50 million Americans suffer from allergies yearly. Allergy, ranking as the sixth leading cause of chronic disease in the United States, was responsible for a staggering $18 billion U.S. healthcare expenditures in 2001.[1] Of those with allergies, up to 25% of adults report symptoms that may be related to foods. However, testing for food reactions can be challenging for both the patient and the clinician. Many healthcare practitioners have not received formal training in allergy and immunology and, as a result, may not be familiar with the proper application and interpretation of available test results.

In the context of the clinical history, both serum antibodies and allergy skin testing can be of considerable assistance in identifying (or excluding) the particular allergens that may be causing the patient's symptoms. Numerous tests are available on the market and are being used by conventional and alternative practitioners to assess for food reactions. There are 2 main categories of tests available: allergy skin tests (skin prick testing) and measurements of allergen-specific antibodies from blood. We review the various tests along with the published evidence for food reactions for the clinician.

Food Allergies

A food allergy is typically defined as an adverse immune response to the proteins in a food. This may occur as the result of a humoral response (immunoglobulin E [IgE] antibody), a cellular response (ie, T cells), or both. IgE-mediated food allergies affect between 1% and 2% of individuals in the U.S. and United Kingdom; specifically, these allergies are seen in 1% of adults and 6%–8% of children.[2] The prevalence of food allergies in American children seems to be on the rise, now affecting 3 million children, according to the Centers for Disease Control and Prevention.[3] Certain foods are more common allergens among specific age groups. Accounting for the majority of immediate food allergies in young children

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ALLERGY VS INTOLERANCE

Category	Allergy	Intolerance
Food	e.g. peanut, shellfish	e.g. gluten, dairy
Mediated	IgE antibodies	IgG antibodies
Rate of Response	Immediate after ingestion	Delayed up to 72 hrs after ingestion
Mechanism	Rapid production of histamine	Gradual formation of Ag/Ab complexes
Symptoms	Classical 'allergic' response	Many symptoms affecting any part of the body
Severity	Can be fatal	Not life-threatening
Permanence	Can last lifetime	Can be reversed of reduced by elimination of foods
Diagnosis	Often self-diagnosed	Rarely self- diagnosed
Skin-prick test	Positive	Negative

CHARACTERISTICS OF IgE & IgG MEDIATED REACTIONS TO FOOD

IgE Mediated - Allergy	IgG Mediated - Intolerance
Incidence is relatively low	Incidence is relatively high
Result from infrequent exposure	Result from frequent exposure
Very predictable short term symptoms	Chronic, variable symptoms
Offending food is usually obvious	Offending food frequently not suspected
Basophil/Mast Cell triggered reactions	Immune complex trigger
Histamine/Leukotriene release	Inflammatory response
Patient aware of offending food	Patient rarely aware of offending food
Antibody persistent for years	Antibody declines within one month
In vitro testing for serum IgE confirmation	In vitro testing for serum IgG shows food offenders and extent of gut permeability
Permanent food avoidance & immunotherapy	Eliminate then rotate food(s), heal gut, improve digestion

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