Omega Diagnostics

The role of IgG hypersensitivity in the pathogenesis and therapy of mental disorders

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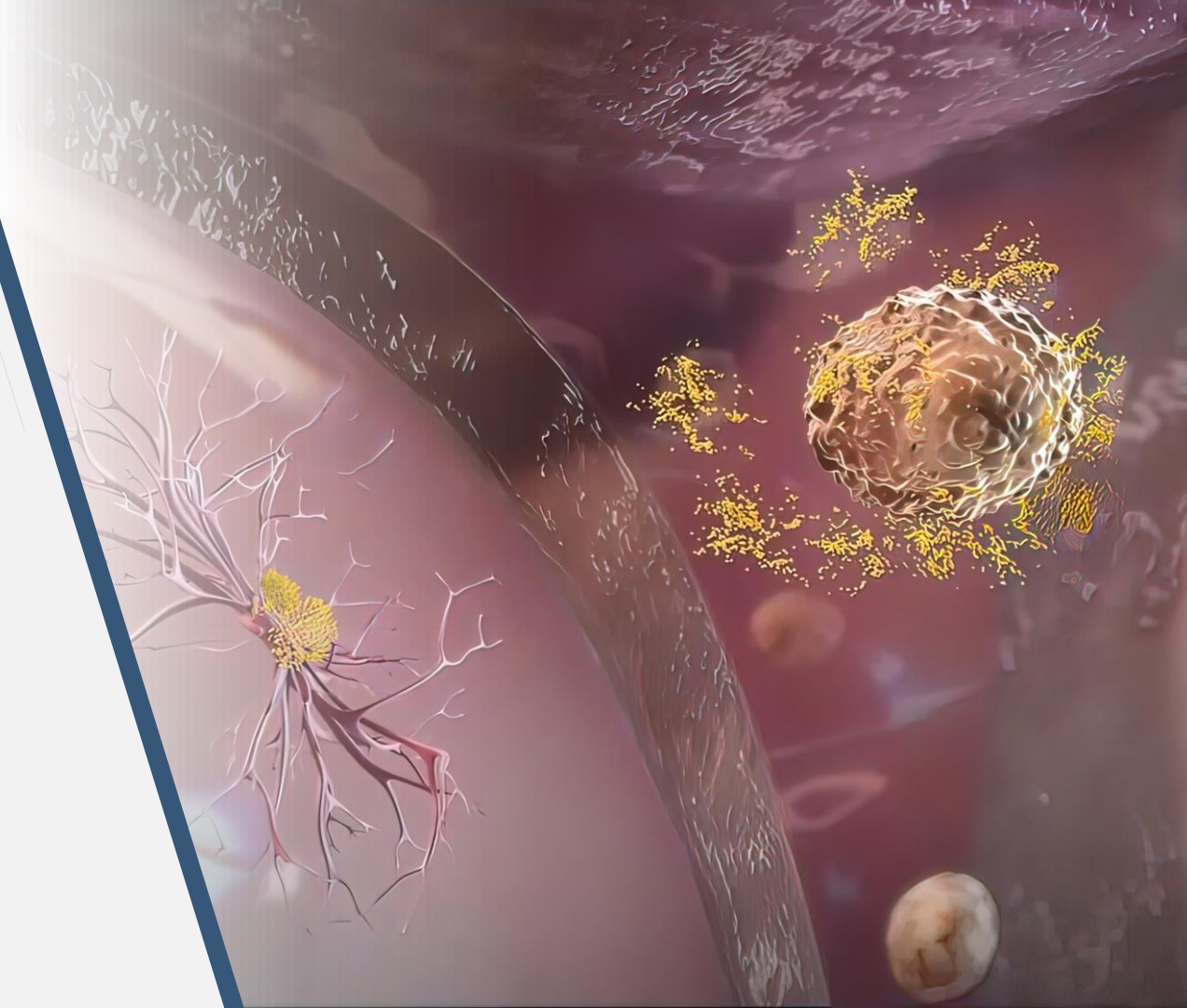


Introduction

- Some studies suggest that what we eat, and drink can affect how we feel.
- Food sensitivity is a prevalent problem that affects millions of individuals globally, resulting in IBS like symptoms, migraine and others.
- However, recent research indicates that food sensitivity can also significantly impact mental health.
- Although the relationship between the two is not fully understood, studies have found a correlation between food sensitivity and various mental health conditions such as anxiety, depression, ADHD, and autism.

Definition of Mental Health

Mental health refers to a person's overall psychological well-being, which encompasses their emotional, social, and cognitive functioning.

It is the state of being able to cope with the normal stresses of life, work productively, and contribute to society.

Mental health is just as important as physical health, and the two are often interrelated.

Types of Mental Illness

- There are many different types of mental illnesses, each with its own set of symptoms and causes. Some of the most common types of mental illnesses include:
  - Anxiety disorders
  - Mood disorders
  - Personality disorders
  - Psychotic disorders
  - Eating disorders
  - Substance abuse disorders
- It is important to note that mental illnesses can occur in combination, and a person may experience symptoms of more than one type of mental illness.

The Link Between Food Sensitivity & Mental Health

Food Sensitivity & Mental Health

- The evidence is increasing to support the link between food sensitivity and mental health.
- Difficulty in digesting certain foods can cause inflammation in the gut, which may affect the brain and contribute to mental health issues.
- In addition, some foods can directly affect the brain by altering neurotransmitter levels, which can impact mood, behaviour, and cognition.

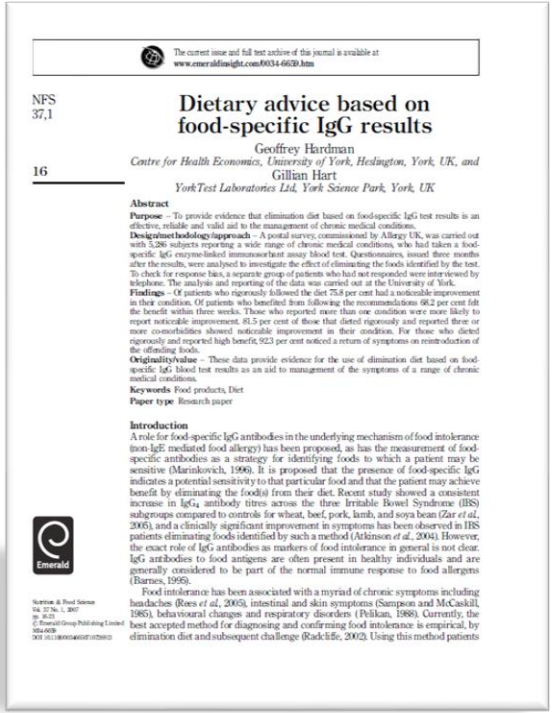
IgG Guided Diet

- Survey commissioned by Allergy UK – 5286 participants
- Questionnaire 3 months after IgG food test

76%
saw significant symptom improvement

68%
saw benefit within three weeks

92%
had symptoms return when reactive food added back to diet



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Dietary advice based on food-specific IgG results

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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 75.8 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

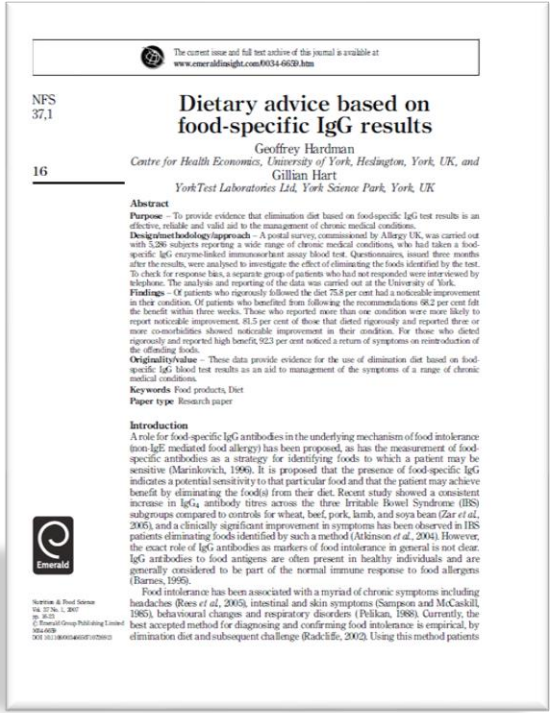
Nutrition & Food Science
Vol. 37 No. 1, 2007
pp. 16-23
© Emerald Group Publishing Limited
0034-6659
DOI 10.1108/00346650710725815

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

IgG Guided Diet

- Symptom relief varied by body system, with digestive symptoms like irritable bowel syndrome and psychological symptoms like anxiety and depression, showing the greatest improvement when reactive foods were removed.

Digestion	Lungs	Neurology	Skin	Joints	Mind
80% reported moderate to high benefit	72% reported moderate to high benefit	78% reported moderate to high benefit	76% reported moderate to high benefit	64% reported moderate to high benefit	81% reported moderate to high benefit



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Research Papers

- General IgG-mediated reactions
- Irritable Bowel Syndrome (IBS)
- Migraine
- Inflammation, obesity & arthritis
- Asthma / respiratory diseases
- IBD: Crohn's disease, Ulcerative Colitis
- Neurological
  - Schizophrenia
  - Depression
  - ASD

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Emerald
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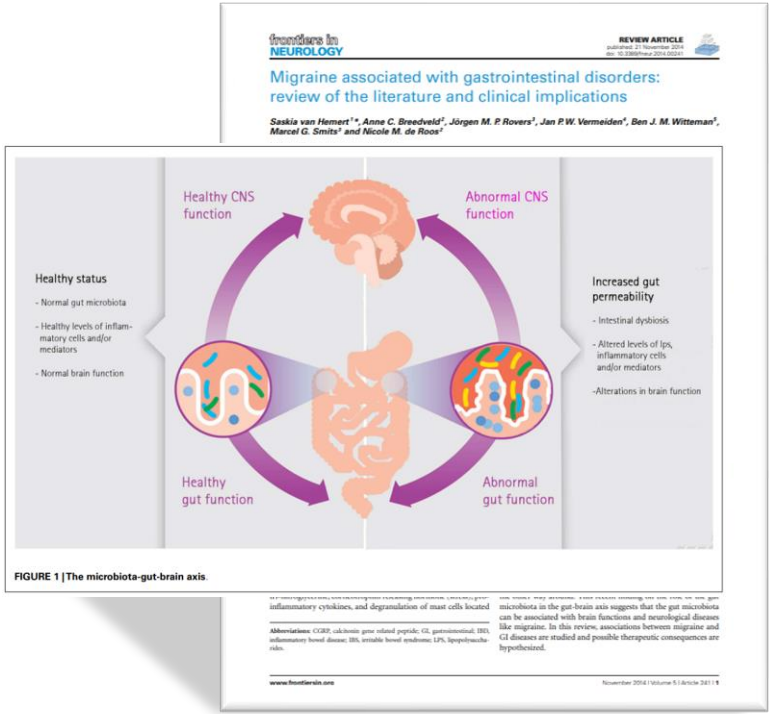
DOI 10.1108/00346650710725813

Food Sensitivity & Migraine

Migraine and the Gut

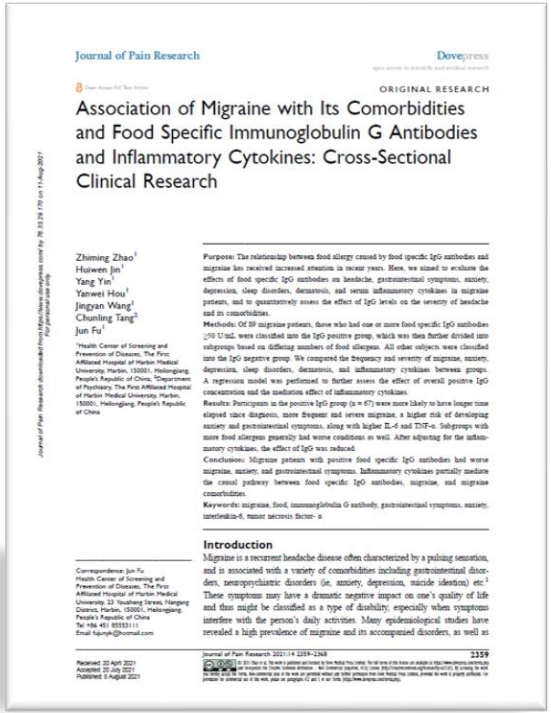
- An overview of the literature suggests that there is a strong relationship between GI disorders and migraine.
- One of the links between the gut and migraine are enhanced pro-inflammatory immune responses.
- Gut permeability and inflammation are bidirectionally related, increased permeability can cause inflammation, but inflammation can also cause increased gut permeability.



1. van Hemert S, Breedveld AC, Rovers JM, et al. Migraine associated with gastrointestinal disorders: review of the literature and clinical implications. Front Neurol. 2014;5:241. Published 2014 Nov 21. doi:10.3389/fneur.2014.00241

IgG & Migraine - Inflammation

- A number of studies have found a pro-inflammatory state in chronic migraine and episodic migraine patients, compared with the healthy controls.
- Increased levels of pro-inflammatory cytokines such as TNF-α and IL-6 are probable indicators of a low grade chronic inflammatory state caused by IgG-mediated food sensitivity.



Journal of Pain Research

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ORIGINAL RESEARCH

Association of Migraine with Its Comorbidities and Food Specific Immunoglobulin G Antibodies and Inflammatory Cytokines: Cross-Sectional Clinical Research

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Huiwen Jin[1]
Yang Yin[1]
Yanwei Hou[1]
Jingyan Wang[1]
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Purpose: The relationship between food allergy caused by food specific IgG antibodies and migraine has received increased attention in recent years. Here, we aimed to evaluate the effects of food specific IgG antibodies on headache, gastrointestinal symptoms, anxiety, depression, sleep disorders, dermatosis, and serum inflammatory cytokines in migraine patients, and to quantitatively assess the effect of IgG levels on the severity of headache and its comorbidities.

Methods: Of 89 migraine patients, those who had one or more food specific IgG antibodies ≥50 U/mL were classified into the IgG positive group, which was then further divided into subgroups based on differing numbers of food allergens. All other subjects were classified into the IgG negative group. We compared the frequency and severity of migraine, anxiety, depression, sleep disorders, dermatosis, and inflammatory cytokines between groups. A regression model was performed to further assess the effect of overall positive IgG concentration and the mediation effect of inflammatory cytokines.

Results: Participants in the positive IgG group (n = 67) were more likely to have longer time elapsed since diagnosis, more frequent and severe migraine, a higher risk of developing anxiety and gastrointestinal symptoms, along with higher IL-6 and TNF-α. Subgroups with more food allergens generally had worse conditions as well. After adjusting for the inflammatory cytokines, the effect of IgG was reduced.

Conclusion: Migraine patients with positive food specific IgG antibodies had worse migraine, anxiety, and gastrointestinal symptoms. Inflammatory cytokines partially mediate the causal pathway between food specific IgG antibodies, migraine, and migraine comorbidities.

Keywords: migraine, food, immunoglobulin G antibody, gastrointestinal symptoms, anxiety, interleukin-6, tumor necrosis factor- α

Introduction

Migraine is a recurrent headache disease often characterized by a pulsing sensation, and is associated with a variety of comorbidities including gastrointestinal disorders, neuropsychiatric disorders (ie, anxiety, depression, suicide ideation) etc.[1] These symptoms may have a dramatic negative impact on one's quality of life and thus might be classified as a type of disability, especially when symptoms interfere with the person's daily activities. Many epidemiological studies have revealed a high prevalence of migraine and its accompanied disorders, as well as

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Received: 25 April 2021
Accepted: 20 July 2021
Published: 5 August 2021

Journal of Pain Research 2021:14 2359–2368

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1. Zhao Z, Jin H, Yin Y, et al. Association of Migraine with Its Comorbidities and Food Specific Immunoglobulin G Antibodies and Inflammatory Cytokines: Cross-Sectional Clinical Research. J Pain Res. 2021;14:2359-2368. Published 2021 Aug 5. doi:10.2147/JPR.S316619

IgG & Migraine - Inflammation

Results: Participants in the positive IgG group:

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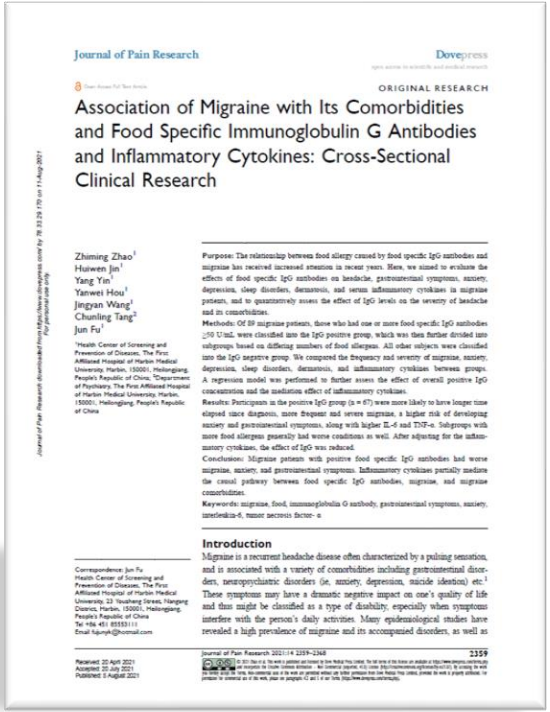

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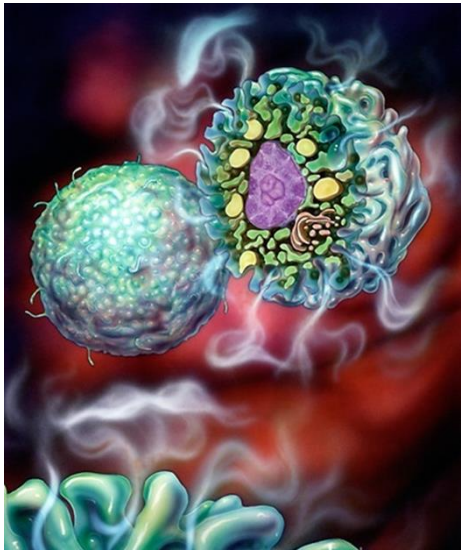
Mast Cells & Food Sensitivity

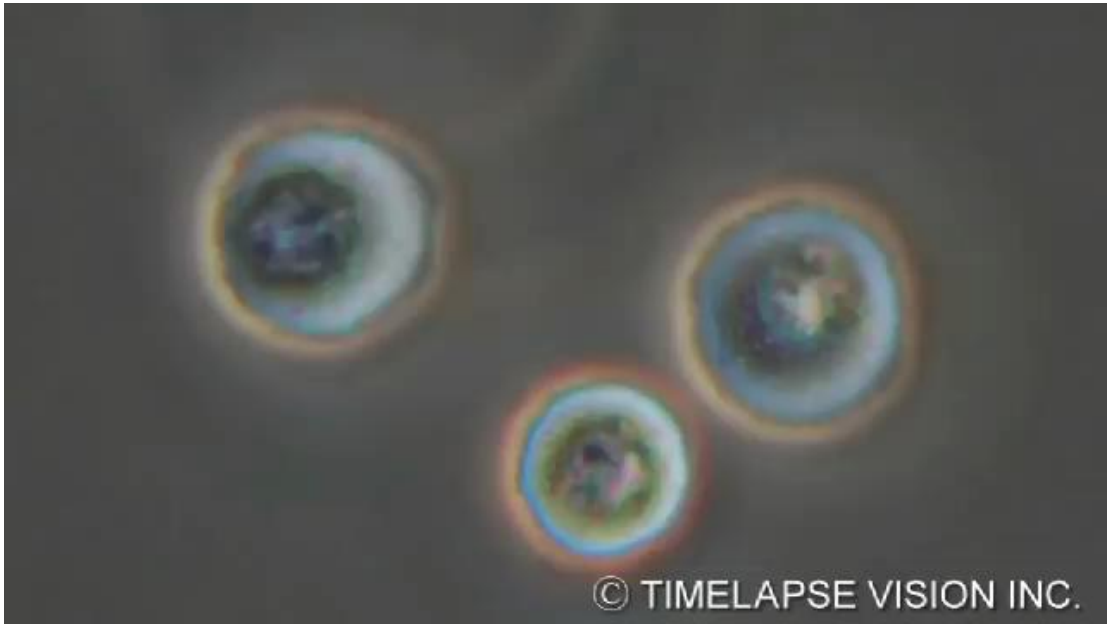
Mast Cells and food specific IgG

- Mast cells have a widespread distribution and are found predominantly at barrier sites of the body such as the skin, gastrointestinal, respiratory and urinary tracts.
- Recently, it has been realised that mast cells are multifunctional immune cells implicated in several health and disease conditions.
- They play a pivotal role in innate and adaptive immunity and immune tolerance.
- They also have an important role in the pathogenesis of several disorders.



1. da Silva EZ, Jamur MC, Oliver C. Mast cell function: a new vision of an old cell. J Histochem Cytochem. 2014;62(10):698-738. doi:10.1369/0022155414545334
2. Jönsson F, Daëron M. Mast cells and company. Front Immunol. 2012;3:16. Published 2012 Feb 20. doi:10.3389/fimmu.2012.00016

Activated Mast Cell Degranulation

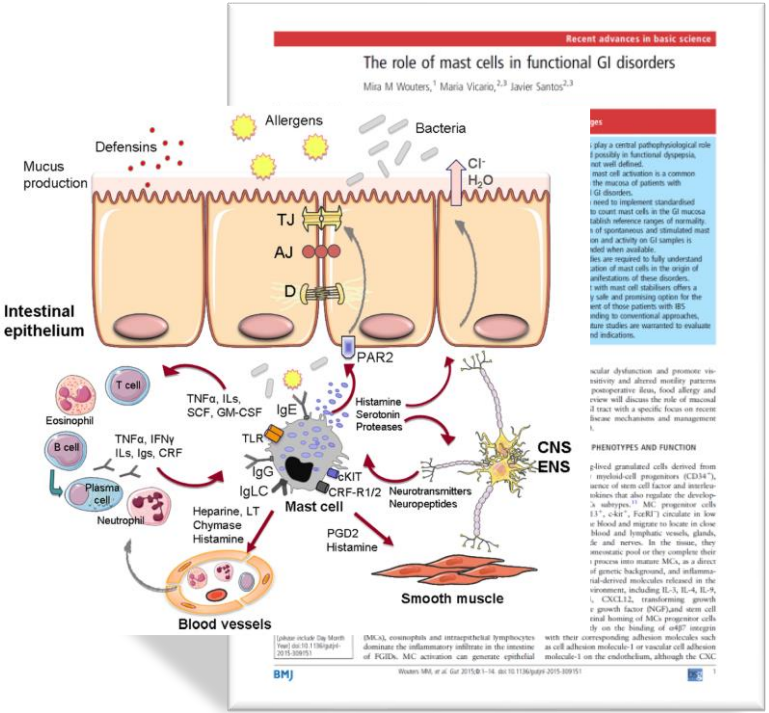


- Mast cells generate and release multi-potent molecules, such as:
  - histamine, proteases,
  - leukotrienes, heparin,
  - many cytokines, chemokines, and growth factors,
- They have the capacity to be involved in regulating the functions of many organs and tissues

1. Timelapse Vision Inc. https://www.youtube.com/watch?v=VT7knZ6_8rk

Mast Cells in GI Disorders

- Adverse reactions to food, including some types of food sensitivity, may occur through IgG-mediated sensitisation of Mast Cells.
- Mast Cell interactions in the regulation of barrier function, include epithelial permeability (through Tight Junction modulation)



1. Wouters MM, Vicario M, Santos J. The role of mast cells in functional GI disorders. Gut. 2016;65(1):155-168. doi:10.1136/gutjnl-2015-309151

Stress & Mast Cell Activation

- On the other hand, it is well known that stressful life events are associated with onset or exacerbation of IBS symptoms.
- CRH which is induced by psychological stress, is one of the factors for mast cell degranulation.
- Increased intestinal permeability via CRH-mediated mast cell activation due to acute psychological stress has been shown.

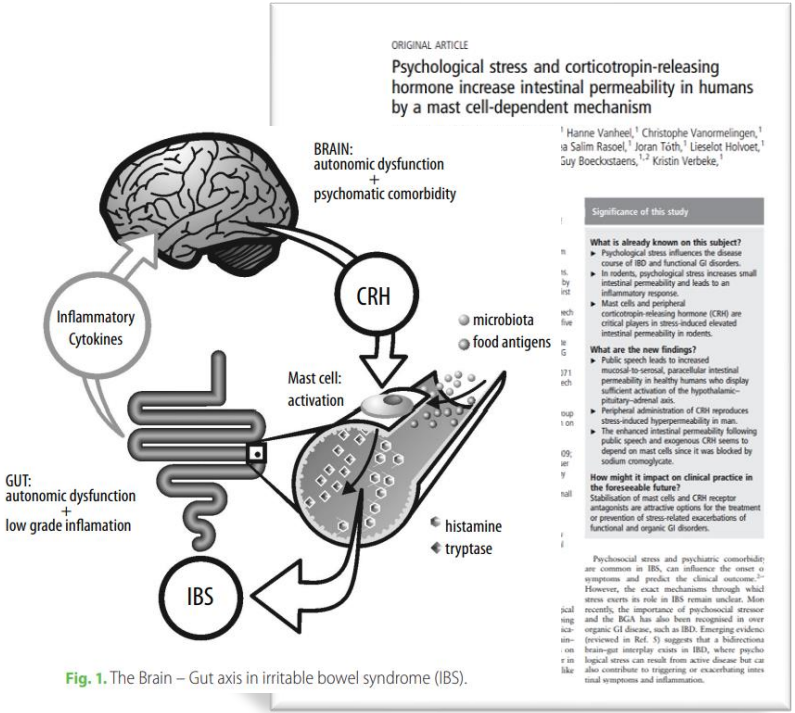
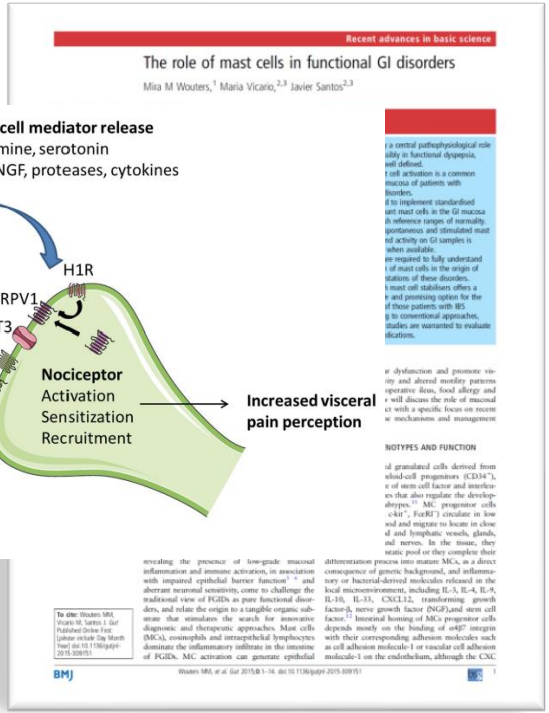


Fig. 1. The Brain – Gut axis in irritable bowel syndrome (IBS).

1. Vanuytsel T, van Wanrooy S, Vanheel H, et al. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. Gut. 2014;63(8):1293-1299. doi:10.1136/gutjnl-2013-305690

Mast Cells in Neuronal Activation

- MCs and nerves communicate bidirectionally, thereby modulating peristalsis and pain signalling.
- The release of bioactive, pro-inflammatory, mediators by mast cells results in a variety of neuronal effects.
- Mast cells also affect disruption/permeability of the blood brain barrier enabling toxin and immune cell entry exacerbating an inflammatory microenvironment.



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Mast Cells in Neurodegenerative Disease

- Neuroinflammation, which is now recognised as a primary pathological component of diseases such as multiple sclerosis, is gaining acceptance as an underlying component of most, if not all, neurodegenerative diseases.
- Whereas past focus has predominantly cantered on glial cells of the CNS, recently mast cells have emerged as potential key players in both neuroinflammation and neurodegenerative diseases.

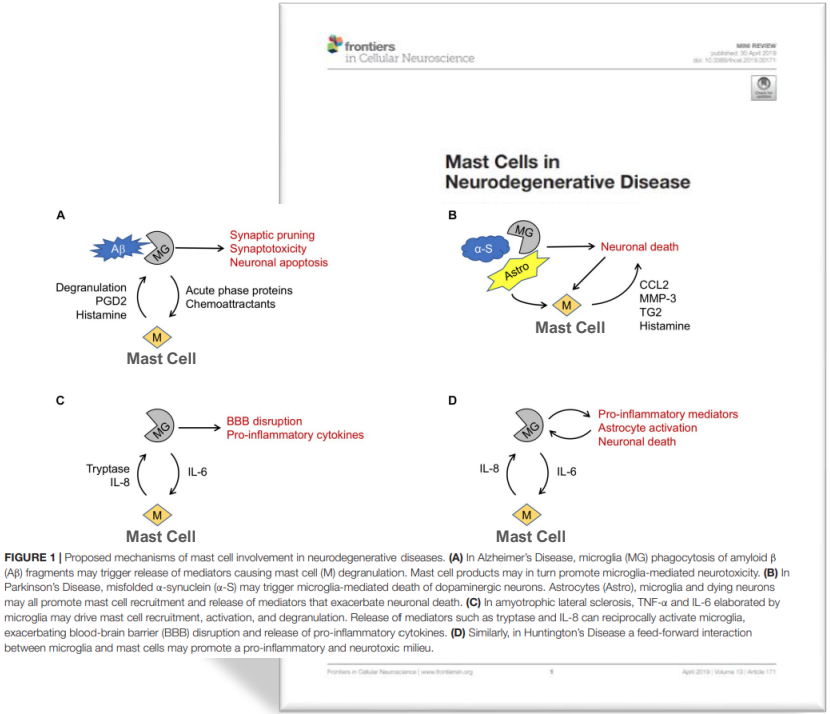

FIGURE 1 | Proposed mechanisms of mast cell involvement in neurodegenerative diseases. **(A)** In Alzheimer's Disease, microglia (MG) phagocytosis of amyloid β (Aβ) fragments may trigger release of mediators causing mast cell (M) degranulation. Mast cell products may in turn promote microglia-mediated neurotoxicity. **(B)** In Parkinson's Disease, misfolded α-synuclein (α-S) may trigger microglia-mediated death of dopaminergic neurons. Astrocytes (Astro), microglia and dying neurons may all promote mast cell recruitment and release of mediators that exacerbate neuronal death. **(C)** In amyotrophic lateral sclerosis, TNF-α and IL-6 elaborated by microglia may drive mast cell recruitment, activation, and degranulation. Release of mediators such as tryptase and IL-8 can reciprocally activate microglia, exacerbating blood-brain barrier (BBB) disruption and release of pro-inflammatory cytokines. **(D)** Similarly, in Huntington's Disease a feed-forward interaction between microglia and mast cells may promote a pro-inflammatory and neurotoxic milieu.

1. Jones MK, Nair A, Gupta M. Mast Cells in Neurodegenerative Disease. Front Cell Neurosci. 2019 Apr 30;13:171. doi: 10.3389/fncel.2019.00171. PMID: 31133804; PMCID: PMC6524694.

Food Sensitivity & Depression

The role of food sensitivity in the pathogenesis depressive disorders

- Depressive episodes are associated not only with changes in neurotransmission in the central nervous system, but also may lead to structural changes in the brain through neuroendocrine, inflammatory, and immunological mechanisms.
- The aim of this article is to present a new hypothesis connecting the inflammatory theory of depression with IgG food hypersensitivity and leaky gut syndrome.

The role of IgG hypersensitivity in the pathogenesis and therapy of depressive disorders

Hanna Karakuła-Juchnowicz[1], Patrycja Szachta[2], Aneta Opolska[3], Justyna Morylowska-Topolska[1], Mirosława Gałecka[2], Dariusz Juchnowicz[4], Paweł Krukow[1], Lasik Zofia[2]

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Depressive episodes are associated not only with changes in neurotransmission in the central nervous system, but also may lead to structural changes in the brain through neuroendocrine, inflammatory, and immunological mechanisms. The aim of this article is to present a new hypothesis connecting the inflammatory theory of depression with IgG food hypersensitivity and leaky gut syndrome. This new potential pathway that may mediate the pathogenesis of depression implies the existence of subsequent developmental stages. Overproduction of zonulin triggered, for example, by gliadin through activation of the epidermal growth factor receptor and protease-activated receptor causes loosening of the tight junction barrier and an increase in permeability of the gut wall ('leaky gut'). This results in a process allowing larger molecules that would normally stay in the gut to cross into the bloodstream and in the induction of IgG-dependent food sensitivity. This condition causes an increased immune response and consequently induces the release of proinflammatory cytokines, which in turn may lead to the development of depressive symptoms. It seems advisable to assess the intestinal permeability using as a marker, for example, zonulin and specific IgG concentrations against selected nutritional components in patients with depression. In the case of increased IgG concentrations, the implementation of an elimination-rotation diet may prove to be an effective method of reducing inflammation. This new paradigm in the pathogenesis of depressive disorders linking leaky gut, IgG-dependent food sensitivity, inflammation, and depression is promising, but still needs further studies to confirm this theory.

Keywords: Depression, Leaky gut, IgG hypersensitivity, Zonulin, Inflammatory theory of depression, Gluten sensitivity

Introduction

Depression is a heterogeneous psychiatric disorder with multifactorial aetiology and therefore needs improved integration models, based on behavioural studies, sociology, and neuroscience to better reflect both the complexity and variety of mood disorders.[1] Among the factors deserving special attention are biological ones, including psychoneuroendocrinology and psychoimmunology, posing a bridge between strictly biological and psychological approaches.[2] More and more evidence indicates that depressive episodes are associated not only with changes in neurotransmission in the central nervous system (CNS), but also may lead to structural changes in the brain through neuroendocrine, inflammatory, and immunological mechanisms.[3–5] Different factors potentially connected with systemic inflammation in depression are taken into consideration; these include psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopy, dental caries, sleep, and Vitamin D deficiency.[6]

The aim of this article is to present a new hypothesis connecting the inflammatory theory of depression with IgG food hypersensitivity and leaky gut syndrome (LGS).

Inflammatory theory of depression

Among many theories of depression, the cytokine (macrophage) theory of depression, first demonstrated in 1991 by Robert Smith,[7] has aroused much interest among researchers. It is assumed that changes in behaviour, typical of depression, are the result of the

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DOI 10.1179/1476830514Y.0000000158
Nutritional Neuroscience 2014 VOL 0 NO 0 1

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The role of food sensitivity in the pathogenesis depressive disorders

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The role of IgG hypersensitivity in the pathogenesis and therapy of depressive disorders

Hanna Karakuła-Juchnowicz[1], Patrycja Szachta[2], Aneta Opolska[3], Justyna Morylowska-Topolska[1], Mirosława Gałecka[2], Dariusz Juchnowicz[4], Paweł Krukow[1], Lasik Zofia[2]

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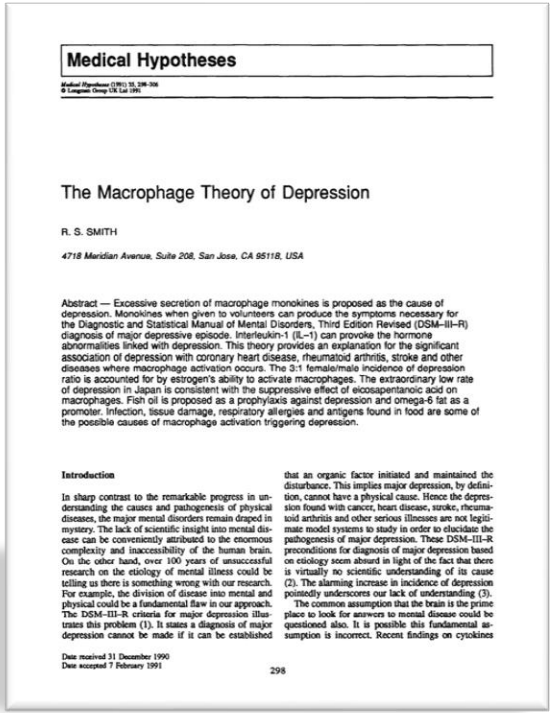
Inflammatory theory of depression

- Among many theories of depression, the cytokine (macrophage) theory of depression, first demonstrated in 1991 by Robert Smith, has aroused much interest among researchers.
- It is assumed that changes in behaviour, typical of depression, are the result of the interaction of proinflammatory cytokines produced in the peripheral and/or CNS with the neuroendocrine system.
- This leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis.



Medical Hypotheses

The Macrophage Theory of Depression

R. S. SMITH

4718 Meridian Avenue, Suite 208, San Jose, CA 95118, USA

Abstract — Excessive secretion of macrophage monokines is proposed as the cause of depression. Monokines when given to volunteers can produce the symptoms necessary for the Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised (DSM–III–R) diagnosis of major depressive episode. Interleukin-1 (IL–1) can provoke the hormone abnormalities linked with depression. This theory provides an explanation for the significant association of depression with coronary heart disease, rheumatoid arthritis, stroke and other diseases where macrophage activation occurs. The 3:1 female/male incidence of depression ratio is accounted for by estrogen's ability to activate macrophages. The extraordinary low rate of depression in Japan is consistent with the suppressive effect of eicosapentanoic acid on macrophages. Fish oil is proposed as a prophylaxis against depression and omega-6 fat as a promoter. Infection, tissue damage, respiratory allergies and antigens found in food are some of the possible causes of macrophage activation triggering depression.

Introduction

In sharp contrast to the remarkable progress in understanding the causes and pathogenesis of physical diseases, the major mental disorders remain draped in mystery. The lack of scientific insight into mental disease can be conveniently attributed to the enormous complexity and inaccessibility of the human brain. On the other hand, over 100 years of unsuccessful research on the etiology of mental illness could be telling us there is something wrong with our research. For example, the division of disease into mental and physical could be a fundamental flaw in our approach. The DSM–III–R criteria for major depression illustrates this problem (1). It states a diagnosis of major depression cannot be made if it can be established that an organic factor initiated and maintained the disturbance. This implies major depression, by definition, cannot have a physical cause. Hence the depression found with cancer, heart disease, stroke, rheumatoid arthritis and other serious illnesses are not legitimate model systems to study in order to elucidate the pathogenesis of major depression. These DSM–III–R preconditions for diagnosis of major depression based on etiology seem absurd in light of the fact that there is virtually no scientific understanding of its cause (2). The alarming increase in incidence of depression pointedly underscores our lack of understanding (3).

The common assumption that the brain is the prime place to look for answers to mental disease could be questioned also. It is possible this fundamental assumption is incorrect. Recent findings on cytokines

Date received 31 December 1990
Date accepted 7 February 1991

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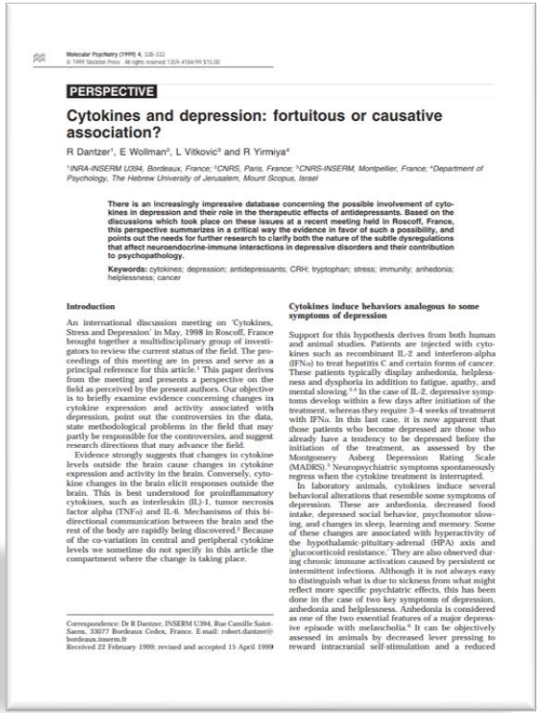
Cytokines & Depression

- Cytokines are a large group of more than 100 regulatory proteins, proinflammatory and anti-inflammatory mediators, which can be considered immune regulating hormones that regulate growth, proliferation, and cell activity.
- The increase in the proinflammatory cytokine concentration and their effects on the CNS contribute to the development of neuropsychological and somatic depressive symptoms.



Molecular Psychiatry (1999) 4, 328–332

PERSPECTIVE

Cytokines and depression: fortuitous or causative association?

R Dantzer[1], E Wollman[2], L Vitkovic[3] and R Yirmiya[4]

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There is an increasingly impressive database concerning the possible involvement of cytokines in depression and their role in the therapeutic effects of antidepressants. Based on the discussions which took place on these issues at a recent meeting held in Roscoff, France, this perspective summarizes in a critical way the evidence in favor of such a possibility, and points out the needs for further research to clarify both the nature of the subtle dysregulations that affect neuroendocrine-immune interactions in depressive disorders and their contribution to psychopathology.

Keywords: cytokines; depression; antidepressants; CRH; tryptophan; stress; immunity; anhedonia; helplessness; cancer

Introduction

An international discussion meeting on 'Cytokines, Stress and Depression' in May, 1998 in Roscoff, France brought together a multidisciplinary group of investigators to review the current status of the field. The proceedings of this meeting are in press and serve as a principal reference for this article.[1] This paper derives from the meeting and presents a perspective on the field as perceived by the present authors. Our objective is to briefly examine evidence concerning changes in cytokine expression and activity associated with depression, point out the controversies in the data, state methodological problems in the field that may partly be responsible for the controversies, and suggest research directions that may advance the field.

Evidence strongly suggests that changes in cytokine levels outside the brain cause changes in cytokine expression and activity in the brain. Conversely, cytokine changes in the brain elicit responses outside the brain. This is best understood for proinflammatory cytokines, such as interleukin (IL)-1, tumor necrosis factor alpha ($TNF\alpha$) and IL-6. Mechanisms of this bidirectional communication between the brain and the rest of the body are rapidly being discovered.[2] Because of the co-variation in central and peripheral cytokine levels we sometime do not specify in this article the compartment where the change is taking place.

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Received 22 February 1999; revised and accepted 15 April 1999

Cytokines induce behaviors analogous to some symptoms of depression

Support for this hypothesis derives from both human and animal studies. Patients are injected with cytokines such as recombinant IL-2 and interferon-alpha (IFNα) to treat hepatitis C and certain forms of cancer. These patients typically display anhedonia, helplessness and dysphoria in addition to fatigue, apathy, and mental slowing.[3–6] In the case of IL-2, depressive symptoms develop within a few days after initiation of the treatment, whereas they require 3–4 weeks of treatment with IFNs. In this last case, it is now apparent that those patients who become depressed are those who already have a tendency to be depressed before the initiation of the treatment, as assessed by the Montgomery Asberg Depression Rating Scale (MADRS).[5] Neuropsychiatric symptoms spontaneously regress when the cytokine treatment is interrupted.

In laboratory animals, cytokines induce several behavioral alterations that resemble some symptoms of depression. These are anhedonia, decreased food intake, depressed social behavior, psychomotor slowing, and changes in sleep, learning and memory. Some of these changes are associated with hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid resistance.[7] They are also observed during chronic immune activation caused by persistent or intermittent infections. Although it is not always easy to distinguish what is due to sickness from what might reflect more specific psychiatric effects, this has been done in the case of two key symptoms of depression, anhedonia and helplessness. Anhedonia is considered as one of the two essential features of a major depressive episode with melancholia.[8] It can be objectively assessed in animals by decreased lever pressing to reward intracranial self-stimulation and a reduced

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Cytokines & Depression

- Many studies conducted so far have shown elevated levels of proinflammatory cytokines in the serum of patients with a major depressive episode.
- In these studies, multiple cytokines such as tumour necrosis factor (TNF-α), interferon-γ, interleukin IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10 were taken into account.
- Two recent meta-analyses confirmed the importance of higher interleukin-1, -6, and TNF-α levels in the serum of patients with depression.
- Elevated levels of these cytokines in the cerebrospinal fluid of depressive patients were also shown in numerous studies.

A Meta-Analysis of Cytokines in Major Depression

Yekta Dowlati, Nathan Herrmann, Walter Swardfager, Helena Liu, Lauren Sham, Elyse K. Reim, and Krista L. Lanctôt

Background: Major depression occurs in 4.4% to 20% of the general population. Studies suggest that major depression is accompanied by immune dysregulation and activation of the inflammatory response system (IRS). Our objective was to quantitatively summarize the data on concentrations of specific cytokines in patients diagnosed with a major depressive episode and controls.

Methods: We performed a meta-analysis of studies measuring cytokine concentration in patients with major depression, with a database search of the English literature (to August 2009) and a manual search of references.

Results: Twenty-four studies involving unstimulated measurements of cytokines in patients meeting DSM criteria for major depression were included in the meta-analysis: 13 for tumor necrosis factor (TNF)-α, 9 for interleukin (IL)-1β, 16 for IL-6, 5 for IL-4, 5 for IL-2, 4 for IL-8, 6 for IL-10, and 4 for interferon (IFN)-γ. There were significantly higher concentrations of TNF-α ($p < .00001$), weighted mean difference (WMD) (95% confidence interval) 3.97 pg/mL (2.24 to 5.71), in depressed subjects compared with control subjects (438 depressed/350 nondepressed). Also, IL-6 concentrations were significantly higher ($p < .00001$) in depressed subjects compared with control subjects (492 depressed/400 nondepressed) with an overall WMD of 1.78 pg/mL (1.23 to 2.33). There were no significant differences among depressed and nondepressed subjects for the other cytokines studied.

Conclusions: This meta-analysis reports significantly higher concentrations of the proinflammatory cytokines TNF-α and IL-6 in depressed subjects compared with control subjects. While both positive and negative results have been reported in individual studies, this meta-analytic result strengthens evidence that depression is accompanied by activation of the IRS.

Key Words: Anti-inflammatory cytokines, depression, meta-analysis, proinflammatory cytokine

Major depression is an important public health issue (1) with a lifetime prevalence of 4.4% to 20% in the general population (2). The DSM-IV (3) stipulates that at least five of nine criteria depressive symptoms must be present, including either sadness or anhedonia, for at least 2 weeks to diagnose a major depressive episode. Depressive symptoms may also include fatigue, feelings of worthlessness or guilt, lack of ability to concentrate, suicidal ideation, or significant changes in weight or sleep. The impact of depression on quality of life is comparable with or greater than that of chronic medical illness (4,5), depending on the severity of symptoms (5), and depression is considered disabling to psychosocial function (6).

The monoamine hypothesis is the most extensively studied etiologic theory of depression (7,8) and virtually all available antidepressants act, at least in part, by increasing monoaminergic transmission. However, meta-analyses suggest that these agents are effective for only one half to one third of patients suffering from depression (9–13) and they often produce side effects that can sometimes limit their usefulness (11,12,14). Those studies underscore the urgent need for alternative or corollary hypotheses to help guide the development of more effective or adjunctive treatment strategies.

Numerous studies have suggested that major depression is accompanied by immune dysregulation. Specifically, activation of the inflammatory response system (IRS) has been demonstrated by increased production of proinflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, the soluble IL-6 receptor (IL-6R), and the IL-1 receptor antagonist (IL-1RA) (15–25). These findings may be clinically important because proinflammatory cytokines can contribute directly to the development of depressive symptoms (26). Proinflammatory cytokines have been shown to induce stress-reactive neuroendocrine and central neurotransmitter changes reminiscent of those in depression (26), and it has been demonstrated that immunotherapy with IFN-α can precipitate depression (27).

Although an association between IRS activation and depression has been documented in individual studies (17–20,28) of various cytokines, the association is not consistently significant in all studies or for all cytokines (29–31). Thus, a generalizable pattern of immune dysfunction in major depression remains to be defined. However, results from individual studies can be combined quantitatively using meta-analytical techniques to improve the strength of the evidence. Therefore, this study reports the results of a meta-analysis conducted to determine whether the concentrations of specific cytokines differ quantitatively between patients diagnosed with a major depressive episode and control subjects.

Methods and Materials

Only original studies that measured cytokine concentrations in depressed and nondepressed subjects were included in the meta-analysis. Studies were included if subjects met DSM-III-R or DSM-IV (3) criteria for major depression. Studies were included if they were published in English, if cytokine concentrations were measured in subjects free of major medical comorbidities (cancer, heart disease, etc.), if subjects were free of antidepressant medications for at least 1 week before the initiation of the study, if psychiatrically healthy subjects were used as control subjects, and if cytokine concentrations were measured in the unstimulated state and in the morning. Studies looking at stimulated levels of cytokines were excluded because they differ in

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Received Jun 9, 2009; revised Aug 31, 2009; accepted Sep 26, 2009.

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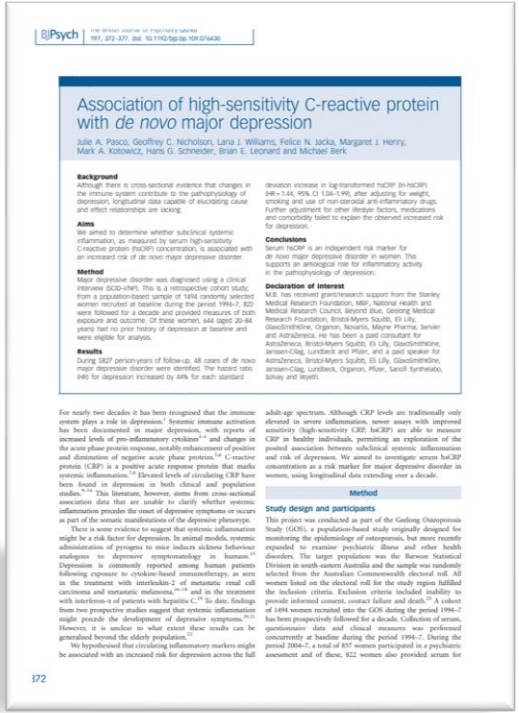
C-Reactive Protein & Depression

- The importance of elevated C-reactive protein is highlighted in the absence of clearly consistent findings with regard to other cytokines.
- An interesting phenomenon, confirming the link between the inflammatory process and depression symptoms, is the co-occurrence of depression with inflammatory diseases such as:
  - asthma, COPD
  - diabetes
  - allergy
  - rheumatoid arthritis



BJPsych | The British Journal of Psychiatry (2010) 197, 372–377. doi: 10.1192/bjp.bp.109.076430

Association of high-sensitivity C-reactive protein with *de novo* major depression

Julie A. Pasco, Geoffrey C. Nicholson, Lana J. Williams, Felice N. Jacka, Margaret J. Henry, Mark A. Kotowicz, Hans G. Schneider, Brian E. Leonard and Michael Berk

Background
Although there is cross-sectional evidence that changes in the immune system contribute to the pathophysiology of depression, longitudinal data capable of elucidating cause and effect relationships are lacking.

Aims
We aimed to determine whether subclinical systemic inflammation, as measured by serum high-sensitivity C-reactive protein (hsCRP) concentration, is associated with an increased risk of *de novo* major depressive disorder.

Method
Major depressive disorder was diagnosed using a clinical interview (SCID-I/NP). This is a retrospective cohort study, from a population-based sample of 1494 randomly selected women recruited at baseline during the period 1994–7. 822 were followed for a decade and provided measures of both exposure and outcome. Of these women, 644 (aged 20–84 years) had no prior history of depression at baseline and were eligible for analysis.

Results
During 5827 person-years of follow-up, 48 cases of *de novo* major depressive disorder were identified. The hazard ratio (HR) for depression increased by 44% for each standard deviation increase in log-transformed hsCRP (ln-hsCRP) (HR=1.44, 95% CI 1.04–1.99), after adjusting for weight, smoking and use of non-steroidal anti-inflammatory drugs. Further adjustment for other lifestyle factors, medications and comorbidity failed to explain the observed increased risk for depression.

Conclusions
Serum hsCRP is an independent risk marker for *de novo* major depressive disorder in women. This supports an aetiological role for inflammatory activity in the pathophysiology of depression.

Declaration of interest
M.B. has received grant/research support from the Stanley Medical Research Foundation, MBF, National Health and Medical Research Council, Beyond Blue, Geelong Medical Research Foundation, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma, Servier and AstraZeneca. He has been a paid consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck and Pfizer, and a paid speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Organon, Pfizer, Sanofi Synthelabo, Solvay and Wyeth.

For nearly two decades it has been recognised that the immune system plays a role in depression.[1] Systemic immune activation has been documented in major depression, with reports of increased levels of pro-inflammatory cytokines[2–4] and changes in the acute phase protein response, notably enhancement of positive and diminution of negative acute phase proteins.[5,6] C-reactive protein (CRP) is a positive acute response protein that marks systemic inflammation.[7,8] Elevated levels of circulating CRP have been found in depression in both clinical and population studies.[9–11] This literature, however, stems from cross-sectional association data that are unable to clarify whether systemic inflammation precedes the onset of depressive symptoms or occurs as part of the somatic manifestations of the depressive phenotype.

There is some evidence to suggest that systemic inflammation might be a risk factor for depression. In animal models, systemic administration of pyrogens to mice induces sickness behaviour analogous to depressive symptomatology in humans.[12] Depression is commonly reported among human patients following exposure to cytokine-based immunotherapy, as seen in the treatment with interleukin-2 of metastatic renal cell carcinoma and metastatic melanoma,[13–15] and in the treatment with interferon-α of patients with hepatitis C.[16] To date, findings from two prospective studies suggest that systemic inflammation might precede the development of depressive symptoms.[10,11] However, it is unclear to what extent these results can be generalised beyond the elderly population.[22]

We hypothesised that circulating inflammatory markers might be associated with an increased risk for depression across the full adult-age spectrum. Although CRP levels are traditionally only elevated in severe inflammation, newer assays with improved sensitivity (high-sensitivity CRP, hsCRP) are able to measure CRP in healthy individuals, permitting an exploration of the posited association between subclinical systemic inflammation and risk of depression. We aimed to investigate serum hsCRP concentration as a risk marker for major depressive disorder in women, using longitudinal data extending over a decade.

Method

Study design and participants

This project was conducted as part of the Geelong Osteoporosis Study (GOS), a population-based study originally designed for monitoring the epidemiology of osteoporosis, but more recently expanded to examine psychiatric illness and other health disorders. The target population was the Barwon Statistical Division in south-eastern Australia and the sample was randomly selected from the Australian Commonwealth electoral roll. All women listed on the electoral roll for the study region fulfilled the inclusion criteria. Exclusion criteria included inability to provide informed consent, contact failure and death.[23] A cohort of 1494 women recruited into the GOS during the period 1994–7 has been prospectively followed for a decade. Collection of serum, questionnaire data and clinical measures was performed concurrently at baseline during the period 1994–7. During the period 2004–7, a total of 857 women participated in a psychiatric assessment and of these, 822 women also provided serum for

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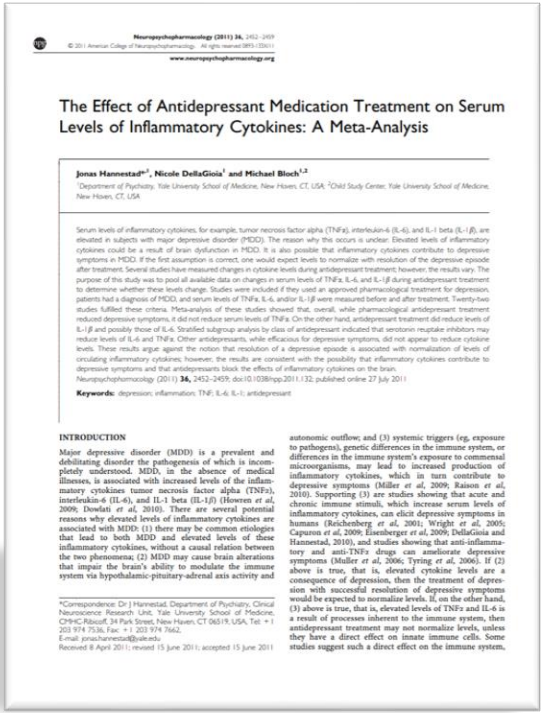
Cytokines & Depression

- Further evidence on the important role of proinflammatory cytokines in the pathogenesis of depression is provided by a study demonstrating that the concentration of inflammatory cytokines correlates positively with the severity of depressive symptoms.
- While antidepressive treatment and clinical improvement leads to reduction of proinflammatory cytokine concentration in patients with depression.



Neuropsychopharmacology (2011) 36, 2452–2459

www.neuropsychopharmacology.org

The Effect of Antidepressant Medication Treatment on Serum Levels of Inflammatory Cytokines: A Meta-Analysis

Jonas Hannestad[*,1], Nicole DellaGioia[1] and Michael Bloch[1,2]

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Serum levels of inflammatory cytokines, for example, tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and IL-1 beta (IL-1β), are elevated in subjects with major depressive disorder (MDD). The reason why this occurs is unclear. Elevated levels of inflammatory cytokines could be a result of brain dysfunction in MDD. It is also possible that inflammatory cytokines contribute to depressive symptoms in MDD. If the first assumption is correct, one would expect levels to normalize with resolution of the depressive episode after treatment. Several studies have measured changes in cytokine levels during antidepressant treatment; however, the results vary. The purpose of this study was to pool all available data on changes in serum levels of TNFα, IL-6, and IL-1β during antidepressant treatment to determine whether these levels change. Studies were included if they used an approved pharmacological treatment for depression, patients had a diagnosis of MDD, and serum levels of TNFα, IL-6, and/or IL-1β were measured before and after treatment. Twenty-two studies fulfilled these criteria. Meta-analysis of these studies showed that, overall, while pharmacological antidepressant treatment reduced depressive symptoms, it did not reduce serum levels of TNFα. On the other hand, antidepressant treatment did reduce levels of IL-1β and possibly those of IL-6. Stratified subgroup analysis by class of antidepressant indicated that serotonin reuptake inhibitors may reduce levels of IL-6 and TNFα. Other antidepressants, while efficacious for depressive symptoms, did not appear to reduce cytokine levels. These results argue against the notion that resolution of a depressive episode is associated with normalization of levels of circulating inflammatory cytokines; however, the results are consistent with the possibility that inflammatory cytokines contribute to depressive symptoms and that antidepressants block the effects of inflammatory cytokines on the brain.

Neuropsychopharmacology (2011) 36, 2452–2459; doi:10.1038/npp.2011.132; published online 27 July 2011

Keywords: depression; inflammation; TNF; IL-6; IL-1; antidepressant

INTRODUCTION

Major depressive disorder (MDD) is a prevalent and debilitating disorder the pathogenesis of which is incompletely understood. MDD, in the absence of medical illnesses, is associated with increased levels of the inflammatory cytokines tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and IL-1 beta (IL-1β) (Howren *et al*, 2009; Dowlati *et al*, 2010). There are several potential reasons why elevated levels of inflammatory cytokines are associated with MDD: (1) there may be common etiologies that lead to both MDD and elevated levels of these inflammatory cytokines, without a causal relation between the two phenomena; (2) MDD may cause brain alterations that impair the brain's ability to modulate the immune system via hypothalamic-pituitary-adrenal axis activity and autonomic outflow; and (3) systemic triggers (eg, exposure to pathogens), genetic differences in the immune system, or differences in the immune system's exposure to commensal microorganisms, may lead to increased production of inflammatory cytokines, which in turn contribute to depressive symptoms (Miller *et al*, 2009; Raison *et al*, 2010). Supporting (3) are studies showing that acute and chronic immune stimuli, which increase serum levels of inflammatory cytokines, can elicit depressive symptoms in humans (Reichenberg *et al*, 2001; Wright *et al*, 2005; Capuron *et al*, 2009; Eisenberger *et al*, 2009; DellaGioia and Hannestad, 2010), and studies showing that anti-inflammatory and anti-TNFα drugs can ameliorate depressive symptoms (Muller *et al*, 2006; Tyring *et al*, 2006). If (2) above is true, that is, elevated cytokine levels are a consequence of depression, then the treatment of depression with successful resolution of depressive symptoms would be expected to normalize levels. If, on the other hand, (3) above is true, that is, elevated levels of TNFα and IL-6 is a result of processes inherent to the immune system, then antidepressant treatment may not normalize levels, unless they have a direct effect on innate immune cells. Some studies suggest such a direct effect on the immune system,

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Received 8 April 2011; revised 15 June 2011; accepted 15 June 2011

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Cytokines & Depression

- It has been established that Proinflammatory cytokines may contribute to the development and progression of depression through the following pathways:

1. **Pathological activation of the immune response:** including the acute-phase reaction
2. **Changes in neurotransmitter systems:** inflammatory cytokines can cross the blood–brain barrier, using both the space with increased permeability and the active transport principle.

The role of IgG hypersensitivity in the pathogenesis and therapy of depressive disorders

Hanna Karakuła-Juchnowicz[1], Patrycja Szachta[2], Aneta Opolska[3], Justyna Morylowska-Topolska[1], Mirosława Gałecka[2], Dariusz Juchnowicz[4], Paweł Krukow[1], Lasik Zofia[2]

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Depressive episodes are associated not only with changes in neurotransmission in the central nervous system, but also may lead to structural changes in the brain through neuroendocrine, inflammatory, and immunological mechanisms. The aim of this article is to present a new hypothesis connecting the inflammatory theory of depression with IgG food hypersensitivity and leaky gut syndrome. This new potential pathway that may mediate the pathogenesis of depression implies the existence of subsequent developmental stages. Overproduction of zonulin triggered, for example, by gliadin through activation of the epidermal growth factor receptor and protease-activated receptor causes loosening of the tight junction barrier and an increase in permeability of the gut wall ('leaky gut'). This results in a process allowing larger molecules that would normally stay in the gut to cross into the bloodstream and in the induction of IgG-dependent food sensitivity. This condition causes an increased immune response and consequently induces the release of proinflammatory cytokines, which in turn may lead to the development of depressive symptoms. It seems advisable to assess the intestinal permeability using as a marker, for example, zonulin and specific IgG concentrations against selected nutritional components in patients with depression. In the case of increased IgG concentrations, the implementation of an elimination-rotation diet may prove to be an effective method of reducing inflammation. This new paradigm in the pathogenesis of depressive disorders linking leaky gut, IgG-dependent food sensitivity, inflammation, and depression is promising, but still needs further studies to confirm this theory.

Keywords: Depression, Leaky gut, IgG hypersensitivity, Zonulin, Inflammatory theory of depression, Gluten sensitivity

Introduction

Depression is a heterogeneous psychiatric disorder with multifactorial aetiology and therefore needs improved integration models, based on behavioural studies, sociology, and neuroscience to better reflect both the complexity and variety of mood disorders.[1] Among the factors deserving special attention are biological ones, including psychoneuroendocrinology and psychoimmunology, posing a bridge between strictly biological and psychological approaches.[2] More and more evidence indicates that depressive episodes are associated not only with changes in neurotransmission in the central nervous system (CNS), but also may lead to structural changes in the brain through neuroendocrine, inflammatory, and immunological mechanisms.[3–5] Different factors potentially connected with systemic inflammation in depression are taken into consideration; these include psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopy, dental caries, sleep, and Vitamin D deficiency.[6]

The aim of this article is to present a new hypothesis connecting the inflammatory theory of depression with IgG food hypersensitivity and leaky gut syndrome (LGS).

Inflammatory theory of depression

Among many theories of depression, the cytokine (macrophage) theory of depression, first demonstrated in 1991 by Robert Smith,[7] has aroused much interest among researchers. It is assumed that changes in behaviour, typical of depression, are the result of the

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DOI 10.1179/1476830514Y.0000000158 Nutritional Neuroscience 2014 VOL 0 NO 0 1

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Cytokines & Depression

3. **The effect on the HPA axis:** Proinflammatory cytokines intensify noradrenergic neurotransmission and activate the HPA axis.

- HPA hyperactivity has been proposed as the neurobiological basis of major depression. It is well documented that patients with major depressive disorder have elevated plasma cortisol levels as well as decreased sensitivity to external dexamethasone and CRH.

The role of IgG hypersensitivity in the pathogenesis and therapy of depressive disorders

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Cytokines & Depression

4. The processes described above, expressed in immunological and glandular malfunctions and neurotransmitters dysregulation, can lead to brain cell loss and reduction in neurogenesis. According to the latest views on the pathogenesis of depression, stress factors can cause atrophy of hippocampal cells (as a result of hypercortisolism caused by HPA axis hyperactivity) and impairment of neurogenesis in predisposed subjects.

The role of IgG hypersensitivity in the pathogenesis and therapy of depressive disorders

Hanna Karakuła-Juchnowicz[1], Patrycja Szachta[2], Aneta Opolska[3], Justyna Morylowska-Topolska[1], Mirosława Gałecka[2], Dariusz Juchnowicz[4], Paweł Krukow[1], Lasik Zofia[2]

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Gluten Sensitivity & Depression

- Only recently has coeliac disease been separated from gluten sensitivity (non-coeliac gluten sensitivity, NCGS) and gluten allergic reactions (IgE-mediated).
- According to the consensus document developed in 2012, a spectrum of gluten-related disorders includes three main forms of gluten reactions: allergic (e.g. food allergy), autoimmune (e.g. coeliac disease, dermatitis herpetiformis, and gluten ataxia), and possibly immune-mediated (e.g. NCGS).

Sapone et al. BMC Medicine 2012, 10:13
http://www.biomedcentral.com/1741-7015/10/13

BMC Medicine

OPINION Open Access

Spectrum of gluten-related disorders: consensus on new nomenclature and classification

Anna Sapone[1,2], Julio C Bai[3], Carolina Ciacci[4], Jernej Dolinsek[5], Peter HR Green[6], Marios Hadjivassiliou[7], Katri Kaukinen[8], Kamran Rostami[9], David S Sanders[10], Michael Schumann[11], Reiner Ullrich[11], Danilo Villalta[12], Umberto Volta[13], Carlo Catassi[1,14] and Alessio Fasano[1*]

Abstract

A decade ago celiac disease was considered extremely rare outside Europe and, therefore, was almost completely ignored by health care professionals. In only 10 years, key milestones have moved celiac disease from obscurity into the popular spotlight worldwide. Now we are observing another interesting phenomenon that is generating great confusion among health care professionals. The number of individuals embracing a gluten-free diet (GFD) appears much higher than the projected number of celiac disease patients, fueling a global market of gluten-free products approaching $2.5 billion (US) in global sales in 2010. This trend is supported by the notion that, along with celiac disease, other conditions related to the ingestion of gluten have emerged as health care concerns. This review will summarize our current knowledge about the three main forms of gluten reactions: allergic (wheat allergy), autoimmune (celiac disease, dermatitis herpetiformis and gluten ataxia) and possibly immune-mediated (gluten sensitivity), and also outline pathogenic, clinical and epidemiological differences and propose new nomenclature and classifications.

Introduction

Wheat, rice and maize are the most widely consumed food grains in the world. Wheat, the most widely grown crop, is immensely diverse, with more than 25,000 different cultivars having been produced by plant breeders worldwide. Much of the world's production of wheat is consumed after it has been processed into bread, other baked goods, pasta and noodles, and, in the Middle East and North Africa, bulgur and couscous. In addition, the wide availability of wheat flour and the functional properties of gluten proteins provide the rationale for their wide use as an ingredient in food processing.

Gluten is the main structural protein complex of wheat with equivalent toxic proteins found in other cereals, including rye and barley. The toxic protein fractions of gluten include gliadins and glutenins, with gliadins containing monomeric proteins and glutenins containing aggregated proteins. Possibly the introduction of gluten-containing grains, which occurred about 10,000 years ago with the advent of agriculture, represented an evolutionary challenge that created the conditions for human diseases related to gluten exposure, the best known of which are mediated by the adaptive immune system: wheat allergy (WA) and celiac disease (CD). In both conditions the reaction to gluten is mediated by T-cell activation in the gastrointestinal mucosa. However, in WA it is the cross-linking of immunoglobulin (Ig)E by repeat sequences in gluten peptides (for example, serine-glutamine-glutamine -glutamine-(glutamine-)proline-proline-phenylalanine) that triggers the release of chemical mediators, such as histamine, from basophils and mast cells [1]. In contrast, CD is an autoimmune disorder, as demonstrated by specific serologic autoantibodies, most notably serum anti-tissue transglutaminase (tTG) and anti-endomysial antibodies (EMA).

Besides CD and WA, there are cases of gluten reactions in which neither allergic nor autoimmune mechanisms are involved. These are generally defined as gluten sensitivity (GS) [2-5]. Some individuals who experience distress when eating gluten-containing products and show improvement when following a GFD may have GS

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Gluten Sensitivity & Depression

- CD is a chronic immune-mediated enteropathy triggered by gluten ingestion in subjects who have genetic compatibility of the HLA DQ2 or DQ8 haplotype.
- This disorder affects one percent of the general population and is characterised by villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes.
- Classic CD manifestations (but only in 50 per cent of patients) are severe diarrhoea and consequent weight loss with failure to thrive due to severe intestinal malabsorption.

MEDICINE

CONTINUING MEDICAL EDUCATION

The Diagnosis and Treatment of Celiac Disease

Detlef Schuppan, Klaus-Peter Zimmer

SUMMARY

Background: Celiac disease is an inflammatory disease of the small intestine with a prevalence of roughly 0.5%–1%. Its symptoms arise in response to gluten consumption by genetically predisposed persons (HLA-DQ2/8). The autoantigen tissue transglutaminase (TG2) plays an important role in the pathogenesis of celiac disease.

Methods: Selective review of pertinent literature, including guidelines from Germany and abroad.

Results: Celiac disease can present at any age with gastrointestinal or extraintestinal manifestations (e.g., malabsorption or Duhring's dermatitis herpetiformis); it can also be found in association with other (auto-)immune diseases, such as type 1 diabetes. Most cases are oligo-symptomatic. The wide differential diagnosis includes food intolerances, intestinal infections, and irritable bowel syndrome, among other conditions. The definitive diagnosis requires the demonstration of celiac disease–specific autoantibody to TG2 (endomysium), which is over 90% sensitive and far over 90% specific, and the characteristic histologic lesions of the small-bowel mucosa and remission on a gluten-free diet.

Conclusion: An understanding of celiac disease ought to inform everyday clinical practice in all medical disciplines, because this is a common condition with diverse manifestations that can be effectively diagnosed and easily treated for the prevention of both acute and long-term complications. Patients should follow a strictly gluten-free diet for life.

► Cite this as:
Schuppan D, Zimmer KP: The diagnosis and treatment of celiac disease. Dtsch Arztebl Int 2013; 110(49): 835–46. DOI: 10.3238/arztebl.2013.0835

Grains were first domesticated for regular consumption in the human diet only about 10 000 years ago in Mesopotamia, and about 3000 years later in central Europe. In the second century AD, Aretaeus of Cappadocia described an "abdominal" *(koiliakos)* disease that was apparently related to nutrition, but S. J. Gee (London, 1888) is considered to be the first describer of what we now know as celiac disease. This disease was much feared in the early decades of the 20th century because of its high mortality, which ran as high as 30% (e1).

The pediatrician K. W. Dicke of Utrecht and the Hague, in the early 1950s, was the first to link celiac disease to wheat consumption (e2). He witnessed the confirmation of his hypothesis when his patients' symptoms improved during the grain shortages prevailing toward the end of the Second World War.

In the early 1950s, Dicke, Weyers and van de Kamer characterized gluten (the storage proteins of wheat) as the precipitating factor of the manifestations of celiac disease (e2).

The morphological correlate of celiac disease—villous atrophy with crypt hyperplasia—was studied in detail by Paulley (Ipswich, 1954) and by Shiner (London, 1956). Anti-gliadin antibodies were discovered by Berger (Basel, 1958), anti-endomysium antibodies by Chorzelski (Warsaw, 1983). A further milestone was the discovery of the autoantigen of celiac disease, tissue transglutaminase (TG2) (1).

Even though precise and rational diagnostic evaluation is now possible, celiac disease remains an underdiagnosed condition, probably because of its broad clinical spectrum and the underuse of serologic screening (2, 3).

The typical latency from the onset of symptoms to diagnosis is now about four years (e3). This is all the more regrettable because very effective treatment is

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Definition

Celiac disease is a common inflammatory disease of the small bowel that is precipitated by the consumption of foods that contain gluten.

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Gluten Sensitivity & Depression

- NCGS is a relatively new term for conditions in which symptoms are triggered by gluten ingestion, in the absence of coeliac-specific antibodies and of classical coeliac villous atrophy, characterised by the presence of anti-gliadin antibodies.
- Although there is some evidence connecting CD with neurologic and psychiatric symptoms, there have been very few studies so far examining connections between NCGS and mental disorders.
- In the mainstream of this trend, there is Fasano's group research, focused on possible links between NCGS and schizophrenia.

NIH Public Access
Author Manuscript
Psychiatr Q. Author manuscript; available in PMC 2013 May 02.

Published in final edited form as:
Psychiatr Q. 2012 March ; 83(1): 91–102. doi:10.1007/s11126-011-9186-y.

Neurologic and Psychiatric Manifestations of Celiac Disease and Gluten Sensitivity

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Abstract

Celiac Disease (CD) is an immune-mediated disease dependent on gluten (a protein present in wheat, rye or barley) that occurs in about 1% of the population and is generally characterized by gastrointestinal complaints. More recently the understanding and knowledge of gluten sensitivity (GS), has emerged as an illness distinct from celiac disease with an estimated prevalence 6 times that of CD. Gluten sensitive people do not have villous atrophy or antibodies that are present in celiac disease, but rather they can test positive for antibodies to gliadin. Both CD and GS may present with a variety of neurologic and psychiatric co-morbidities, however, extraintestinal symptoms may be the prime presentation in those with GS. However, gluten sensitivity remains undertreated and underrecognized as a contributing factor to psychiatric and neurologic manifestations. This review focuses on neurologic and psychiatric manifestations implicated with gluten sensitivity, reviews the emergence of gluten sensitivity distinct from celiac disease, and summarizes the potential mechanisms related to this immune reaction.

Keywords

Gluten; Schizophrenia; Neurologic; Immune; Celiac; Psychiatric

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Conflict of interest All authors report no conflicts of interest.

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Gluten Sensitivity & Depression

- Carr, described a case of an 11-year-old girl who had been on a gluten-free diet since early childhood due to health issues associated with wheat consumption.
- At the age of 10 she had to consume a wheat-containing diet for a week. After this short period, her mood dropped suddenly, and she also claimed that she had wanted to kill herself.
- Her diet was immediately changed back to a strictly gluten-free and after several days her mental state improved significantly.
- In the pilot study, Peters et al. evidenced that even short-term gluten exposure in patients with NCGS can cause symptoms similar to depression.

APT Alimentary Pharmacology and Therapeutics

Randomised clinical trial: gluten may cause depression in subjects with non-coeliac gluten sensitivity – an exploratory clinical study

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Publication data
Submitted 12 September 2013
First decision 11 October 2013
Resubmitted 12 March 2014
Accepted 12 March 2014
EV Pub Online 1 April 2014

This article was accepted for publication after full peer-review.

SUMMARY

Background
Current evidence suggests that many patients with self-reported non-coeliac gluten sensitivity (NCGS) retain gastrointestinal symptoms on a gluten-free diet (GFD) but continue to restrict gluten as they report 'feeling better'.

Aim
To investigate the notion that a major effect of gluten in those with NCGS is on mental state and not necessarily on gastrointestinal symptoms.

Methods
Twenty-two subjects (24–62 years, five male) with irritable bowel syndrome who had coeliac disease excluded but were symptomatically controlled on a GFD, undertook a double-blind cross-over study. Participants randomly received one of three dietary challenges for 3 days, followed by a minimum 3-day washout before crossing over to the next diet. Challenge gluten-free food was supplemented with gluten (16 g/day), whey (16 g/day) or not supplemented (placebo). End-points included mental state as assessed by the Spielberger State Trait Personality Inventory (STPI), cortisol secretion and gastrointestinal symptoms.

Results
Gluten ingestion was associated with higher overall STPI state depression scores compared to placebo [$M = 2.03$, 95% CI (0.55–3.51), $P = 0.010$] but not whey [$M = 1.48$, 95% CI (−0.14 to 3.10), $P = 0.07$]. No differences were found for other STPI state indices or for any STPI trait measures. No difference in cortisol secretion was identified between challenges. Gastrointestinal symptoms were induced similarly across all dietary challenges.

Conclusions
Short-term exposure to gluten specifically induced current feelings of depression with no effect on other indices or on emotional disposition. Gluten-specific induction of gastrointestinal symptoms was not identified. Such findings might explain why patients with non-coeliac gluten sensitivity feel better on a gluten-free diet despite the continuation of gastrointestinal symptoms.

Aliment Pharmacol Ther 2014; **39**: 1104–1112

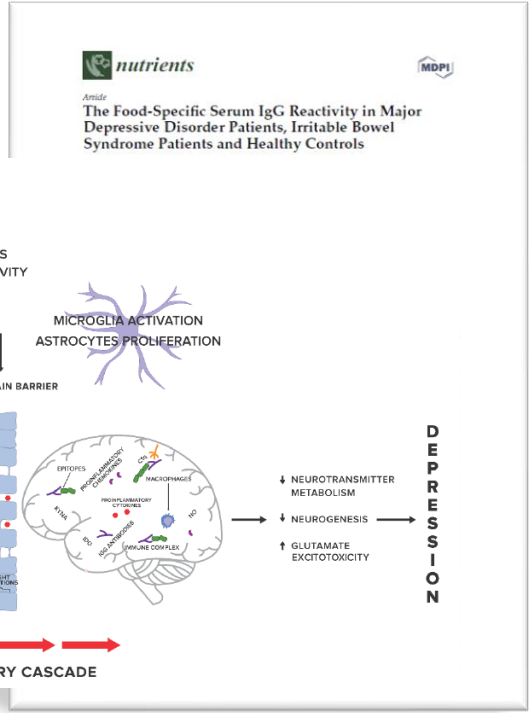
1104

doi:10.1111/apt.12730

1. Carr AC. Depressed mood associated with gluten sensitivity--resolution of symptoms with a gluten-free diet. N Z Med J. 2012 Nov 23;125(1366):81-2. PMID: 23254531.
2. Peters SL, Biesiekierski JR, Yelland GW, Muir JG, Gibson PR. Randomised clinical trial: gluten may cause depression in subjects with non-coeliac gluten sensitivity - an exploratory clinical study. Aliment Pharmacol Ther. 2014 May;39(10):1104-12. doi: 10.1111/apt.12730. Epub 2014 Apr 1. PMID: 24689456

IBS and Depression

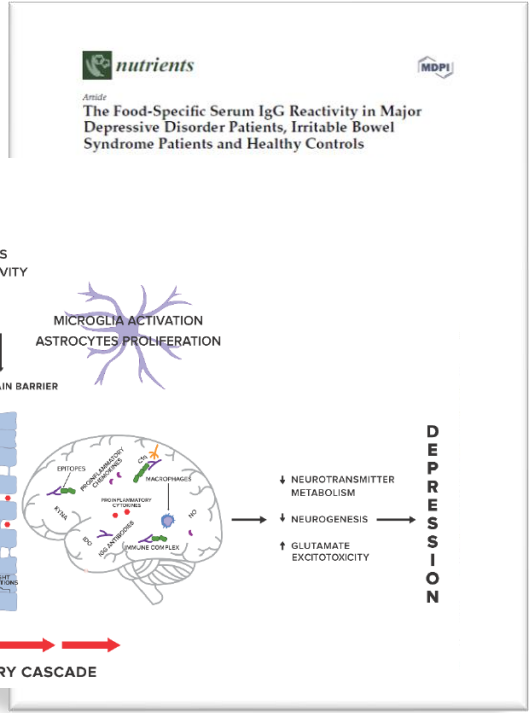
- The gut-immune-inflammatory-brain model for Major Depressive Disorder is associated with food IgG hyperreactivity.
- Genetic and environmental factors may lead to disruption of tight junctions, the loss of their integrity and both gut and BBB permeability.
- Undigested food compounds, which would normally breakdown in the gut, translocate into the blood circulation, and combine with food IgG antibodies to form immune complexes.



1. Karakula-Juchnowicz H, Gałęcka M, Rog J, et al. The Food-Specific Serum IgG Reactivity in Major Depressive Disorder Patients, Irritable Bowel Syndrome Patients and Healthy Controls. Nutrients. 2018;10(5):548. Published 2018 Apr 28. doi:10.3390/nu10050548

IBS and Depression

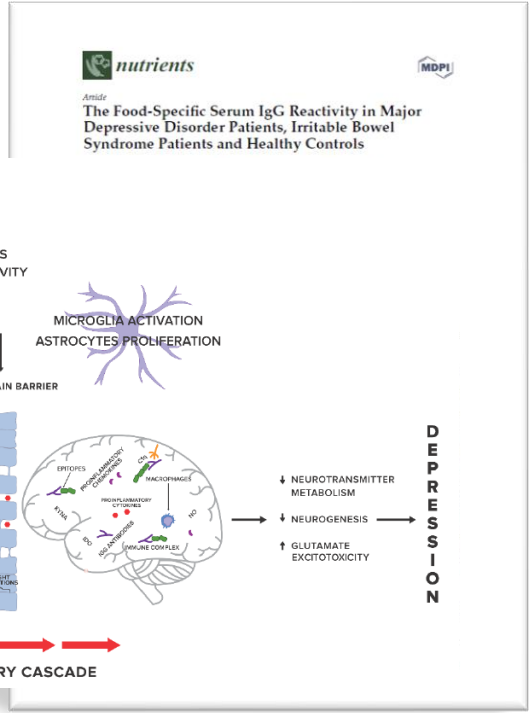
- This, in turn, provokes an abnormal response and triggers immune-inflammatory cascade.
- Uncontrolled release of the proinflammatory mediators may contribute to low-grade systemic inflammation and low-grade neuroinflammation.
- Which may in consequence induce and then maintain and prolong depression.



1. Karakula-Juchnowicz H, Gałęcka M, Rog J, et al. The Food-Specific Serum IgG Reactivity in Major Depressive Disorder Patients, Irritable Bowel Syndrome Patients and Healthy Controls. Nutrients. 2018;10(5):548. Published 2018 Apr 28. doi:10.3390/nu10050548

IBS and Depression

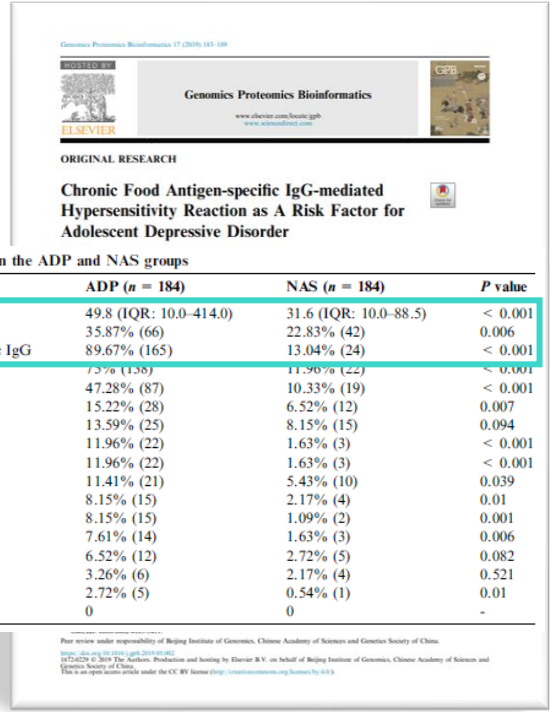
- Our findings suggest food-specific serum IgG hyperreactivity among patients with IBS and MDD is more common compared with healthy controls.
- This may be one of the mechanisms leading to the development of immune activation and low-grade inflammation observed in these disorders.



1. Karakula-Juchnowicz H, Gałęcka M, Rog J, et al. The Food-Specific Serum IgG Reactivity in Major Depressive Disorder Patients, Irritable Bowel Syndrome Patients and Healthy Controls. Nutrients. 2018;10(5):548. Published 2018 Apr 28. doi:10.3390/nu10050548

Food Specific IgG & Depression

- Major depressive disorder (MDD) is the most common nonfatal disease burden worldwide.
- Systemic chronic low-grade inflammation has been reported to be associated with MDD progression.
- Significantly higher serum food antigen-specific IgG positive rates were found in the patient group.



Genomics Proteomics Bioinformatics

ORIGINAL RESEARCH

Chronic Food Antigen-specific IgG-mediated Hypersensitivity Reaction as A Risk Factor for Adolescent Depressive Disorder

Table 1 Serum IgE and food antigen-specific IgG levels in the ADP and NAS groups

	ADP (n = 184)	NAS (n = 184)	P value
IgE (KU/l)	49.8 (IQR: 10.0–414.0)	31.6 (IQR: 10.0–88.5)	< 0.001
Percentage (No.) of subjects with high IgE	35.87% (66)	22.83% (42)	0.006
Percentage (No.) of subjects positive for food antigen-specific IgG	89.67% (165)	13.04% (24)	< 0.001
Egg	73% (138)	11.96% (22)	< 0.001
Milk	47.28% (87)	10.33% (19)	< 0.001
Soybean	15.22% (28)	6.52% (12)	0.007
Wheat	13.59% (25)	8.15% (15)	0.094
Rice	11.96% (22)	1.63% (3)	< 0.001
Tomato	11.96% (22)	1.63% (3)	< 0.001
Codfish	11.41% (21)	5.43% (10)	0.039
Crab	8.15% (15)	2.17% (4)	0.01
Corn	8.15% (15)	1.09% (2)	0.001
Mushroom	7.61% (14)	1.63% (3)	0.006
Shrimp	6.52% (12)	2.72% (5)	0.082
Pork	3.26% (6)	2.17% (4)	0.521
Chicken	2.72% (5)	0.54% (1)	0.01
Beef	0	0	-

1. Tao R, Fu Z, Xiao L. Chronic Food Antigen-specific IgG-mediated Hypersensitivity Reaction as A Risk Factor for Adolescent Depressive Disorder. Genomics Proteomics Bioinformatics. 2019;17(2):183-189. doi:10.1016/j.gpb.2019.05.002

Food Specific IgG & Depression

- The detection of IgG, IgE, histamine, and other indicators would provide a new objective basis for the early diagnosis of depression, and also provide a reliable basis for the evaluation of the treatment of depression.
- In addition to MDD, other CNS diseases such as Alzheimer's disease, Parkinson's disease, and Epilepsy are also associated with increased BBB permeability.
- *'Therefore, we conclude that long-term food antigen-specific IgG-mediated hypersensitivity may also be associated with the pathogenesis of these CNS diseases.'*

Genomics Proteomics Bioinformatics 17 (2019) 183–189

Genomics Proteomics Bioinformatics

www.elsevier.com/locate/gpb

ORIGINAL RESEARCH

Chronic Food Antigen-specific IgG-mediated Hypersensitivity Reaction as A Risk Factor for Adolescent Depressive Disorder

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Received 21 November 2018; revised 24 March 2019; accepted 31 May 2019
Available online 21 June 2019

Handled by Yun-Gui Yang

KEYWORDS
Major depressive disorder; Blood-brain barrier; Histamine; Hypersensitivity reaction; Inflammation

Abstract **Major depressive disorder** (MDD) is the most common nonfatal disease burden worldwide. Systemic chronic low-grade **inflammation** has been reported to be associated with MDD progression by affecting monoaminergic and glutamatergic neurotransmission. However, whether various proinflammatory cytokines are abnormally elevated before the first episode of depression is still largely unclear. Here, we evaluated 184 adolescent patients who were experiencing their first episode of depressive disorder, and the same number of healthy individuals was included as controls. We tested the serum levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), IgE, 14 different types of food antigen-specific IgG, **histamine**, homocysteine, S100 calcium-binding protein B, and diamine oxidase. We were not able to find any significant differences in the serum levels of hs-CRP or TNF-α between the two groups. However, the histamine level of the patients (12.35 μM) was significantly higher than that of the controls (9.73 μM, $P < 0.001$, Mann–Whitney U test). Moreover, significantly higher serum food antigen-specific IgG positive rates were also found in the patient group. Furthermore, over 80% of patients exhibited prolonged food intolerance with elevated levels of serum histamine, leading to

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Peer review under responsibility of Beijing Institute of Genomics, Chinese Academy of Sciences and Genetics Society of China.

https://doi.org/10.1016/j.gpb.2019.05.002
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1. Tao R, Fu Z, Xiao L. Chronic Food Antigen-specific IgG-mediated Hypersensitivity Reaction as A Risk Factor for Adolescent Depressive Disorder. Genomics Proteomics Bioinformatics. 2019;17(2):183-189. doi:10.1016/j.gpb.2019.05.002

Food Sensitivity & Schizophrenia

Food IgG & Schizophrenia

- Certain patterns of antibodies, involving some agents, were predictive of developing schizophrenia, with the magnitude of association rising when the level of antibodies increased to two or more agents.
- A heightened antibody response to a combination of several infectious/food antigens (casein, gliadin) might be an indicator of an altered immune response to antigenic stimuli.

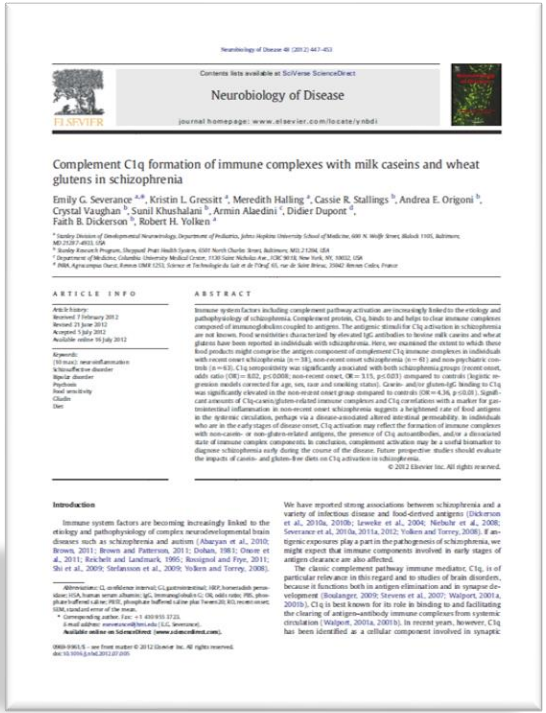
Schizophrenia Research

Association between antibodies to multiple infectious and food antigens and new onset schizophrenia among US military personnel

1. Li Y, Weber NS, Fisher JA, et al. Association between antibodies to multiple infectious and food antigens and new onset schizophrenia among US military personnel. Schizophr Res. 2013;151(1-3):36-42. doi:10.1016/j.schres.2013.10.004

Food IgG & Schizophrenia

- Immune system factors including complement pathway activation are increasingly linked to the aetiology and pathophysiology of schizophrenia.
- Food sensitivities characterised by elevated IgG antibodies to bovine milk caseins and wheat glutens have been reported in individuals with schizophrenia.
- Complement protein, C1q, binds to and helps to clear immune complexes composed of immunoglobulins coupled to antigens.



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,*], 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

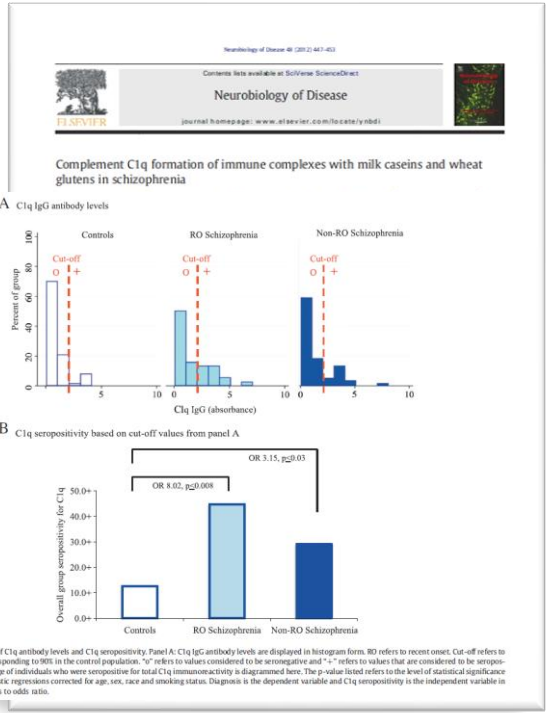
ABSTRACT

Introduction

1. Severance EG, Gressitt KL, Halling M, et al. Complement C1q formation of immune complexes with milk caseins and wheat glutens in schizophrenia. Neurobiol Dis. 2012;48(3):447-453. doi:10.1016/j.nbd.2012.07.005

Food IgG & Schizophrenia

- Casein- and/or gluten-IgG binding to C1q was significantly elevated compared to controls.
- Significant amounts of C1q-casein/gluten-related immune complexes correlated with a marker for gastrointestinal inflammation in schizophrenia
- This suggests a heightened rate of food antigens in the systemic circulation, perhaps via a disease-associated altered intestinal permeability.
- Exposure to food antigens in susceptible individuals may represent a plausible means by which C1 activation could ultimately result in symptoms and behaviour characteristic of schizophrenia.



1. Severance EG, Gressitt KL, Halling M, et al. Complement C1q formation of immune complexes with milk caseins and wheat glutens in schizophrenia. Neurobiol Dis. 2012;48(3):447-453. doi:10.1016/j.nbd.2012.07.005

Food Sensitivity & ASD

Food IgG & ASD

- Immune system of some autistic patients could be abnormally triggered by gluten/casein
- IgG anti-gliadin titers were found to be higher in ASDs compared to controls.
- IgG anti-casein titers were found to be more frequent and significantly higher in ASDs than in controls.

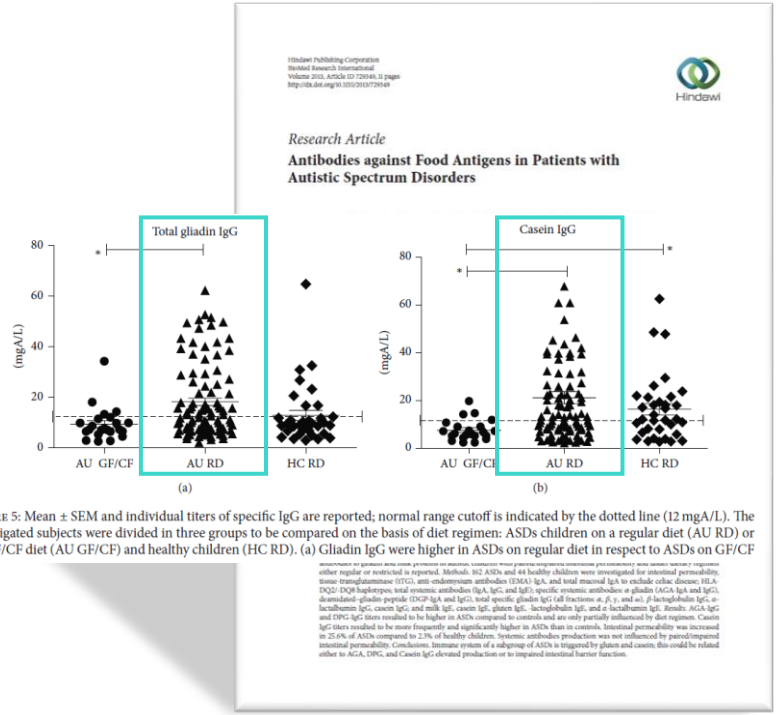


FIGURE 5: Mean ± SEM and individual titers of specific IgG are reported; normal range cutoff is indicated by the dotted line (12 mgA/L). The investigated subjects were divided in three groups to be compared on the basis of diet regimen: ASDs children on a regular diet (AU RD) or on GF/CF diet (AU GF/CF) and healthy children (HC RD). (a) Gliadin IgG were higher in ASDs on regular diet in respect to ASDs on GF/CF

1. de Magistris L, Picardi A, Siniscalco D, et al. Antibodies against food antigens in patients with autistic spectrum disorders. Biomed Res Int. 2013;2013:729349. doi:10.1155/2013/729349

Food IgG & ASD

- Data supports the hypothesis that immune system of a subgroup of ASDs is triggered by gluten and casein; related to impaired intestinal barrier function.
- The determination of antibody titers to food antigens could be useful to identify the ASDs subjects in whom the implementation of a GF/CF diet might be considered as medical nutrition therapy.

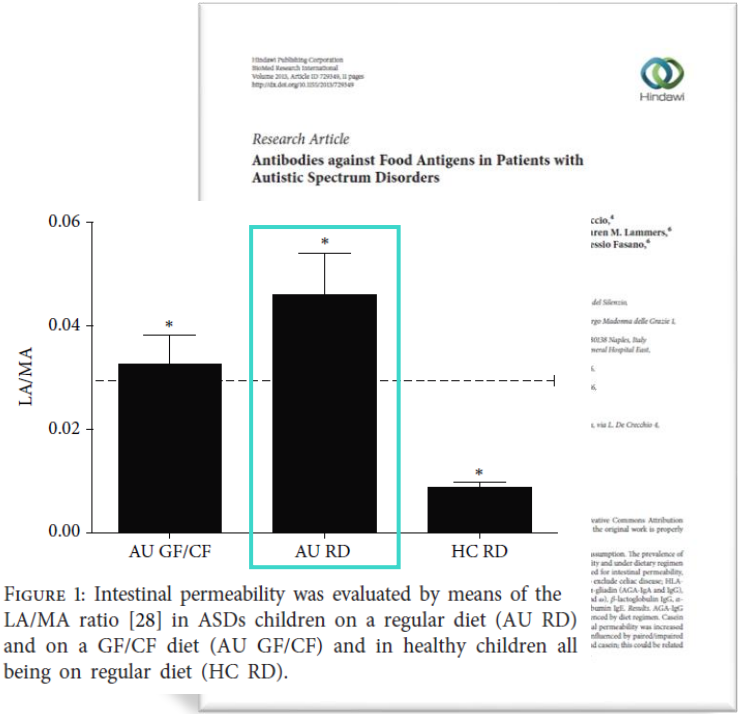
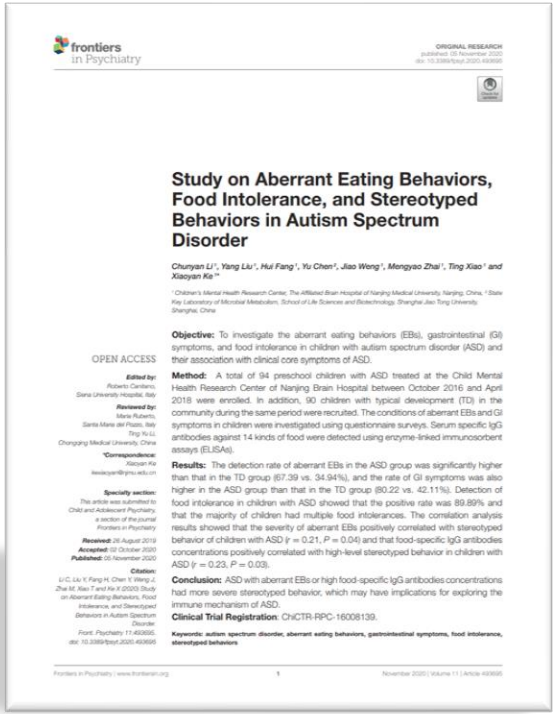


FIGURE 1: Intestinal permeability was evaluated by means of the LA/MA ratio [28] in ASDs children on a regular diet (AU RD) and on a GF/CF diet (AU GF/CF) and in healthy children all being on regular diet (HC RD).

1. de Magistris L, Picardi A, Siniscalco D, et al. Antibodies against food antigens in patients with autistic spectrum disorders. Biomed Res Int. 2013;2013:729349. doi:10.1155/2013/729349

Food Sensitivity & ASD

- Some researchers believe that food sensitivity is associated with microbiota-gut brain (MGB) axis, and impaired intestinal mucosal barrier.
- Children with ASD are usually reported to have a “leaky gut”.
- The results in this study showed that stereotyped behaviours of preschool children with ASD correlated with food-specific IgG antibody levels, which may have implications for exploring the immune mechanism of ASD.



frontiers in Psychiatry

ORIGINAL RESEARCH

Study on Aberrant Eating Behaviors, Food Intolerance, and Stereotyped Behaviors in Autism Spectrum Disorder

OPEN ACCESS

Objective: To investigate the aberrant eating behaviors (EBs), gastrointestinal (GI) symptoms, and food intolerance in children with autism spectrum disorder (ASD) and their association with clinical core symptoms of ASD.

Method: A total of 94 preschool children with ASD treated at the Child Mental Health Research Center of Nanjing Brain Hospital between October 2016 and April 2018 were enrolled. In addition, 90 children with typical development (TD) in the community during the same period were recruited. The conditions of aberrant EBs and GI symptoms in children were investigated using questionnaire surveys. Serum specific IgG antibodies against 14 kinds of food were detected using enzyme-linked immunosorbent assays (ELISAs).

Results: The detection rate of aberrant EBs in the ASD group was significantly higher than that in the TD group (67.39 vs. 34.94%), and the rate of GI symptoms was also higher in the ASD group than that in the TD group (80.22 vs. 42.11%). Detection of food intolerance in children with ASD showed that the positive rate was 89.89% and that the majority of children had multiple food intolerances. The correlation analysis results showed that the severity of aberrant EBs positively correlated with stereotyped behavior of children with ASD ($r = 0.21$, $P = 0.04$) and that food-specific IgG antibodies concentrations positively correlated with high-level stereotyped behavior in children with ASD ($r = 0.23$, $P = 0.03$).

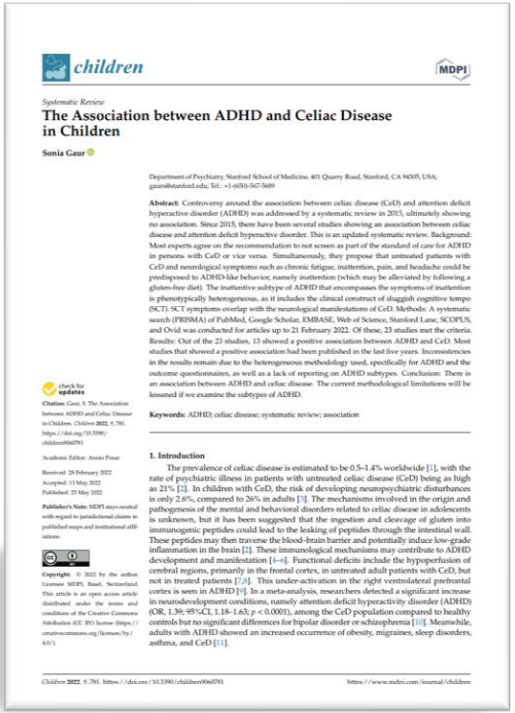
Conclusion: ASD with aberrant EBs or high food-specific IgG antibodies concentrations had more severe stereotyped behavior, which may have implications for exploring the immune mechanism of ASD.

Clinical Trial Registration: ChiCTR-RPC-16008139.

1. Li C, Liu Y, Fang H, et al. Study on Aberrant Eating Behaviors, Food Intolerance, and Stereotyped Behaviors in Autism Spectrum Disorder. Front Psychiatry. 2020;11:493695. Published 2020 Nov 5. doi:10.3389/fpsyt.2020.493695

ADHD & Coeliac Disease

- Untreated coeliac disease (CeD) can be accompanied by an array of neurological symptoms. Some of these symptoms are similar to those observed in attention deficit hyperactive disorder (ADHD).
- Thought to be linked to low-grade inflammation in the brain as a result of permeability in the gut and blood-brain barrier.
- This is an updated systematic review including 23 studies of children and young adults, which found an association between ADHD and CeD, in contrast to previous reviews that found no clear association.



children

MDPI

Systematic Review

The Association between ADHD and Celiac Disease in Children

Sonia Gaur

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Abstract: Controversy around the association between celiac disease (CeD) and attention deficit hyperactive disorder (ADHD) was addressed by a systematic review in 2015, ultimately showing no association. Since 2015, there have been several studies showing an association between celiac disease and attention deficit hyperactive disorder. This is an updated systematic review. Background: Most experts agree on the recommendation to not screen as part of the standard of care for ADHD in persons with CeD or vice versa. Simultaneously, they propose that untreated patients with CeD and neurological symptoms such as chronic fatigue, inattention, pain, and headache could be predisposed to ADHD-like behavior, namely inattention (which may be alleviated by following a gluten-free diet). The inattentive subtype of ADHD that encompasses the symptoms of inattention is phenotypically heterogeneous, as it includes the clinical construct of sluggish cognitive tempo (SCT). SCT symptoms overlap with the neurological manifestations of CeD. Methods: A systematic search (PRISMA) of PubMed, Google Scholar, EMBASE, Web of Science, Stanford Lane, SCOPUS, and Ovid was conducted for articles up to 21 February 2022. Of these, 23 studies met the criteria. Results: Out of the 23 studies, 13 showed a positive association between ADHD and CeD. Most studies that showed a positive association had been published in the last five years. Inconsistencies in the results remain due to the heterogeneous methodology used, specifically for ADHD and the outcome questionnaires, as well as a lack of reporting on ADHD subtypes. Conclusion: There is an association between ADHD and celiac disease. The current methodological limitations will be lessened if we examine the subtypes of ADHD.

Keywords: ADHD; celiac disease; systematic review; association

1. Introduction

The prevalence of celiac disease is estimated to be 0.5–1.4% worldwide [1], with the rate of psychiatric illness in patients with untreated celiac disease (CeD) being as high as 21% [2]. In children with CeD, the risk of developing neuropsychiatric disturbances is only 2.6%, compared to 26% in adults [3]. The mechanisms involved in the origin and pathogenesis of the mental and behavioral disorders related to celiac disease in adolescents is unknown, but it has been suggested that the ingestion and cleavage of gluten into immunogenic peptides could lead to the leaking of peptides through the intestinal wall. These peptides may then traverse the blood–brain barrier and potentially induce low-grade inflammation in the brain [2]. These immunological mechanisms may contribute to ADHD development and manifestation [4–6]. Functional deficits include the hypoperfusion of cerebral regions, primarily in the frontal cortex, in untreated adult patients with CeD, but not in treated patients [7,8]. This under-activation in the right ventrolateral prefrontal cortex is seen in ADHD [9]. In a meta-analysis, researchers detected a significant increase in neurodevelopment conditions, namely attention deficit hyperactivity disorder (ADHD) (OR, 1.39; 95%CI, 1.18–1.63; $p < 0.0001$), among the CeD population compared to healthy controls but no significant differences for bipolar disorder or schizophrenia [10]. Meanwhile, adults with ADHD showed an increased occurrence of obesity, migraines, sleep disorders, asthma, and CeD [11].

1. Gaur S. The Association between ADHD and Celiac Disease in Children. Children (Basel). 2022 May 25;9(6):781. doi: 10.3390/children9060781. PMID: 35740718; PMCID: PMC9221618.
2. Expert Review https://www.nutrition-evidence.com/

The role of IgG-based elimination diet in mental health

- There is some evidence confirming the fact that the quality of diet has an influence on leaky gut syndrome, immune functioning and systemic inflammation in a variety of metal disorders.
- Tight junction damage between enterocytes leads to increased intestinal permeability that causes absorption of undigested proteins in small intestine and higher levels of specific IgG antibodies as a consequence.
- The essential treatment in this case should be implementation of an appropriate diet. An elimination-rotation diet may be a good choice in patients with IgG food sensitivity in many diseases (e.g. migraine).
- In the case of increased IgG concentrations, the implementation of an elimination–rotation diet may prove to be an effective method of reducing inflammation.
- It is necessary to evaluate the concentration of all subclasses of specific IgG (IgG 1–4) using validated CE marked assay systems.

Conclusion

- The evidence is increasing to support the link between food sensitivity and mental health.
- Food sensitivity has the potential to significantly impact mental health, with symptoms such as brain fog, irritability, anxiety, and depression being linked to food sensitivities.
- Furthermore, chronic inflammation in the gut caused by food sensitivity can lead to chronic inflammation in the brain, which has been associated with conditions like Alzheimer's disease, Parkinson's disease, and multiple sclerosis.
- Identifying and eliminating foods that trigger sensitivity can help to alleviate mental health symptoms and improve overall well-being.
- It is crucial to note that while eliminating certain foods may alleviate mental health symptoms, it is equally important to maintain a balanced and nutritious diet to support overall physical and mental health.

Omega Diagnostics

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Improving health

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