Celiac Disease, Gluten Sensitivity and Neuropsychiatric Disease

Featuring:
Armin Alaedini, PhD
Columbia University Medical Center

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Watch & Win!

Five lucky webinar participants will win a Mary’s Gone Crackers reusable tote bag filled with product!
Welcome!

Armin Alaedini, PhD

• Assistant Professor of Medical Sciences at Columbia University’s Department of Medicine and Institute of Human Nutrition

• Member of the Celiac Disease Center at Columbia University

• Research aims: Understanding the link between immune response to foreign antigens and the development of disease processes affecting the gastrointestinal and nervous systems
Presentation Objectives

① Provide history of research on celiac disease and its effects on the nervous system

② Identify neurological manifestations of celiac disease

③ Explain current research on the potential role of gluten in conditions including ataxia, peripheral neuropathy, schizophrenia and autism

④ Discuss research findings regarding the immune response to gluten in neurologic and psychiatric disease

⑤ Answer your questions!
• **Proteins** of wheat (80%), giving dough its elastic and cohesive nature

• Comprised of ~70 different proteins with similarities in amino acid sequence and biochemical properties

• Water insoluble; divided into **gliadins** and **glutenins**

What is gluten?

![Image of gluten composition]

- High molecular wt glutenins
- Omega gliadins
- Alpha and gamma gliadins, low molecular wt glutenins
General Public’s Interest in “Gluten”

Search Volume Index

![Graph showing search volume index for Celiac Disease and Gluten from 2005 to 2013. The graph demonstrates a steady increase in search interest for both topics, with Gluten showing a more pronounced upward trend.]
What is (non-celiac) gluten sensitivity?

- **Celiac Disease**
  - Celiac disease-specific antibodies (anti-TG2, anti-D-gliadin), Biopsy positive

- **Wheat Allergy**
  - Wheat-specific IgE antibodies, Clinical symptoms, Skin prick tests

- **Non-Celiac Gluten Sensitivity (NCGS)**
  - Negative for celiac disease serologic markers, biopsy, and IgE antibodies; Many are positive for anti-gliadin antibody

**Gluten**

**Gluten & Non-Gluten**

? Not clear if trigger is gluten and/or other wheat proteins.
# Overlapping Symptoms

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Celiac Disease

1. An autoimmune enteropathy with ~1% prevalence

2. Primary target organ: Small intestine

3. Humoral (mediated by antibodies) immune response:
   - Anti-gliadin
   - Anti-deamidated gliadin
   - Anti-transglutaminase 2 (tTG)

4. Genetic component:
   - 75% concordance rate in monozygotic twins
   - Linked to specific class II HLA genes – DQ2/DQ8
Pathogenic Mechanism

A 
Gluten peptides
Increased intestinal permeability
Mucosal epithelial cells
Lamina propria
Intraepithelial lymphocytes

B 
Increased intestinal permeability
Deamidated and negatively charged peptides

C 
Peptide uptake and presentation through HLA-DQ2 or -DQ8 MHC II molecule

D 
Gluten-specific T cell
Anti-gluten antibodies
TG2-specific B cell
Anti-TG2 antibodies


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Pathogenic Mechanism

A. Gluten peptides enter the intestinal mucosa and are degraded into smaller peptides.

B. Deamidated and negatively charged peptides stimulate the immune system.

C. Antigen-presenting cells (APCs) process the peptides and present them to T cells.

D. Gluten-specific T cells activate gluten-specific B cells, leading to the production of gluten antibodies.

E. Increased intestinal permeability allows gluten peptides to enter the body, initiating an immune response. T cell cytokines further activate B cells, leading to the release of matrix metalloproteinases that cause cell death and degradation of the mucosal matrix.

Pathogenic Mechanism

A

Gluten peptides

Increased intestinal permeability

Villous damage

Mucosal epithelial cells

Lamina propria

Intraepithelial lymphocytes

B

Desamidated and negatively charged peptides

Peptide uptake and presentation through HLA-DQ2 or −DQ8 MHC II molecule

C

Gluten-specific T cell

DQ2/B

Antigen presenting cell

CD4

Gluten-specific B cell

TG2-specific B cell

T-helper 2 cytokines

T-helper 1 cytokines

Intermolecular help

D

Release of matrix metalloproteinases in response to specific cytokines, causing cell death and degradation of the mucosal matrix

E

Anti-gluten antibodies

Anti-TG2 antibodies

F

MIC, HLA-E

NKR receptors

Autoimmune receptor

NKG2D, CD94


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Celiac Disease

• **Classic symptoms:**
  • *Diarrhea, abdominal pain, weight loss*

• **A multisystem disorder:**
  • *Extraintestinal manifestations and associations*
Neurological Manifestations in Celiac Disease

1. **Common: Up to a third of biopsy-proven celiac patients**
   - Anti-gliadin antibodies are associated with neurologic deficits, even in absence of mucosal pathology

2. **Affects the central and peripheral nervous systems**

3. **To date, most commonly reported presentations include:**

   - Ataxia
   - Peripheral neuropathy
   - Schizophrenia
   - Bipolar disorder
   - ADHD
   - Autism
   - Headache
   - Cognitive deficits
   - Seizures

*May occur with or without intestinal symptoms*
Cerebellar Ataxia

- Results from damage to cerebellum (cerebellar degeneration)
- Affects control movement and balance
- Hereditary or sporadic
Ataxia and Celiac Disease

• First report in 1966 (Cook and Smith, Brain)

• Association based primarily on the basis of high levels of antibody to gliadin in patients with cerebellar ataxia

• Some have reported the anti-gliadin antibodies only in sporadic ataxia, while others have demonstrated equal prevalence in hereditary and sporadic ataxia

Bushara et al., 2001; Burk et al., 2001; Luorastinen et al., 2001; Hadjivassiliou et al., 2003; Ihara et al., 2006.
Ataxia and Celiac Disease

• Post-mortem findings have included cerebellar atrophy, gliosis, and Purkinje cell loss

• The response to a gluten-free diet has been mixed
  • A positive response has been described by some groups, while others have reported no benefit

• There are case reports of response to intravenous immunoglobulin (IVIg)

• Patients shown to have antibodies to transglutaminase 6 (TG6)

• Whether affected individuals have “celiac disease” remains a controversial issue
Peripheral Neuropathy

- Affects peripheral nervous system
- Results from injury to peripheral nerves
- Characterized by pain, numbness, weakness, and loss of reflexes in face, arms and legs
Peripheral Neuropathy and Celiac Disease

Studies indicate a clear trend in association:

- 23% - 28% of celiac disease patients have signs of neuropathy compared to 4% - 7% of controls

- Celiac disease was seen in 2.5% - 9% of patients with neuropathy in two studies

- Two studies indicate that celiac-associated neuropathy may respond to gluten-free diet

Shen et al., 2012; Luostarinen et al., 2003; Cicarelli et al., 2003; Brannagan et al., 2005; Chin et al., 2003.
Pathogenesis

What is the cause of the idiopathic ataxia and neuropathy in celiac disease/gluten sensitivity?

• **Nutritional deficiency**: Rare

• **Immune-mediated**:
  
  • Lymphocytic infiltration in central and peripheral nervous system
  
  • Patients respond in some cases to gluten-free diet or therapy with intravenous immunoglobulins (IVIg)
  
  • Patients have serum anti-neuronal antibody activity
    
    • Passive transfer of patient serum to animals cause motor coordination deficits

Alaedini et al., 2007; Boscolo et al., 2007; Hadjivassiliou et al., 2002.
Schizophrenia

- Pervasive (persistent) psychiatric disorder
  - Characterized by a breakdown of thought processes and emotional responsiveness
  - Auditory hallucination, paranoid delusions, disorganized speech and thinking
  - Highly debilitating

- ~1% prevalence

- Limited understanding of pathogenic mechanism and limited effects of therapeutic options

- No specific biomarkers for diagnosis and follow-up

- Believed to result from: Genetic, environmental, immunologic factors
Timeline of History:
Schizophrenia and Celiac Disease

- **1961:** First report (Graff and Handford, Psychiatr Q, 1961)
- **1960s-1970s:** Curtis Dohan and Dohan Hypothesis
- **1980s:** Subsequent studies could not confirm connection with celiac disease
- **1990s:** Idea abandoned
- **2009-2010:** Re-emergence
The levels of circulating anti-gliadin antibodies are significantly higher in patients with schizophrenia compared to control subjects

- 20% - 30% schizophrenia patients vs. ~5% - 10% control

Case studies and small trials indicate positive response to gluten-restriction in some patients.

Dohan et al., 1972; Reichelt and Landmark, 1995; Cascella et al., 2009; Kalaydjian et al., 2006; Jin et al., 2010; Dickerson et al., 2010; Fanciulli et al., 2005; Takahashi et al., 2000.
Schizophrenia and Celiac Disease

- Whether affected patients have true celiac disease is unclear in many studies
  - Do schizophrenia patients with anti-gliadin antibody have celiac disease?
  - Does the immune response to gluten in individuals with schizophrenia target the same proteins as celiac disease patients?
  - Is the mechanism of anti-gluten immune response the same in schizophrenia and celiac disease?
Celiac Disease Markers in Gluten-Sensitive Schizophrenia Patients

- Schizophrenia with anti-gluten (n=17)
- Celiac disease with anti-gluten (n=25)
- Healthy (n=20)

Celiac Disease Markers in Gluten-Sensitive Schizophrenia Patients

- **HLA DQ2/DQ8:**
  - 38.5% of schizophrenia
  - >98% of celiac disease
  - 30% - 40% of general population

- Most schizophrenia patients with antibodies to gluten do not have celiac disease

- Antibody response to gluten in schizophrenia is independent of enzymatic activity of TG2 enzyme and presentation by HLA-DQ2/DQ8 molecules

Molecular Specificity of the Anti-Gluten Immune Response

SDS-PAGE of Whole Gluten Extract

SEC of Whole Gluten Extract

SDS-PAGE of SEC-Separated Extract

Fractions 1-6 are from BioGel P-100 gel filtration separation of a gliadin-glutenin mixture obtained from white flour of the cultivar 'Cheyenne' by extraction with acetic acid.

High molecular mass glutenins

ω gliadins

α/β and γ gliadins, low molecular mass glutenins

Coomassie-stained gluten proteins (Cheyenne) on nitrocellulose membrane
Molecular Specificity of the Anti-Gluten Immune Response

Could there be a signature pattern of anti-gluten antibody reactivity in schizophrenia?
Autism Spectrum Disorders (ASD)

- A heterogeneous group of childhood neuro-developmental diseases
  - Deficits in communication skills and social interaction
  - Presence of repetitive and stereotyped patterns of behavior
- Prevalence is 1 in 88 children, but its causes and treatment have remained elusive
- No specific biomarkers to aid in the diagnosis and follow-up of patients
- Result of genetic, environmental and immunologic factors
Gluten and Autism

Connection between autism and celiac disease?

• Some studies have pointed to an increase in the prevalence of celiac disease or family history of the disease among ASD patients

• Others have ruled out an association; no controlled studies

Dietary gluten has been suggested to play a role in autism:

• Directly as circulating partially digested peptides with opioid-like properties

• Through the body’s immune response to these peptides
Autism and Gluten-Free/Casein-Free Diet

• There is great interest in diets that exclude gluten and casein!

• Effectiveness has not been clearly shown in controlled studies:
  • Small sample size
  • Difficulty in monitoring diet
  • Not targeted towards a specific subset of patients who might benefit
Neurologic/Psychiatric Conditions Associated with Anti-Gliadin Antibody

- Schizophrenia
- Cerebellar Ataxia
- Cerebral Palsy
- Bipolar Disorder
- Mania

Characteristics:

- Increased intestinal permeability
- Possible unique patterns of antibody response to gluten
- Association with specific HLAs

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Pathogenic Relevance of Anti-Gluten Immune Response

- Anti-gliadin antibodies bind to neural cells
Other Nervous System Auto-Antigens in Celiac Disease/Gluten Sensitivity

Antibodies to neural antigens in celiac disease/gluten sensitivity:

- Anti-ganglioside antibodies: Associated with peripheral neuropathy
- Anti-TG6 antibodies: Associated with ataxia
- Anti-synapsin I antibodies

Alaedini et al., 2001; Volta et al., 2005 & 2006; Hadjivassiliou et al., 2008; Alaedini et al., 2005
Significance of antibodies to neural antigens: Can they cause disease?

Potential mechanisms:

1. Bind to and inhibit or block molecular function
2. Induce tissue injury by initiating an inflammatory cascade through complement activation
3. Induce tissue injury by binding to Fc receptors on macrophages, neutrophils, and NK cells
4. Non-pathogenic markers signaling a loss of self tolerance
Ongoing Work

① Molecular specificity of antibody response in gluten-related conditions

② Identification of patient subsets who may benefit from specific interventions

③ Pathogenic potential of identified antibodies in *in vitro* (i.e. test tube) and *in vivo* (i.e. animal testing) models
• Increased rate of peripheral neuropathy in patients with celiac disease

• There may be increased prevalence of celiac disease in ataxia and peripheral neuropathy of unknown cause

• Increased antibody response to gluten in persons with ataxia, schizophrenia, cerebral palsy, mania and bipolar disorder - but the significance remains unknown

• Different mechanism for generating antibody to gluten

• Antibodies to gliadin cross-react with neurons; pathogenic relevance
As we finish...

Questions from the audience?
Save The Date!

CeliacCentral.org/Webinars

• Topic: “Gluten-Free Menu Planning: Budget-Friendly Tips"
• Date: Wednesday, May 8, 2013
• Time: 8:30 p.m. Eastern/5:30 p.m. Pacific
• Speaker: Kathleen Reale, BeFreeForMe.com

• Topic: “Drug Development 101: Implications for Celiac Disease"
• Date: Tuesday, June 11, 2013
• Time: 8:30 p.m. Eastern/5:30 p.m. Pacific
• Speakers: Francisco Leon, MD PhD, Vice President of Immunology Translational Medicine at Janssen Pharmaceutical Companies of Johnson and Johnson; and Ken Kilgore, MS, PhD, Director of ImmunoPharmacology in the Immunology Therapeutic Area at Janssen Pharmaceutical Companies of Johnson and Johnson, and Executive of NFCA Scientific/Medical Advisory Council

• Topic: “Shifting the Focus: Lessons Learned from the Physical & Emotional Well-Being of Gluten-Free Athletes"
• Date: Thursday, July 18, 2013
• Time: 2 p.m. Eastern/11 a.m. Pacific
• Speaker: Dr. KC Wilder, Sports Performance Coach
Resources

National Foundation for Celiac Awareness:

- **Q&A with Dr. Stephanie Moleski, February Webinar Panelist** – CeliacCentral.org/Webinars/Archive

- **Collaboration with The Jefferson Celiac Center - a survey for persons with celiac disease:** http://tinyurl.com/bpe96f7

- **Joint events with Mary’s Gone Crackers:**
  - "The Role of Organic Ingredients” - Live Facebook Q&A on Earth Day, Monday, April 22 at 1 p.m. ET/10 a.m. PT
  - "The Gluten-Free Diet: Health Trend vs. Medical Necessity” Twitter Chat on Wednesday, April 24 at 1 p.m. ET/10 a.m. PT
  - Learn more, including how to enter products from Mary’s Gone Crackers: CeliacCentral.org/GoneCrackers2013
Mary’s Gone Crackers is a line of delicious gourmet snacks that unite taste appeal with satisfying nutrition. Loaded with whole grains and nutritious ingredients, Mary’s Gone Crackers line of snacks is organic, non-GMO, kosher and gluten-free, and contains no trans-fats, dairy, eggs or nuts. While many gluten-free foods lack in flavor and texture, Mary’s Gone Crackers provides uniquely tasty and mouth-pleasing options with its Crackers, Pretzels, Cookies and Crumbs.
Thank you!

Questions? Comments? Feedback?

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kvoorhees@CeliacCentral.org