Schizophrenia and Gluten: New Target and Precision Medicine

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What is Gluten?

• Gluten is a protein composite found in foods containing wheat*, barley, rye and triticale (a cross between wheat and rye)

• One of gluten’s two main proteins, GLIADIN, is a densely packed protein and digested into long amino acid chains with a low surface area to volume ratio, making it difficult to digest.

• Immune reactions to gliadin can occur in 3 forms: Celiac Disease, Non-Celiac Gluten Sensitivity and wheat allergy

Celiac Disease vs Gluten Sensitivity?

• Celiac Disease 1% of population
• Primary antibodies:
  • tissue transglutaminase (tTg)
  • endomysial antibodies (EMA)
  • deaminated gliadin peptide (DGP)
    - only in Celiac Disease

• Gluten Sensitivity 10% of population:
• Antibodies:
  • native gliadin antibodies (AGA IgA)- not different in schizophrenia
  • native gliadin antibodies (AGA IgG)
• During World War II, as wheat consumption decreased in Scandinavia, admissions for schizophrenia decreased.

• As wheat consumption in the United States increased, admissions for schizophrenia increased.

Dohan FC, Acta Psychiatr Scand. 1966;42(1):1-2, with permission
AGA (IgG) in Schizophrenia vs. Healthy Controls

Cihakova, et al 2017

- AGA IgG Mean Values 17.9 ± 21.4  SZ
- AGA IgG Mean Values 9.2 ± 13.2  HC

Two other published papers have shown increased OR of 2-5 for AGA IgG in schizophrenia

Could this be a schizophrenia subgroup??

• A subgroup with inflammation?
• A subgroup with different underlying disease etiology?
• A subgroup with a different treatment strategies?
• Moving towards precision medicine in schizophrenia?
Correlation of AGA IgG: Serum and Cerebral Spinal Fluid (CSF)

<table>
<thead>
<tr>
<th>Schizophrenia</th>
<th>Controls</th>
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<td>n=105</td>
<td>n=61</td>
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\[ R^2 = 0.34, \quad p < 0.0001 \] ns

Results independent of Antipsychotic treatment (N=75 naïve)

Leaky Gut and Blood Brain Barrier?

Severance EG, et al. *Brain Behav Immun*, 2015;44: 148-158; figure provided and used with permission
AGA IgG Linked to Peripheral and Brain Inflammation?
Can brain function be altered by removing gluten?

33 year old man with schizophrenia having severe diarrhea and weight loss.

Use of single photon emission computed tomography (SPECT) showed hypoperfusion in the left prefrontal cortex without evidence of structural cerebral abnormalities.

Jejunal biopsy showed villous atrophy and EMA antibodies present. Gluten free diet started.

Six months after a gluten-free diet, cerebral blood flow normalized, duodenal findings resolved and all psychiatric symptoms disappeared.
Pilot Study Results – 2 patients for 2 weeks

Jackson et al. Schiz Research 2012:140(1-3):262-3
Randomized Double-Blind Gluten-Free Diet Study

• Double-blind randomized gluten-free inpatient feasibility study for 5 weeks

• All participants received a gluten free diet
  • Protein shake daily with 10 gm of Gluten flour or 10 gm of Rice flour

• First gluten free diet study in schizophrenia to recruit a subgroup

• Clinical Trials.gov NCT#01927276 (NIMH funded R34)

Results?

• Exciting results to share at Grand Rounds in October
• Replication randomized double blind inpatient study underway with larger sample

• Screening approximately 500-800 people with schizophrenia or schizoaffective disorder at University of Maryland and Johns Hopkins for AGA IgG positive

NCT03183609   NIMH
R01MH112617-01  Kelly and Eaton PIs

Call Megan Powell: 410-402-6413 for free screening information
With Many Thanks!

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https://www.youtube.com/watch?v=y-9lOpPUDg0

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