How Gluten can affect the Brain: From Seizures and Headaches to Anxiety and Inattention

GIG
Gluten intolerance Group
Corte Madera
Tuesday, February 8th, 2011

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Why is GIG important? Importance of this lecture?

- James Braly and Ron Hoggan, the authors of *Dangerous Grains*, estimate the incidence of gluten sensitivity to be around 30% of the population.
- Dr Fine of Enterolab, based on results of IgA antibody tests and gene tests from his laboratory, estimates gluten sensitivity to be 30-40% of the general population.
- (Pts. with) Celiac disease comprise at least 1% of the healthy population (Sanders et al, 2003; West and Logan, 2003)
- Of Celiac patients, 10-22.5% have neurological disease (Holmes, 1997; Briani et al, 2008)
Facts-gluten sensitivity and neurological disease

• 1966 first comprehensive report neurological manifestations in tissue biopsy proven Celiac disease (Cook et al, 1966)

• For every 7 patients who present to a gastroenterologist and are diagnosed with Celiac disease, there will be 2 patients who present to a neurologist (Hadjivassiliou et al, 2010) (with Celiac).

• Most patients who present with neurological manifestations of gluten sensitivity have no gastrointestinal symptoms (Hadjivassiliou et al, 2010). Therefore, gluten sensitivity cannot be diagnosed on a clinical basis alone.*
**Difficulties presenting outline of gluten-induced neurological disease due to overlap between conditions**

**Celiac**
- Celiac enteropathy, without neurological disease
  Celiac with enteropathy with neurological disease in 10-22.5% (Holmes, 1997; Briani et al, 2008)
- Celiac disease without gastrointestinal symptoms
- Neurological disease without enteropathy was identified in 1990’s (majority of patients with neurological disease) (Hadjivassiliou, et al 2010)
- Neurological presentations are thought to occur in 6 to 10% with cerebellar ataxia being the most frequent symptom, (Bürk et al, 2009).
  - Non celiac gluten-induced disease
    Antibodies to gluten, barley, rye and wheat
    Food allergies can cause anxiety, inattention/cognitive fog and fatigue
  - Maldigestion- glutemorphin elevation on urine testing-spaciness, pupil dilation
Possible gluten-associated neurological and neuropyschiatric disease

- Anxiety
- Ataxia (idiopathic, familial) with or without neuropathy
- Attention deficit
- Developmental delay
- Encephalopathy
- Epilepsy, especially temporal lobe
- Headache
- Hypoperfusion
- Hypotonia
- Neuropathy (poor, conflicting evidence)
  - peripheral, sensory, motor
- Sleep disorders
- misc. possible: myopathy, autonomic neuropathy, white matter lesions, multiple system atrophy, dystonia, childhood stroke (Grossman, 2008; Zingone et al, 2010)
Supporting information

1. Labs
2. Bibliography
4 gluten sources. Top - gluten flour, Right - Spelt, Bottom - Barley, Left - Rolled Rye flakes

[Link to Wikipedia page](en.wikipedia.org/wiki/Pdeitiker)
Gluten ingestion and anxiety

- Anxiety and depression in adult patients with celiac disease on a gluten-free diet.
- Häuser W, Janke KH, Klump B, Gregor M, Hinz A. Germany.

AIM: To compare anxiety and depression levels in adult patients with celiac disease (CD) on a gluten-free diet (GFD) with controls.

METHODS: The levels of anxiety, depression and of a probable anxiety or depressive disorder were assessed by the Hospital Anxiety and Depression Scale in 441 adult patients with CD recruited by the German Celiac Society, in 235 age- and sex-matched patients with inflammatory bowel disease (IBD) in remission or with slight disease activity, and in 441 adult persons of a representative German general population sample (GP). Potential demographic (age, sex, social class, family status) and disease-related (latency to diagnosis, duration of GFD, compliance with GFD, thyroid disease) predictors of anxiety and depression in CD were tested for by regression analyses.

RESULTS: The level of anxiety in CD patients was predicted ($R^2 = 0.07$) by female gender ($P = 0.01$). Female sex (OR = 3.6, 95% CI: 1.3-9.4, $P = 0.01$) was associated with a probable anxiety disorder. Living alone (OR = 0.5, 95% CI: 0.2-0.9, $P = 0.05$) was associated with a reduced risk of an anxiety disorder. The level of depression and a probable depressive disorder were not predicted by any of the demographic and medical variables tested for. The levels of anxiety in patients with CD (6.6 +/- 3.4) and with IBD (6.9 +/- 3.7) were higher than those of persons in the GP (4.6 +/- 3.3) (both $P < 0.001$). The levels of depression in persons with CD (4.2 +/- 3.4), IBD (4.6 +/- 3.4) and of the GP (4.2 +/- 3.8) did not differ ($P = 0.3$). The prevalence of a probable anxiety disorder in persons with CD (16.8%) and IBD (14.0%) was higher than that of the GP (5.7%) ($P < 0.001$). The prevalence of a probable depressive disorder did not differ significantly between the three groups ($P = 0.1$).

CONCLUSION: Anxiety in adult German female celiacs on a GFD is higher than in persons of the GP. Female celiacs on a GFD should be screened for anxiety.
Anxiety and encephalopathy

- **Gluten encephalopathy with psychiatric onset: case report.**
- Poloni N, Vender S, Bolla E, Bortolaso P, Costantini C, Callegari C.
- Italy.
- **ABSTRACT:** A 38-year-old man was admitted as to our department an inpatient for worsening anxiety symptoms and behavioural alterations. After worsening of his neuropsychiatric conditions, with the onset of a frontal cognitive deficit, bradykinesia and difficulty walking, dysphagia, anorexia and hypoferraemic anaemia, SPECT revealed a reduction of cerebral perfusion and EMG/NCS results were compatible with a mainly motor polyneuropathy. Extensive laboratory investigations gave positive results for anti-gliadin antibodies, and an appropriate diet led to a progressive remission of the encephalopathy.
Anxiety lowers with removing gluten in Celiac disease

- Psychoneurotic symptoms and alexithymia in coeliac disease.
  - Collin P, Kaukinen K, Mattila AK, Joukamaa M. Finland.

OBJECTIVE: Depression, psychological problems and the impairment of quality of life are reported to occur in untreated coeliac disease. Alexithymia ("no words for feelings") is associated with various gastrointestinal disorders. The aim of this study was to evaluate whether patients with coeliac disease suffer from psychoneurotic symptoms or alexithymia, and whether a gluten-free diet has an impact on the symptoms.

MATERIAL AND METHODS: The Crown-Crisp Experiential Index (CCEI) and its six subscales were applied to measure neurotic psychopathology, and the 20-item version of the Toronto Alexithymia Scale (TAS-20) and its 3-factor scales to measure alexithymia. The testing was carried out in 20 consecutive adult patients with biopsy-proven coeliac disease before and after one year of treatment on a gluten-free diet. The data were compared with those obtained earlier in non-coeliac Finnish subjects.

RESULTS: Somatic anxiety was higher in coeliac disease patients before the introduction of the gluten-free diet than after adhering to the diet. Otherwise, the diet had no significant impact on the CCEI scores. The patients were not suffering from alexithymia, but the TAS-20 score improved significantly during the follow-up. The scores did not differ from those published in the Finnish population.

CONCLUSIONS: Psychological problems were not common in adult coeliac disease patients. Gluten-free diet had only a minor influence on the symptoms. Common knowledge about coeliac disease and the readily available gluten-free products may have had an impact on these results.
Anxiety subset-social phobia in Celiac

- Social phobia in coeliac disease.
- Rome, Italy.

OBJECTIVE: A high prevalence of anxiety and depression has been reported in coeliac disease (CD). Although social phobia is included among the anxiety disorders, its presence in CD has never been investigated. The aim of the present study was to evaluate social phobia in CD patients.

MATERIAL AND METHODS: A total of 40 CD patients were consecutively enrolled in the study. Fifty healthy subjects were studied as controls. Social phobia was assessed by the Liebowitz Social Anxiety Scale (LSAS) and current depression by the modified version of the Zung Self-rating Depression Scale (M-SDS).

RESULTS: The percentage of subjects with social phobia was significantly higher in CD patients than in controls (70% versus 16%; p<0.0001), and also when the more severe generalized form was considered (15.0% versus 0%; p=0.006). The percentage of subjects with social phobia was not statistically different between newly diagnosed subjects and patients on a gluten free diet (73.3% versus 68%; p: NS), nor considering its generalized form (7.0% versus 20%; p: NS). Current depression was present in a significantly higher percentage of CD patients in comparison with controls (52.5% versus 8%; p<0.0001). A direct correlation between social phobia and current depression was found in CD patients (r=0.582; p<0.0001).

CONCLUSIONS: Despite the limited number of cases evaluated, the present study showed a significantly higher prevalence of social phobia in CD patients compared with in healthy subjects. Future studies are needed to clarify the possible social phobia-induced risks such as school and/or work failure in CD patients.
Anxiety-proposed mechanisms and treatment

- Food allergies
  histamine release, chemical cascade, leaky blood vessels, brain hypoperfusion

- Nutritional deficiencies leading to anemia
  (not enough oxygen carrying RBC’s to brain, get anxious)
  not enough protein in blood, low oncotic pressure, low blood pressure, low blood perfusion to brain

- Celiac-anxiety lowers with gluten removal
Anxiety

• Test comprehensively for food allergies (IgE and IgG-mediated)
• Test for difficulties digesting food (gas by history, low pancreatic elastase 1 on stool testing, fats spilling into stool on stool testing, elevation urine peptides)
• Test for nutritional deficiencies and replace with good diet (protein, 5 veget/d, fruit, nuts, oils, grains if tolerate, no food allergens)
  nutritional supplements
  digestive enzymes
  antiinflammatory diet (omega 3,6,9 oils to increase PGE3)
• Therapy: b12 and folate (and pyridoxal 5 phosphate) lowered anxiety in patients with chronic Celiac  (Hallert et al, 2009)
Ataxia-(idiopathic, familial) with or without neuropathy

- **Ataxia** refers to a loss of the ability to coordinate muscular movement; staggering walk.
Ataxia and antibody elevation

- 500 patients with progressive ataxia, UK
- 101/215 with idiopathic sporadic ataxia, sero+, gluten sensitivity
- Gluten sensitivity
  - 20% of all pts with ataxia
<table>
<thead>
<tr>
<th>Condition</th>
<th>Anti-TG2 IgA</th>
<th>Anti-TG2 IgA/IgG</th>
<th>Anti-TG6 IgA/IgG</th>
<th>Anti-TG3 IgA/IgG</th>
<th>Anti-DGP IgA/IgG</th>
<th>DGP/TG antibodies</th>
</tr>
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<tbody>
<tr>
<td>Gluten ataxia and enteropathy on intestinal biopsy</td>
<td>82% (14/17)</td>
<td>88% (15/17)</td>
<td>65% (11/17)</td>
<td>57% (8/14)</td>
<td>94% (16/17)</td>
<td>0% (0/17)</td>
</tr>
<tr>
<td>Gluten ataxia and no enteropathy on intestinal biopsy</td>
<td>17% (3/28)</td>
<td>43% (12/28)</td>
<td>50% (14/28)</td>
<td>32% (6/19)</td>
<td>14% (4/28)</td>
<td>39% (11/28)</td>
</tr>
<tr>
<td>All gluten ataxia</td>
<td>38% (17/45)</td>
<td>60% (27/45)</td>
<td>56% (25/45)</td>
<td>42% (14/33)</td>
<td>44% (20/45)</td>
<td>24% (11/45)</td>
</tr>
<tr>
<td>Idiopathic sporadic ataxia</td>
<td>6% (1/17)</td>
<td>24% (4/17)</td>
<td>18% (3/17)</td>
<td>6% (1/17)</td>
<td>65% (11/17)</td>
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Antibodies crossreactive between transglutaminase isozymes were found in some patients and might therefore contribute to a positive test result in more than one assay. However, inhibition studies showed that TG6 antibodies did not crossreact with TG2 in most of these patients. – = no data. DGP = deamidated gliadin peptide. TG = transglutaminase.

Table 1: Antibody prevalence in patients with gluten ataxia defined as idiopathic sporadic ataxia with positive antigliadin antibodies and in patients with idiopathic sporadic ataxia negative for antigliadin antibodies.
Attention deficit hyperactivity disorder

- A preliminary investigation of ADHD symptoms in persons with celiac disease.
- Niederhofer H, Pittschieler K.
- Regional Hospital of Bolzano, Bolzano, Italy. helmutniederhofer@yahoo.de
- OBJECTIVE: Several studies report a possible association of celiac disease (CD) with psychiatric and psychological disturbances, such as ADHD.
- METHOD: The authors assess 132 participants from 3 to 57 years of age (M = 19.3 years) affected by CD for the possibility of an associated ADHD-like symptomatology, using the Conner Scale Hypescheme, a behavioral scale similar to the Conners Rating Scales, before their gluten-free diet was started and 6 months later.
- RESULTS: The overall score improves significantly as well as most of the ADHD-like symptomatology specific features (Bonferroni-corrected, paired-sample t tests).
- CONCLUSION: The data indicate that ADHD-like symptomatology is markedly overrepresented among untreated CD patients and that a gluten-free diet may improve symptoms significantly within a short period of time. The results of this study also suggest that CD should be included in the list of diseases associated with ADHD-like symptomatology.
Encephalopathy

- **Gluten encephalopathy with psychiatric onset: case report.**
- Poloni N, Vender S, Bolla E, Bortolaso P, Costantini C, Callegari C.
- Department of Clinical Medicine-Psychiatry, University of Insubria, Via O, Rossi 9, 21100 Varese, Italy. nicola.poloni@uninsubria.it.
- **Abstract**
- ABSTRACT: A 38-year-old man was admitted as to our department an inpatient for worsening anxiety symptoms and behavioural alterations. After worsening of his neuropsychiatric conditions, with the onset of a frontal cognitive deficit, bradykinesia and difficulty walking, dysphagia, anorexia and hypoferraemic anaemia, SPECT revealed a reduction of cerebral perfusion and EMG/NCS results were compatible with a mainly motor polyneuropathy. Extensive laboratory investigations gave positive results for anti-gliadin antibodies, and an appropriate diet led to a progressive remission of the encephalopathy.
Figure 2: MRI in four patients with gluten encephalopathy
The extent and variability of white matter abnormalities caused by gluten sensitivity can be seen in these four patients (A–D). A and C show diffuse white matter changes, whereas B and D show more focal and patchy changes. Gluten-free diet results in complete resolution of the headaches but the white matter changes do not reverse. Repeat scanning while on the diet shows no progression.
Epilepsy-especially temporal lobe

- [Evaluation of mental status of children with malabsorption syndrome after long-term treatment with gluten-free diet (preliminary report)]. Kozłowska ZE. Poland
- The author examined 41 children, suffering from celiac disease with psychiatric methods and EEG. The children, aged 7-17 y., were many years on gluten-free diets. Various psychiatric symptoms were found in 48.8%, and EEG abnormalities in 70.7%. Only 9 children (21.9%) were free from any psychiatric disorders and EEG abnormalities.
Celiac calcifications removed surgically stopped seizures

- Coeliac disease, unilateral occipital calcifications, and drug-resistant epilepsy: successful lesionectomy.
  Nakken KO, Røste GK, Hauglie-Hanssen E. Norway. karl.otto.nakken@epilepsy.no

PURPOSE: To draw attention to the triad of coeliac disease (CD), occipital calcifications, and drug-resistant epilepsy, with focus on the outcome of epilepsy surgery.

METHODS: We describe a male patient who despite a diagnosis of CD from the age of 9 did not comply with the gluten-free diet. At the age of 11 he developed simple and complex partial seizures with visual symptoms, anxiety, and ambulatory automatisms. His epilepsy appeared to be drug resistant, and after having tried nine antiepileptic drugs (AEDs), alone or in combinations, he underwent a presurgical evaluation at the age of 30. Interictal standard electroencephalograms (EEGs) disclosed frequent biparieto-occipital epileptiform discharges. Computed tomography showed cortical-subcortical punctate calcifications in the right parieto-occipital region, where his seizures seemed to start, according to ictal EEG registrations from intracranial strip electrodes.

RESULTS: At the age of 31 he underwent epilepsy surgery. A 5 x 6 cm large area of the right parieto-occipital region was resected, including the area with calcifications. Except for a few short-lasting episodes of anxiety (simple partial seizures?) he has now been seizure-free for 12 years. AEDs were withdrawn 5 years ago. Postoperatively he was left with an upper left-sided quadrant anopsia, which is not bothering him.

CONCLUSIONS: In patients with CD, unilateral occipital calcifications, and drug-resistant epilepsy, epilepsy surgery should be considered, as a lesionectomy might be very successful.
Celiac disease-Headache

- Headache in pediatric patients with celiac disease and its prevalence as a diagnostic clue.

OBJECTIVES: To establish the prevalence of headache in children with celiac disease (CD), the response to a gluten-free diet, and the prevalence of CD in children affected by headache.

METHODS: This hospital-based study included 2 steps. In the retrospective part, 354 children with CD answered a questionnaire investigating the presence of headache before and after the gluten-free diet. The same questionnaire was administered to 200 healthy children matched for sex and age. In the prospective part, 79 children affected by headache were screened for CD by antitransglutaminase IgA. Diagnosis of CD was confirmed by duodenal biopsy; before starting a gluten-free diet patients underwent a brain positron emission tomography study. After 6 months of follow-up children were reevaluated for the presence of headache.

RESULTS: Overall, 88 patients with CD complained of headaches before the diagnosis of CD as compared with 16 in the control group (24.8% vs 8%, P < 0.001). After the institution of a gluten-free diet, the headaches significantly improved in 68 children (77.3%), of whom 24 (27.3%) were headache-free during the study period. Four of 79 (5%) headache patients were found to have CD compared with 0.6% of the general population (P = 0.005). The brain positron emission tomography studies did not show any anomalies. During the follow-up, headaches improved in all 4 children with CD.

CONCLUSIONS: Screening for CD could be advised in the diagnostic work-up of patients with headache.
Child neurology-gluten and neurological disease

- Range of neurologic disorders in patients with celiac disease.
- METHODS: Children and young adult patients with CD - questionnaire regarding the presence of neurologic disorders or symptoms. Their medical charts were reviewed, and those who were reported as having neurologic manifestations underwent neurologic examination and brain imaging or electroencephalogram if required. Their neurologic data were compared with that of a control group matched for age and gender.
- RESULTS: Pediatric and young adult patients with CD were more prone to develop neurologic disorders (51.4%) in comparison with control subjects (19.9%). These disorders include hypotonia, developmental delay, learning disorders and ADHD, headache, and cerebellar ataxia. Epileptic disorders were only marginally more common in CD. Therapeutic benefit, with gluten-free diet, was demonstrated only in patients with transient infantile hypotonia and migraine headache.
Hypoperfusion and Celiac

- Regional cerebral hypoperfusion in patients with celiac disease.

**BACKGROUND:** Neurological and psychiatric disorders occur in approximately 10% of patients with celiac disease. Although some of these alterations respond to a gluten-free diet, the etiology of these abnormalities is uncertain. Because of a case report that cerebral hypoperfusion in a celiac patient resolved after a gluten-free diet, we studied brain perfusion changes in untreated celiac patients, treated celiac patients, and healthy controls.

**METHODS:** A total of 15 untreated celiac patients without conditions affecting brain perfusion were enrolled; none had neurological or psychiatric disorders other than anxiety or depression. We also studied 15 celiac patients who were on a gluten-free diet for almost 1 year, and 24 healthy volunteers of similar sex and age. All subjects underwent cerebral single photon emission computed tomography examination.

**RESULTS:** Of the 15 untreated celiac patients, 11 (73%) had at least one hypoperfused brain region, compared with only 1 (7%) of the 15 celiac patients on a gluten-free diet and none of the controls (P = 0.01). Cerebral perfusion was significantly lower (P <0.05) in untreated celiac patients, compared with healthy controls, in 7 of 26 brain regions. No significant differences in cerebral perfusion were found between celiac patients on a gluten-free diet and healthy controls.

**CONCLUSION:** There is evidence of regional cerebral blood flow alteration in untreated celiac patients.
"Maybe she's gluten intolerant."
Gluten sensitivity-induced sensory neuropathy (vs B12 deficiency)

- 409 patients with different types of peripheral neuropathies, 53 (13%) had clinical and neurophysiologic evidence of sensory ganglionopathy. Out of these 53 patients, 17 (32%) had serologic evidence of gluten sensitivity. The mean age of those with gluten sensitivity was 67 years and the mean age at onset was 58 years. Seven of those with serologic evidence of gluten sensitivity had enteropathy on biopsy. Fifteen patients went on a gluten-free diet, resulting in stabilization of the neuropathy in 11. The remaining 4 had poor adherence to the diet and progressed, as did the 2 patients who did not opt for dietary treatment. Autopsy tissue from 3 patients demonstrated inflammation in the dorsal root ganglia with degeneration of the poster columns of the spinal cord. Hadjivassiliou M, Rao DG, Wharton SB, Sanders DS, Grünewald RA, Davies-Jones AG. Neurology. 2010 Sep 14;75(11):1003-8. Sensory ganglionopathy due to gluten sensitivity.
Sleep disorders (secondary to anxiety, depression, fatigue) in patients with Celiac disease

- Italy.

METHODS: The participants were coeliacs at diagnosis; coeliacs on a gluten-free diet at follow-up and healthy volunteers. Participants completed the Pittsburgh Sleep Quality Index (PSQI), SF36, Zung and Fatigue scales and State-Trait Anxiety Inventory (STAI).

RESULTS: The PSQI score was higher in coeliacs at diagnosis and in a gluten-free diet than in healthy volunteers (P < 0.001). A gluten-free diet did not improve the PSQI score (P = 0.245) in coeliac disease. The other test scores were similar between coeliacs at diagnosis and those on a gluten-free diet, whereas significant differences were found between coeliacs and volunteers. PSQI score was inversely associated with the quality of the physical (r = -0.327, P = 0.002) and mental (r = -0.455, P < 0.001) component scores. The poor sleep quality scores were related to depression (r = 0.633, P < 0.001), fatigue (r = 0.377, P < 0.001), state anxiety (r = 0.484, P < 0.001) and trait anxiety (r = 0.467, P < 0.001).

CONCLUSIONS: Sleep disorders are common in coeliac disease not only at diagnosis but also during treatment with a gluten-free diet. Sleep disorders are related to depression, anxiety and fatigue, and inversely related to quality of life scale scores.
Help! I'm Coeliac.
Get me out of here!!
Lab testing
Gluten intolerance (nonCeliac) lab testing

- **Non Celiac**
  - IgE and IgG Type 4 to gluten, wheat, barley and rye (Alcat, IBT, Meridian Valley labs)
  - Elevated gluteomorphin (urine peptide test)
  - Swab inside mouth - HLA-DQ testing - HLA genes having DQ2 or DQ3 subtype 8 (or simply DQ8) are the two main HLA-DQ genes that account for the villous atrophy accompanying gluten sensitivity (in America, 90% of celiacs have DQ2 [a more Northern European Caucasian gene], and 9% have DQ8 [a more southern European/Mediterranean Caucasian gene], with only 1% or less usually having DQ1 or DQ3).
  - Gluten sensitivity to result in celiac sprue (i.e., result in villous atrophy of small intestine), it requires at least 2 other genes also. Thus, not everyone with DQ2 or DQ8 get the villous atrophy of celiac disease. My hypothesis is that everyone with these genes will present gluten to the immune system for reaction, i.e., will be gluten sensitive.
  - Dr. Fine and other published research has shown that DQ1 and DQ3 also predispose to gluten sensitivity, and certain gluten-related diseases (microscopic colitis for DQ1,3 in my research and gluten ataxia for DQ1 by another researcher).

Dr. Fine. Enterolab.
Celiac disease lab testing

Celiac
- anti TG2 (IgA and IgG), anti TG6, deamidated gliadin antibodies
- duodenal biopsy (villous atrophy )
- buccal swab for genetic predisposition to Celiac

HLA genes HLA-DQ testing from swab of inside of mouth

HLA-DQ3 subtype 8 (one of the main celiac genes) acts almost identically in the body as HLA-DQ3 subtype 7, 9, or other DQ3 subtypes. Having DQ2 or DQ3 subtype 8 (or simply DQ8) are the two main HLA-DQ genes that account for the villous atrophy accompanying gluten sensitivity (in America, 90% of celiacs have DQ2 [a more Northern European Caucasian gene], and 9% have DQ8 [a more southern European/Mediterranean Caucasian gene], with only 1% or less usually having DQ1 or DQ3). Gluten sensitivity to result in celiac sprue (i.e., result in villous atrophy of small intestine), it requires at least 2 other genes also. Thus, not everyone with DQ2 or DQ8 get the villous atrophy of celiac disease. My hypothesis is that everyone with these genes will present gluten to the immune system for reaction, i.e., will be gluten sensitive. My more recent research, when DQ1,1 or DQ3,3 are present together, the reactions are even stronger than having one of these genes alone (like DQ2,2, DQ2,8, or DQ8,8 can portend a more severe form of celiac disease).

Dr. Fine. Enterolab.
- Patient with neurological presentation, for which the aetiology could be explained by gluten sensitivity (e.g., idiopathic ataxia or neuropathy)
- Patient should be on a normal diet (i.e., containing wheat, barley, rye)
- Absence of gastrointestinal symptoms should not affect the decision to test for gluten sensitivity

Testing for gliadin, deamidated gliadin and anti-TG2 (largely replacing endomysium antibodies) IgA and IgG antibodies

If positive for one or more antibodies, patient should be referred for duodenal biopsy

If negative for all antibodies, try to test for anti-TG6 and HLA DQ2 or DQB variants or refer to a specialist centre

Enteropathy

No enteropathy or borderline histology

Test for IgA deposits against TG on the biopsy (limited availability)

Gluten sensitive
Strict gluten-free diet with regular clinical and serological monitoring

Gluten sensitivity excluded

Uncertain diagnosis
- Consider referral to a specialist centre or discuss the option of strict gluten-free diet with patient if no alternative aetiology and progressive disease
- Close clinical and serological monitoring (improvement or stabilisation does not manifest until after a year of strict gluten-free diet with serological elimination of the antibodies)

Gluten sensitivity excluded
Lab testing-possibilities

- when eating gluten:
  IgA and IgG to TG2 (transglutaminase)
  antiTG6 (neurological) (not available clinically yet)
  antiTG3 (dermatitis herpetiformis-itchy vesicular rash)
  Antigliadin (gluten sensitivity, may not be Celiac)
  IgG to deamidated gliadin peptides (Celiac specifically) 100% positive predictive value in adults

- Untreated patients have elevated AGA and TG antibodies
  *IgG testing, instead of IgA testing, is useful if there is an IgA deficiency

- Gold std has been: endoscopy with small bowel biopsy (villous atrophy, crypt hyperplasia and inflammation) but may be changing to serological tests (da Silva Neves et al, 2010)
- Anti TG2 IgA within the intestinal mucosa seems to be present in patients with neurological disorders (Hadjivassilious et al, 2006)
Adjunctive labs

- Fasting amino acids (to determine if can even make antibodies and may pick up mito. d/o)
- IgA (to determine if there is IgA deficiency, which would make it difficult to find an elevation of IgA to TG, for example.
- IgE (immediate allergy) and IgG Type 4 (delayed hypersensitivity) to gluten and each to gliaden and to foods that contain gluten (wheat, rye, barley) i.e. Alcat, IBT, Meridian Valley Labs, Metametrix, etc.
- Urine peptide test (Great Plains, Metametrix)
- Stool calprotectin (inflammation), pancreatic elastase 1 (lack of digestive enzymes), bacterial culture, fungal culture, ova and parasite, antibacterial and antifungal sensitivities, other gut disease evaluation (giardia, h. pylori, cryptosporidium, etc)
Pathophysiology of gluten-induced neurological disease

1) immune mediated
2) nutritional deficiencies
3) brain hypoperfusion
4) leaky gut (increased permeability of gut) due to food allergy
   a) gastroenteritis
   b) Inflammation in gut
   c) Loss digestive enzymes
Pathophysiology continued

- Immune-mediated
  a. Patchy loss of Purkinje cells of the cerebellar cortex
  b. Diffuse infiltration of T lymphocytes within the cerebellar white matter as well as marked perivascular cuffing with inflammatory cells
Figure 3: The immunopathology of gluten ataxia
Cerebellar tissue from a patient with gluten ataxia (A). This perivascular inflammatory infiltrate is a characteristic finding in patients with neurological manifestations of gluten sensitivity and might contribute to the loss of the integrity of the blood-brain barrier, enabling circulating antibodies to enter the CNS. Serum from patients with gluten ataxia reacts with Purkinje cell epitopes (B). Perivascular TG6 deposits are present in the cerebellum of a patient with gluten ataxia (C). The end result of these events is the loss of Purkinje cells (D) shown here in a cerebellar section from a patient with gluten ataxia showing profound loss of Purkinje cells.
Pathophysiology of neuropathy

• Sparse lymphocytic infiltrates with perivascular cuffing in sural nerve biopsy in patients with gluten neuropathy and in dorsal root ganglia in patients with sensory neuronopathy and patients with myopathy caused by gluten sensitivity

• Celiac disease patients, similar findings (Cook, 1966)
Pathophysiology-cross reactivity of antibodies

- AGA antibodies bind to Purkinje cells of human cerebellum
(Hadjivassiliou, 2010)
Neuronopathy-cross reactivity

- Antibody cross reactivity with neuronal protein synpasin I
- Gliadin binds to GM1 ganglioside
  (ganglioside antibodies are associated with autoimmune peripheral neuropathies)
- Blood from Celiac disease patients with neurological manifestations evoke a mitochondrial-dependent apoptosis in vitro suggesting neurotoxic antibodies (Cervio et al, 2007)
Treatment

- Gluten free diet
- Nutritional supplementation, check, supplement
  - Amino acids
  - Vitamins A, D, E, fat soluble, EFA, cholesterol
  - B vitamins (esp B12, B6, folate (B9))
- Removing other food allergens (and/or environmental allergens)
- Checking stool for other disease, treat other disease
- Consider mitochondrial support
  - ribose 5 phosphate, l-carnitine, coenzyme Q10, NADH
- Steroids (last resort)
B vitamin supplementation

In a double blind placebo controlled multicentre trial, 65 coeliac patients (61% women) aged 45-64 years on a strict gluten-free diet for several years were randomized to a daily dose of 0.8 mg folic acid, 0.5 mg cyanocobalamin and 3 mg pyridoxine or placebo for 6 months. The outcome measures were psychological general well-being (PGWB) and the plasma total homocysteine (tHcy) level, marker of B vitamin status.

The tHcy level was baseline median 11.7 micromol/L (7.4-23.0), significantly higher than in matched population controls [10.2 micromol/L (6.7-22.6) (P < 0.01)]. Following vitamin supplementation, tHcy dropped a median of 34% (P < 0.001), accompanied by significant improvement in well-being (P < 0.01), notably Anxiety (P < 0.05) and Depressed Mood (P < 0.05) for patients with poor well-being.

• CONCLUSIONS: Adults with longstanding coeliac disease taking extra B vitamins for 6 months showed normalized tHcy and significant improvement in general well-being, suggesting that B vitamins should be considered in people advised to follow a gluten-free diet. (Hallert et al, 2009)
Treatment-gluten free diet

- Studies of gluten-free diet in patients with gluten sensitivity and neurologic syndromes have shown variable results. Diet trials also have been inconclusive in autism and schizophrenia, 2 diseases in which sensitivity to dietary gluten has been implicated. Further studies clearly are needed to assess the efficacy of gluten-free diet and to address the underlying mechanisms of nervous system pathology in gluten sensitivity (Bushara, 2005).
Efficacy of nutritional therapies
Anti gliadin and gluten-sensitive HLA alleles- apraxia and autism-treatment

• Verbal apraxia is a neurologically based motor planning speech disorder of unknown etiology common in autism spectrum disorders.

• A total of 187 children with verbal apraxia received vitamin E + polyunsaturated fatty acid supplementation. A blood celiac panel, fat-soluble vitamin test, and carnitine levels were analyzed. A common clinical phenotype of male predominance, autism, sensory issues, low muscle tone, coordination difficulties, food allergy, and GI symptoms emerged. In all, 181 families (97%) reported dramatic improvements in a number of areas including speech, imitation, coordination, eye contact, behavior, sensory issues, and development of pain sensation. Plasma vitamin E levels varied in children tested; however, pretreatment levels did not reflect clinical response. Low carnitine, high antigliadin antibodies, gluten-sensitivity HLA alleles, and zinc and vitamin D deficiencies were common abnormalities. Fat malabsorption was identified in 8 of 11 boys screened.

• A subgroup of children with a previously unrecognized syndrome of allergy, apraxia, and malabsorption, are responsive to nutritional interventions in addition to traditional speech and occupational therapy. (Morris and Agin, 2009)
"Breathtaking!"

THE ZEN OF FARTING

Teachings from Original Zen Master

Reepah Cud Wan
Celiac disease

• Ataxia
• Cerebral calcifications
• Dementia
• Depression in the elderly
• Migraines (some with calcifications)
• Multiple sclerosis (IgG to TG and AGA), not IgA
• NMO (neuromyelitis optica)
• Neuropathy (peripheral)
• encephalopathy, chorea, brain stem dysfunction, myelopathy, mononeuritis multiplex, Guillain-Barre-like syndrome, and neuropathy with positive antiganglioside antibodies
Celiac disease-serological abnormalities and abnormal intestinal biopsy  (Grossman, 2008)

• Celiac disease is caused by a reaction to gliadin, a prolamin (gluten protein) found in wheat, and similar proteins found in the crops of the tribe Triticeae (which includes other common grains such as barley and rye). Upon exposure to gliadin, and specifically to three peptides found in prolamins, the enzyme tissue transglutaminase modifies the protein, and the immune system cross-reacts with the small-bowel tissue, causing an inflammatory reaction. That leads to a truncating of the villi lining the small intestine (called villous atrophy). This interferes with the absorption of nutrients, because the intestinal villi are responsible for absorption. The only known effective treatment is a lifelong gluten-free diet. While the disease is caused by a reaction to wheat proteins, it is not the same as wheat allergy. (Binning, 2010; Di Sabatino et al, 2009; (Adams, 1856; Losowsky, 2008).
Celiac disease

- autoimmune disorder caused by a permanent sensitivity to gluten in genetically susceptible individuals (Bernini et al, 2010) leading to an inappropriate T-cell-mediated immune response (da Silva Neves et al, 2010), causing a disorder of the small intestine, a chronic enteropathy (Schippa et al, 2010),

- In children: abdominal pain, diarrhea or constipation, vomiting, and meteorism Barbato M, Curione M, Amato S, Carbone J, Briani C, Pannone V, Maiella G, Di Camillo C, Panetti D, Cucchiara S.

- Growth failure, infertility and neurological disorders (da Silva Neves et al, 2010).

- CD has a well-defined metabonomic signature
• meteorism - accumulation of gas in the abdomen or the intestine, usually with distension.
CD has a well-defined metabonomic signature.

There was a significant higher microbiota biodiversity among active and remission state ($P = 0.000224$) Celiac disease patients and between active CD and controls ($P < 0.001$). Bacteroides vulgatus and Escherichia coli were detected more often in CD patients than in controls ($P < 0.0001$).


A distinctive 'microbial signature' in celiac pediatric patients.
Celiac disease metabonomics

- Sera of CD patients were characterized by lower levels (P < 0.01) of several metabolites such as amino acids, lipids, pyruvate and choline, and by higher levels of glucose and 3-hydroxybutyric acid, while urines showed altered levels (P < 0.05) of, among others, indoxyl sulfate, meta-\text{[hydroxyphenyl]}propionic acid and phenylacetylglucose. Bertini I, Calabrò A, De Carli V, Luchinat C, Nepi S, Porfirio B, Renzi D, Saccenti E, Tenori L., J Proteome Res. 2009 Jan;8(1):170-7.

- The metabonomic signature of celiac disease.
Celiac disease-neurologic conditions

- Cerebellar ataxia, 5%
- Elderly-depression
- Headache, RR 3.2
- Neuropathy, peripheral
- Neuropsychiatric disease
- Restless leg syndrome
- Seizures, 2.1 vs 1.7% incidence
- Sensorineural hearing loss-children, unilateral or bilateral and adults
- Sympathetic tone increased
- White matter lesions in brain
Celiac-ataxia and dementia

- Up to 8% of patients with gluten sensitivity (GS) develop neurological symptoms such as ataxia, dementia, seizures or peripheral neuropathy. A 68 yr man with progressive ataxia and dementia associated with chronic diarrhea and both elevated IgG and IgA antigliadin-antibodies. At autopsy, frequent argyrophilic glial and neuronal inclusions within the basal nucleus of Meynert (Alzheimer’s center in the frontal lobes) were considered as the structural correlate for the cognitive decline. Significant neuronal loss in the cerebellar cortex and the inferior olives (lesions in these structures can cause ataxia) was accompanied by infiltrating CD8(+) /perforin(+) /granzyme B(+) cells as well as reactive astroglialosis and microglial activation. These CD8(+) cytotoxic T and NK cells are likely to act as effector cells responsible for neuronal cell death in patients with gluten sensitivity and neurological disease and might therefore at least partly be responsible for cerebellar symptoms in gluten ataxia. Prominent cytotoxic effects in neuropathogenesis of GS (not humoral) (Mittelbronn et al, 2010).
Celiac-meta-analysis Pediatric neurological disease

- University of Catania, Italy.

Meta-analysis of the paediatric literature on the neurology of coeliac disease.

- (1950-2009). Fifteen studies were analysed (11 772 participants). The meta-analysis showed that (1) the relative risk of epilepsy in individuals with celiac disease, and of celiac disease in individuals with epilepsy, compared with the general population, was 2.1 and 1.7, respectively, and the risk difference was close to zero, probably a chance association; and (2) the relative risk of headache in individuals with the disease compared with comparison groups was 3.2. In two studies, cerebellar ataxia was documented in 2.7 to 5.4% of participants; in two further studies, the risk of cerebellar dysfunction was zero. Two studies found an association between celiac disease and peripheral neuropathy. Brain white matter lesions were recorded in two other studies. An association between autism and celiac disease is disputed. Interpretation Children with celiac disease are at risk of developing neurological complications, but the risk is lower than in adulthood. The discrepancy might be due to short disease duration, early elimination of gluten from the diet, stricter adherence to diet, or different susceptibility to immune-mediated disorders.
Celiac and other noted neurological diseases

- encephalopathy, chorea, brain stem dysfunction, myelopathy, mononeuritis multiplex, Guillain-Barre-like syndrome, and neuropathy with positive antiganglioside antibodies (Bushara, 2005). The association between most neurologic syndromes described and gluten sensitivity remains to be confirmed by larger epidemiologic studies.
Celiac-cerebral calcifications

• occipital cerebral calcifications, sometimes it means the existence of a syndrome called "Gobby's Syndrome". We show a patient with a mild unknown celiac disease, a woman who had occipital cerebral calcifications in a TAC cerebral, which was made because of her intractable migraines and that it lead to the diagnosis. Migraine disappeared after a gluten free-diet. Benito Conejero S, Díaz Espejo C, López Domínguez JM, Pujol de la Llave E. An Med Interna. 2006 Mar;23(3):127-9.

• [Cerebral calcifications: a clue for a diagnostic process in a nonspecific clinical case].
Fig. 1. TAC de cráneo que muestra las típicas calcificaciones occipitales bilaterales de tipo giriformes en una paciente con enfermedad celíaca.
Fig. 2. RNM de cráneo de la misma paciente.
Elderly and depression

- 52-74 years. Depression (and Rheumatoid arthritis) were found more often in antigliadin positive antibodies than in controls. (some are Celiac + by biopsy (AGA and tTGA+ and some are Celiac – on bx , i.e. some of whom were AGA +, tTGA-).


- Positive serum antigliadin antibodies without celiac disease in the elderly population: does it matter?

•
Celiac disease and multiple sclerosis

- We determined the level of serum IgA and IgG antigliadin and antitissue transglutaminase antibodies in 98 patients with multiple sclerosis. We found a highly significant increase in titers of IgG antibodies against gliadin and tissue transglutaminase in the MS patients. 7 patients had a positive IgG AGA, whereas only 2 controls presented positive titers ($P = 0.03$). 4 patients had positive IgG anti-tTG while all the controls tested negative ($P = 0.02$). (However, IgA antibodies against gliadin and tTG were not statistically higher in the MS group in comparison to the control group.) Our findings support the associations between antibodies against gliadin and tTG to MS (Shor et al, 2009).
NMO (neuromyelitis optica) and Celiac disease

• 2 Caucasian women who, nineteen and two years after diagnosis of CD, respectively, had recurrent episodes of myelitis and optic neuritis consistent with the diagnosis of NMO. Despite numerous relapses, NMO followed an unusually mild course with no persistent neurological deficit (Bergamaschi et al, 2009).
Celiac and neuromyelitis optica (NMO)

- NMO is a condition which preferentially affects demyelination of the optic nerves and spinal cord, and is distinct pathogenically from MS.
- Neuromyelitis optica IgG is the first antibody marker for any inflammatory central nervous system disorder, and is both sensitive and specific for NMO. Its target antigen, aquaporin-4, is the most abundant water channel in the central nervous system.
- NMO-IgG may be the initiator of the NMO lesion.
- NMO-IgG has been identified in patients with recurrent optic neuritis or longitudinally extensive myelitis and its presence predicts subsequent relapse.
- NMO-IgG can modulate AQP4 function and fix complement (Wingerchuk, 2007).
NMO clinically

- The NMO IgG has been associated, in some patients, single-episode or recurrent longitudinally extensive myelitis, recurrent isolated optic neuritis, Asian optic-spinal multiple sclerosis, and patients with co-existing systemic autoimmune diseases such as lupus erythematosus or Sjögren's syndrome (Weinshenker and Wingerchuk, 2008).
NMO and autoimmune disease

• NMO is associated with other autoimmune disorders in around 30% of cases (Pittock, 2008).
“I HOPE THIS IS GLUTEN-FREE!”
Celiac disease and neuropsychiatric manifestations

• Although neurological and psychiatric conditions affect celiac patients, no disorder specifically associated with celiac disease has been identified. Lewis NR, Holmes GK. Expert Rev Gastroenterol Hepatol. 2010 Dec;4(6):767-80.

• Risk of morbidity in contemporary celiac disease.
Celiac-restless leg syndrome

- 31% prevalence of RLS in the CD population significantly higher than the prevalence in the control population (4%; P < 0.001). The average severity of RLS in CD population was moderate (17 +/- 6.5). In the CD population, no significant correlation was found between RLS and either gluten-free diet or iron metabolism, despite hemoglobin levels were significantly lower in CD patients with RLS than without RLS (P = 0.003). Moccia M, Pellecchia MT, Erro R, Zingone F, Marelli S, Barone DG, Ciacci C, Strambi LF, Barone P. Mov Disord. 2010 May 15;25(7):877-81.

- Restless legs syndrome is a common feature of adult celiac disease.
sensorineural hearing loss was found in 13 (40.6%) patients (group A), bilateral in 6, unilateral in 7 patients (mean = 11 yrs). The frequency of hearing loss was significantly higher in CD group than in group C (p<0.001). Hizli S, Karabulut H, Ozdemir O, Acar B, Abaci A, Dağlı M, Karaşen RM. Int J Pediatr Otorhinolaryngol. 2011 Jan;75(1):65-8. Epub 2010 Nov 10.

Autonomic imbalance in celiac children.
Celiac disease and stroke

- The first patient had experienced several transient ischemic strokes in the past 2 years and then had an acute ischemic stroke involving the territory of the right posterior cerebral artery. No other cause except Celiac disease. Persistent visual aftereffects, but no new vascular event.

- The second patient had Celiac disease confirmed by pathology and serology tests. She was on a gluten-free diet. The patient had an ischemic stroke involving the territory of the left middle cerebral artery. Apart from a positive serology for celiac disease and iron deficiency anemia, the etiological work-up was negative.

- DISCUSSION: The mechanisms of vascular involvement in celiac disease are controversial. The most widely incriminated factor is autoimmune central nervous system vasculitis, in which tissue transglutaminase, the main auto-antigen contributing to maintaining the integrity of endothelium tissue, plays a major role. Other mechanisms are still debated, mainly vitamin deficiency.

- CONCLUSION: Being a potentially treatable cause of ischemic stroke, celiac disease must be considered as a potential etiology of stroke of unknown cause, particularly in young patients, and even without gastrointestinal manifestations. (El Moutawakil, 2009)
Treatment-Celiac

- Strict 100% gluten free diet
- Check for nutritional deficiencies, replete
- Check for other autoimmune disease
- Antiinflammatory diet
- Check for food allergies, environmental allergies
- Check for other gut disease
- Consider head MRI, NeuroSPECT, EEG
- Steroids (last resort)
Steroids stabilized spastic paraparesis

- A 41-year-old woman. Celiac disease resistant to gluten-free diet, developed rapidly spastic paraparesis, cerebellar syndrome, horizontal diplopia and decline of visual acuity. The diagnosis of neurological complications of Celiac disease was established and the patient was treated with methylprednisolone, followed by oral prednisone. For 9 years, the patient's neurological status remained stabilized with a prednisone dose at 20mg per day. The patient relapsed when progressive reduction of prednisone dose was attempted; neurological and gastrointestinal signs worsening at 15mg per day; increasing the dose to 30mg improved the clinical status (Haddou et al, 2009).
Mimicker of gluten-induced neurologic dysfunction

- The mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE) is a rare and life-threatening, autosomal recessive, multisystem disorder, caused by the mutations in the thymidine phosphorylase gene. 21 year-old male long history of intestinal pseudo-obstruction. Pseudo-obstruction and neurologic manifestations. The patient was a member of a consanguineous family of six children, in whom two sisters had died due to this disorder and one sister was affected and is still alive. The patient presented with cachexia, abdominal pain, diarrhea and muscle weakness, and was previously considered to have gluten sensitive enteropathy and treated with dietary solutions. Oztas E, Ozin Y, Onder F, Onal IK, Oguz D, Kocaefe C. J Gastrointestin Liver Dis. 2010 Jun;19(2):195-7.

- Chronic intestinal pseudo-obstruction and neurological manifestations in early adulthood: considering MNGIE syndrome in differential diagnosis.
MNGIE (not gluten sensitivity)

- 1. ptosis/ophthalmoparesis
- 2. gastrointestinal dysmotility
- 3. peripheral neuropathy
- 4. ragged red fibers or succinate dehydrogenase activity in muscle biopsy
- (5. brain MRI leukodystrophy)
- (6. mtDNA defects in peripheral blood or muscle biopsy)

- Nausea, vomiting
- Ataxia
- Weight loss
- Sensory neuropathy in extremities
- Absent tendon reflexes
- (Oztas et al, 2010)
MNGIE clinically (not gluten sensitivity)

- Lactic acid, pyruvic acid, amino acids look at alanine/lysine ratio
- Xray-air-fluid levels SI diffuse thickening SI wall after dilute barium ingestion
- EMG bilateral sensorimotor neuropathy, esp LE
- Head MRI increased T2 signal subcortical and periventricular white matter bihemispheres (Oztas et al, 2009)
Labs-resources

- Labs

- Alcat, Deerfield Beach, FL, IgE and IgG against gluten, 800 US ALCAT, www.ALCAT.com
- Enterolabs, Dallas, TX (stool genetic testing for Celiac and gluten sensitivity) 972 686 6869, www.enterolab.com
- Genova Asheville, NC, 800 522-4762, www.GDX.net
  **(urine peptide test)**
- IBT labs-, Lenexa, KS, can test individual IgE and IgG against gluten, 800 637 0370, www.ibtreflab.com
- Meridian Valley Lab, Renton, WA 425 271-8689 www.meridianvalleylab.com  
  blood testing IgE and IgG antibodies to food (including gluten)
- Metametrix, Duluth, GA, 800 221-4640, www.metametrix.com