

Conflict of Interest

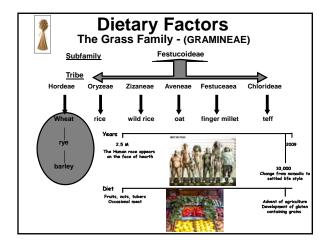
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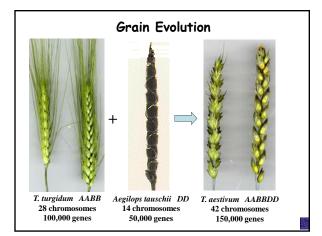
I will not discuss any product from Alba Therapeutics in my presentation. I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.

NEWS #1: Why Gluten is Toxic

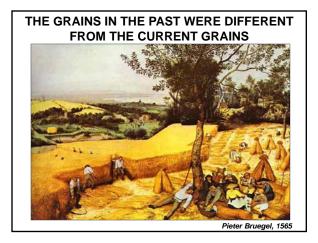




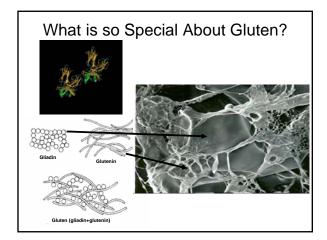




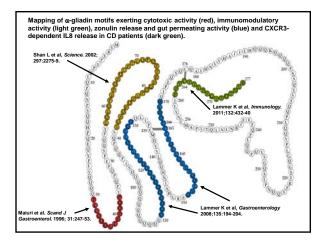




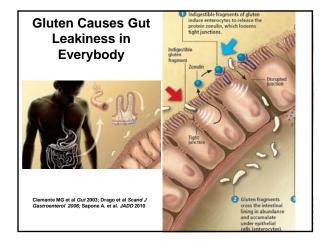
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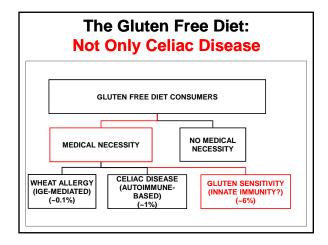




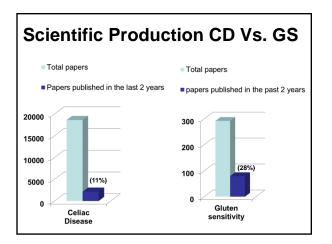




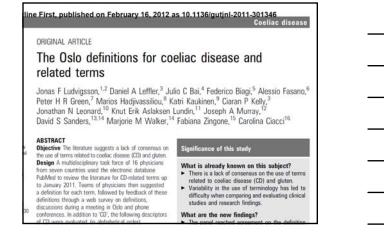
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Case Presentation: Diagnosis of Gluten Sensitivity

Description of the Case

AJ 19 y old F

- 6 months history of:
- 0 1 2 3 4 5 6
- Recurrent abdominal pain (mainly epigastric)
- Heartburn

Suspecting GERD, pt was placed on PPI, but no resolution of symptoms.

One month after the onset of GERD symptoms pt developed headaches, dizziness, numbness of fingers, paresthesia, gradual reduction of legs' muscle strength that forced her on a wheelchair.

Description of the Case

23456

0 1 Suspecting neurological cause, patient underwent to:

MRI

Evoked potentials

Both resulted negative

Other diagnoses that were considered include:

- · Lyme disease;
- Epstein Barr Virus
- Pernicious Anemia
- Lupus

All were ruled out

Description of the Case

0

1 2 3 4 5 6

Because of the persistence of GERD symptoms pt underwent to an EGD reported as normal (including duodenal biopsy that showed only increased IEL). She was also screened for CD and tested negative Despite negative results, pt decided to embrace a GFD

Within 3 weeks her GI symptoms resolved

Within 2 months her neurological symptoms ٠ also improved. Six month after implementation of the GFD she was able to walk with the assistance of a cane. Twelve months later she regained completely her walking function.

Gluten Sensitivity: Definition

Cases of gluten reaction in which both allergic and autoimmune mechanisms have been ruled out (diagnosis by exclusion criteria)

- · Negative immuno-allergy tests to wheat;
- Negative CD serology (EMA and/or tTG) and in which IgA deficiency has been ruled out;
- Negative duodenal histopathology;
- · Presence of biomarkers of gluten immune-reaction (AGA+);
- Presence of clinical symptoms that can overlap with CD or wheat allergy symptomatology;
- Resolution of the symptoms following implementation of a GFD (double blind)

Gluten Sensitivity: What is the Magnitude of the Problem? The CFCR Experience (2004-2010)

- Nr. of the patients seen at the CFCR clinic: 5,896
- Nr. of patients fulfilling criteria for GS: 347
- Prevalence in our cohort: 1:17 (6%)

Symptoms:

- Abdominal pain: 68% Eczema and/or rash: 40%
- Headache: 35%
- "Foggy mind": 34% Fatigue: 33% Diarrhea: 33% •

- Depression: 22%
- Anemia: 20% •
- Numbness legs/arms/fingers: 20% •
- Joint pain: 11%

Gluten Sensitivity and IBS

<u>Cell Mol Immunol.</u> 2013 Aug 12. doi: 10.1038/cmi.2013.28. [Epub ahead of print] Non-celiac gluten sensitivity: questions still to be answered despite increas awareness. <u>Volta U, Caio G, Tovoli F, De Giorgio R.</u> reasing

Abstract Recently, the increasing number of patients worldwide who are sensitive to dietary gluten without evidence of celiac disease or wheat allergy has contributed to the identification of a new gluten-related syndrome defined as non-celiac gluten sensitivity. Our knowledge regarding this syndrome is still lacking, and many sapects of this syndrome remain unknown. Its pathogenesis is heterogeneous, with a recognized pixel of lof rinnait immuny, many other factors also controbust, chung how grave measurements in other in increase my measurements and are then and charges in the tractors also controbust, chung how grave measurements in other in increase my measurements and are then and charges in the tractors also controbust, chung how grave measurements in other in increase my measurements and are then and charges in the tractors also but it has also been hypothesized for 00.53% to 65. Form a cincing point of wive, non-celiac gluten and improve or distributing from 0.53% to 65. Form a cincing point of wive, non-celiac gluten assertisity is characterized by a wide array of gastrointestinal and extraintestinal symptoms that occur shortly after the ingestion of spluten and improve or disappear when gluten is withmarken from the der. These symptoms recur when gluten is relative or disappear when gluten is withmarken from the der. These symptoms recur when gluten is relative or disappear when gluten is withmarken from the der. These symptoms recur when gluten is relative or disappear when gluten is withmarken from the der.

Cellular & Molecular Immunology advance online publication, 12 August 2013; doi:10.1038/cmi.2013.28.

Am J Gastroenterol. 2012 Dec;107(12):1898-906; quiz 1907. doi: 10.1038/ajg.2012.236.

Am J Gastroenterol, 2012 Dec;10/(12):1898-906; quiz 1907. doi: 10.1038/ajg.2012.236. Epub 2012 Jul 24. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. Carroccio A, Mansueto P, Iacono G, Soresi M, D'Alcamo A, Cavataio F, Brusca I, Florena AM, Ambrosiano G, Seidita A, Pirrone G, Rini GB. Source

Source Division of Internal Medicine, Hospital of Sciacca, ASP, Agrigento, Italy. acarroccio@hotmail.com

Abstract OBJECTIVES: Non-cellia wheat sensitivity (WS) is considered a new clinical entity. An increasing percentage of the general population avoids gluten ingestion. However, the real existence of this condition is debated and specific markers are lacking. Our aim was thus to demonstrate the existence of WS and define its clinical, serologic, and histological markers. METHODS:

mc INUUS: We reviewed the clinical charts of all subjects with an initiable bowel syndrome (IBS)-like presentation who had been diagnosed with WS using a double-bind placebo-controlled (DBPC) challenge in the years 2001-2011. One hundred cellac disease (CD) platients and fifty IBS patients served as controls. **RESULTS**:

RESULTS: Two hundred and seventy-six patients with WS, as diagnosed by DBPC challenge, were included. Two groups showing distinct clinical characteristics were identified: WS alone (group 1) and WS associated with multiple lood hypersensitivity (group 2). As a whole group, the WS patients showed a higher frequency of anonia, weight local, self-reported wheat inclearance, coexistent atopy, and lood allergy in infancy than the IBS controls. There was also a higher frequency of positive serum assays for (gG/lgA and igidant and cytometric baschal adviction in "n trior bascs. The main histology characteristical WS patients was esciencial influence on the double on in "to the same transmission" in WS alone were characterized by clinical features was initiar to these found in CD patients. Patients with multiple lood sensitivity were characterized by clinical features similar to these found in altergic patients.

CurveLUSUURS: Our data confirm the existence of non-celiac WS as a distinct clinical condition. We also suggest the existence of two district populations of subjects with WS: one with characteristics more similar to CD and the other with characteristics pointing to food allergy.

J Gastroenterol. 2011 Mar;106(3):508-14; quiz 515. doi: 10.1038/ajg.2010.487. Epub 2011 Jan 11.

Gluten causes gastrointestinal symptoms in subjects without celiac disease: a doubleblind randomized placebo-controlled trial. Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, Shepherd SJ,

Muir JG, Gibson PR.

Source — — Monash University Department of Medicine and Gastroenterology, Box Hill Hospital, Box Hill, Victoria, Australia.

Abstract OBJECTIVES: Despite increased prescription of a gluten-free diet for gastrointestinal symptoms in individuals who do not have celiac disease, there is minimal evidence that suggests that gluten is a trigger. The aims of this study were to determine whether gluten ingestion can induce symptoms in non-celiac individuals and to examine the mechanism. Instrument in the symptome study of the stud

METHODS: A colubi-bilind, randomized, placebo-controlled rechallenge trial was undertaken in patients with irritable bowel syndrome in whom celiac disease was excluded and who were symptomatically controlled on a guten-free det. Participants received either guten or placebo in the from r hot bread sides plus con multifin perd aywith a guten-free det or up to sweeks. Symptoms were evaluated using a visual analog scale and markers of intestinal inflammation, injury, and immune activation were

monitored. RESULTS: A total of 34 patients (aged 29-59 ears, 4 men) completed the study as per protocol. Overall, 56% had human leukocyte antiger (HLA)-DQ2 and/HLA-DQ8. Adhreence to det and supplements was very high. Of 19 patients (68%) in the gluten group, 13 reported that symptoms were not adequately controlled compared with 6 of 15 (40%) on placeto (P=0.0001; generalized selamiating equation). Dn a visual analog scale, platent were significantly works with gluten within 1 week for overall symptoms gliadin antibodies were not induced. There were no significant charges in fecal lactorerin, levels of celiac antibodies, highly sensitive C-reactive protein, or intestinal permeability. There were no differences in any end point in individuals with or without DQ2DQ8. sensitive dreature process DO2D08. CONCLUSIONS: "Non-celiac gluten intolerance" may exist, but no clues to the mechanism were elucidated.

No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR.

Department of Gastroenterology, Eastern Health Clinical School, Monash University, Box Hill, Victoria, Australia; Department of Gastroenterology, Central Clinical School, Monash University, The Alfred Hospital, Melbourne, Victoria, Australia.

Abstract BACKGROUND & AIMS:

BACKNOUND 4 Aller Patients with non-cellie gluten sensitivity (NCGS) do not have celliac disease but their symptoms improve when they are placed on gluten-free detes. We investigated the specific effects of gluten after detary reduction of ferminetable, poort absorbed, short-chain carbohystrates (termentable, log), -d. nonoschandes, and poologis (FDDMAPB) in subjects belief

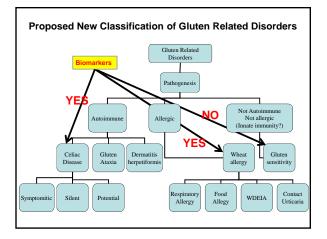
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RESULTS: In all participants, gastrointestinal symptoms consistently and significantly improved during reduced FODMAP intake, but significantly worsened to a similar degree when their dels included gluten or whey protein. Gluten-specific effects were observed in only 5% of participants. There were no decepticit changes in any biomarker. During the 3-day reduilange, and the second An order effect was observed.

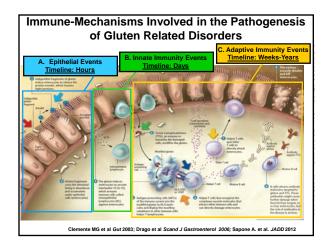
In a placebo-controlled, cross-over rechallenge study, we found no evidence of specific or dose-dependent effects of gluten in patients with NCGS placed diets low in FODMAPs. www.anzctr.org.au. ACTRN12610000524099.

FODMAP		uitable alto		ng size)
Problem high FODMAP food	Honey Sweeteners: fructose, high fructose corn syrup Large total fructose dose: concentrated fruit sources; arge serves of fruit, dried fruit, fruit juice	Mik: cow, goat and sheep (regular & low-fat), ice cream Yoghurt (regular & low-fat) Cheeses: soft & fresh (e.g. ricotta, cottage)	Vegetables: artichokes, asparagus, beetroot, Brussels sprout, broccoli, cabbage, fernet, garic, leeks, okra, onions, peas, shallots. Cereals: wheat & rye when eater in large amounts (e.g. bread, pasta, couscous, crackers, biscuits) (Lagumes: chickpeas, lentils, red biscuits)	Fruits: apples, apricots, cherries, longon, lychee, nashi pears, netatine, pears, pearse, peins, prunse, naatemeton Soperatives: avocado, caudiflower, mushrooms, anow peas Sweeteners: sorbiol(420), statistic (865), partial (963) & athers ending in "of
Suitable alternative low- FODMAP food source	Fruit: banana, blueberry, carambola, durian, grapetru, grape, honeydew melon, isma, mandatin, orange, passionfruit, jenoon, lime, mandatin, orange, passionfruit, jeno paw, raspberry, rockmelon, strawberry, tangelo. Horey substitutes: maple syrtup, golden syrup Sweeteners: any except polyols	Cheese:'hard' cheeses including brie, camembert Yoghurt: lactose-free Ice cream substitutes: gelati, sorbet Butter	capsicum, choko, choy sum, corn, eggplant, green beans, lettuce, chives, parsnip, pumpkin, silverbeet, spring	Fruits: banana, blueberry, carambola, durian, grapefuri, grape, honeydew melon, kwihrui, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rockmelon Sweeteners: sugar (sucrose), glucose, other artificial sweeteners not ending in 'of





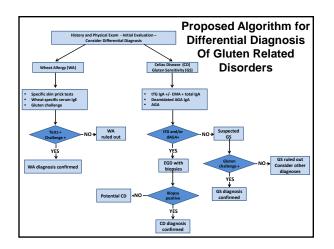






	Celiac Disease	Gluten Sensitivity	Wheat Allergy
Time interval between gluten exposure and onset of symptoms	Weeks-Years	Hours-Days	Minutes-Hours
Pathogenesis	Autoimmunity (Innate+ Adaptive Immunity)	Immunity? (Innate Immunity?)	Allergic Immune Response
HLA	HLA DQ2/8 restricted (~97% positive cases)	Not-HLA DQ2/8 restricted (50% DQ2/8 positive cases)	Not-HLA DQ2/8 restricted (35-40% positive cases as in the general population)
Auto-antibodies	Almost always present	Always absent	Always absent
Enteropathy	Almost always present	Always absent (slight increase in IEL)	Always absent (eosinophils in the lamina propria)
Symptoms	Both intestinal and extra-intestinal (not distinguishable from GS and WA with GI symptoms)	Both intestinal and extra- intestinal (not distinguishable from CD and WA with GI symptoms)	Both intestinal and extra- intestinal (not distinguishable from CD and GS when presenting with GI symptoms)
Complications	Co-morbidities Long term complications	Absence of co-morbidities and long term complications (long follow up studies needed to confirm it)	Absence of co-morbidities. Short-term complications (incliuing anaphylaxis)







Diagnosis of Gluten Sensitivity

Take Home Messages:

- Gluten Sensitivity is not rare;
- Gluten Sensitivity cannot be distinguished from Celiac Disease purely on the clinical basis;
- Gluten Sensitivity can present with vague, nonspecific symptoms;
- A gluten free diet can be considered only when other forms of gluten reactions and other causes of pt's symptoms have been ruled out;
- Listen to your patient!!!