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ALSUntangled No. 32: Gluten-free diet

The ALS Untangled Group

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RESEARCH ARTICLE

ALSUntangled No. 32: Gluten-free diet

THE ALS UNTANGLED GROUP*

Overview

Gluten is a protein found in wheat, rye and barley (1). It causes adverse reactions in 5% of those who ingest it (1). There are several specific gluten-related disorders (GRDs) including celiac disease (CD), wheat allergy (WA), non-celiac gluten sensitivity (NCGS) and gluten ataxia (GA). These immune-mediated conditions often (but not always) cause gastrointestinal symptoms such as abdominal pain, bloating and diarrhea (1,2). Some can also cause neurological problems such as confusion, seizures, ataxia and neuropathy (2–5). Here we investigate the possible connections between GRDs and ALS, and the potential use of a gluten-free diet (GFD) to treat ALS.

Mechanism(s)

There have been multiple previous attempts to associate GRDs with ALS. Two studies looked to see if CD and ALS occurred together more commonly than expected by chance. The first used records from hospital admissions in England between 1999 and 2011 to identify cohorts of patients with various autoimmune diagnoses including CD, and then compared the frequency of an emerging ALS diagnosis (coded after the original autoimmune one) in each cohort with the frequency in matched otherwise healthy controls (6). Here, patients with CD were more likely than expected (relative risk 1.57, $p = .005$) to develop ALS. Problems with this study include failure to confirm the coded CD or ALS diagnoses, failure to adequately describe the matched controls, failure to describe the follow-up interval, and potential for bias incurred by focusing only on hospitalized patients. The second study used the Swedish Patient Register to identify a cohort of 29,093 individuals with CD confirmed by small intestine biopsy between 1969 and 2008 (7). Over 11 years of follow-up, the frequency of an emerging ALS diagnosis (established by International Classification of Disease codes) in this cohort was compared to the frequency in 144,515 well-matched otherwise healthy controls. No increased risk of ALS was detected in the CD cohort. A weakness of this study is the failure to confirm the coded ALS diagnoses.

One very recent study looked for antibodies typically found in GRDs in PALS without gastrointestinal symptoms or autoimmune diagnoses. Here, the frequencies of detectable tissue transglutaminase 2 (TG2) and tissue transglutaminase 6

*The ALSUntangled Group currently consists of the following members: Richard Bedlack, Colin Quinn, Chafic Karam, Alex Sherman, Lyle Ostrow, Orla Hardiman, Terry Heiman-Patterson, Laurie Gutmann, Mark Bromberg, Gregory Carter, Edor Kabashi, Tulio Bertorini, Tahseen Mozaffar, Peter Andersen, Jeff Dietz, Josep Gamez, Mazen Dimachkie, Yunxia Wang, Paul Wicks, James Heywood, Steven Novella, L. P. Rowland, Erik Pioro, Lisa Kinsley, Kathy Mitchell, Jonathan Glass, Sith Sathornsumetee, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlayne Jackson, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorenson, Christen Shoesmith, Steven Nash, Nicholas Maragakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, Dan Pastula, Gleb Levitsky, Mieko Ogino, Jeffrey Rosenfeld, Efrat Carmi, Merit Cudkowicz, Christina Fournier, Paul Barkhaus, Brett Morrison, Lorne Zinman, Craig Oster, Eric Valor, Neta Zach, Ahmad Ghavanini, Yvonne Baker, Kristiana Salmon.

Note: this paper represents a consensus of those weighing in. Every investigator in this group does not necessarily share the opinions expressed in this paper.

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Table 1. TOE Grades for GFD as an ALS Treatment.

	Grade	Explanation
Mechanism	C	GFD can reduce inflammation, including levels of tissue transglutaminase antibodies, and thus might theoretically prevent immune-mediated damage to motor neurons
Pre-clinical	U	No known studies of GFD in preclinical ALS models
Cases	A	One peer-reviewed publication reporting benefits with validated diagnosis and benefits
Trials	U	No known trials of GFD in ALS
Risks	C	At least! 0% of patients on GFD may experience side-effects including weight loss (but no serious adverse events)

(TG6) antibodies, anti-endomysial (EM) antibodies, and deaminated gliaden peptide (DGP) antibodies were compared between a cohort of 150 patients with ALS by El Escorial criteria and a cohort of 115 healthy volunteers of similar age and gender (8). No difference was found in TG2, EM or DGP antibodies, but 15% of PALS had TG6 antibodies compared to only 4% of controls (a difference that was statistically significant).

In addition to these association studies, overlapping pathophysiology between GRDs and ALS also strengthens a potential link. GRDs are thought to be autoimmune diseases, involving certain antibodies and alterations in T-lymphocytes and cytokines (1–5,9,10). The pathophysiology of ALS may also involve immune dysregulation (reviewed in (11)). Interestingly, TG6, one of the antigens targeted by certain GRD antibodies, is found on spinal motor neurons (12), pointing to a specific way that gluten-induced autoimmunity could create a motor neuron disease.

Since GFD can reduce gluten-induced immune dysregulation, including tissue transglutaminase antibody levels (13), it could thus theoretically be useful in PALS. ALSUntangled assigns a TOE 'Mechanism' grade of C based on this information (Table I).

Pre-clinical data

We found no trials of GFD in any pre-clinical model of ALS. ALSUntangled assigns a TOE 'Pre-clinical' grade of U based on this information (Table I).

Data in PALS

There are two published case-reports claiming that GFD helped PALS. One describes a 32-years-old male with one year of worsening balance difficulties and tremor in the setting of chronic weight loss and diarrhea (14). Exam showed ataxia on finger-to-nose testing, and a Babinski sign, but no definite lower motor neuron signs. EMG was normal. Brain MRI showed T2 hyperintensities in corticospinal tracts and corona radiata. Total spine MRI and CT of the chest, abdomen and pelvis were normal. Blood work was notable for EMA, and intestinal biopsy was consistent with CD. GFD was initiated. Over 'several months' his 'symptoms' and neuroimaging improved. No more details are given. Although MRI abnormalities such as his have been described in PALS (15), these are not specific. This patient would not have met criteria for ALS due to lack of lower motor neuron signs. The ataxia described would also be unusual in ALS.

The other describes a 44-years-old male with six months of progressive lower extremity onset weakness (16). Exam showed upper and lower motor neuron signs in the right arm and leg, nerve conductions were normal, and EMG showed fasciculations and reinnervation in bulbar, cervical and lumbosacral segments. Brain MRI showed T2 hyperintensities in the corticospinal tracts and right subcortical pre-central gyrus. CSF testing was unremarkable. Blood work showed a mild microcytic anemia with low ferritin. Testing for HIV and JC virus was unremarkable. As part of the work-up for anemia and low ferritin, EM antibody was drawn and found to be elevated. Intestinal biopsy confirmed a diagnosis of CD. GFD was started. Nine months into GFD he had marked objective improvements in his ability to walk, and writing and dressing returned to normal. EMA and MRI abnormalities also improved. These improvements lasted at least 2.5 years (date of last follow-up). In our opinion this patient met Awaji criteria for 'probable ALS' (17). Although spontaneous ALS reversals have been reported (18,19), these are very rare, and the temporal correlation between starting GFD and motor improvement here is impressive. Based on this, ALSUntangled assigns a 'Cases' grade of A (Table I).

We found no trials of GFD in PALS. ALSUntangled assigns a TOE 'Trials' grade of U based on this information (Table I).

Dosing, risks and costs

Instructions for initiating and maintaining GFD are widely available, but are fairly complex to follow (20). Vitamin and mineral deficiencies as well as weight loss may occur on GFD (20,21). These risks are especially concerning for PALS, since those who lose weight progress and die faster than those who do not (22). Referral to a dietician may be helpful in initiating and maintaining GFD, and monitoring

for nutritional deficiencies and weight loss (20). Based on this information, ALSUntangled assigns a 'Risks' grade of C (Table I).

There are an increasing number of 'gluten-free' food options available, but the cost of these is on average at least four times higher than comparable gluten-containing ones (23).

Conclusions

Theoretically, gluten-induced autoimmunity could trigger ALS. However, the data supporting this link are weak, consisting of two association studies and a single case-report. Further studies are needed to confirm the relationship between GRDs and ALS, and the utility of the GFD in patients with both conditions. In spite of the fact that GFD is reasonably safe, it is a complex undertaking and is more expensive than a standard diet. While we wait for better data, it would be reasonable to screen PALS who have GI symptoms, iron-deficiency anemia, or an abnormal brain MRI for the antibodies associated with GFDs. Those with elevated antibodies could be referred to a gastroenterologist for further work-up, and if this is consistent with a GRD, then GFD could be tried under the guidance and monitoring of a dietician.

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