Gluten Ataxia

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Gluten related disorders have been classified in three clinical entities:

- Autoimmune (celiac disease, gluten ataxia and dermatitis herpetiformis)
- Allergic (wheat allergy)
- Not-autoimmune/not allergic (gluten sensitivity)
Celiac neuropathy. Neurology. 2003 May

- Neurologic complications are estimated to occur in 10% of patients
- Ataxia and peripheral neuropathy being the most common problems
- Seizure disorders, schizophrenia, depression, migraine, and anxiety disorders, autism, MS, myasthenia gravis, myopathy
Gluten ataxia is an immune-mediated disease triggered by the ingestion of gluten in genetically susceptible individuals.

Should be considered in the DD of all patients with idiopathic sporadic ataxia.

Early diagnosis and treatment with a GFD can improve ataxia and prevent its progression.
Progressive gait and limb ataxia may be the sole manifestation of disease.

Ataxia related to celiac disease is not often associated with typical GI symptoms or malabsorption.

Gluten ataxia are believed to result from immunologic damage to the cerebellum, posterior column of spinal cord and peripheral nerves.
Its predominant clinical manifestations include:

- dysarthria, dysphonia
- pyramidal signs
- abnormal movements of eyes
- progressive ataxia of gait
Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics

Brain

A Journal of Neurology

Brain, 2003 - Oxford Univ Press
clinical characteristics

- In 68 patients with gluten ataxia:
  - mean age at onset of the ataxia was 48 years (range 14–81 years) with a mean duration of the ataxia of 9.7 years (range 1–40 years)
  - Ocular signs in 84% and dysarthria in 66%.
  - Upper limb ataxia in 75%, lower limb ataxia in 90%
  - Gait ataxia in 100% of patients.
GI symptoms in only 13%

Gluten-sensitive enteropathy in 24%

MRI revealed atrophy of the cerebellum in 79% and white matter hyperintensities in 19%

HLA DQ2 was present in 72% of patients
Gluten ataxia is the single most common cause of sporadic idiopathic ataxia.

AGA is essential at first presentation of patients with sporadic ataxia.
Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase.

Ann Neurol. 2008 Sep

- Anti-TG 2 IgA is linked with GI disease, an anti-transglutaminase 6 IgG and IgA is prevalent in gluten ataxia, independent of intestinal involvement.

- Studies showed that in those patients with ataxia and enteropathy, separate antibody populations react with the two different transglutaminase isozymes.
Transglutaminase 6 antibodies in the diagnosis of gluten ataxia

Neurology. 2013 May 7;80(19)

- Immunologic response primarily directed against transglutaminase (TG)6 in patients with gluten ataxia

- The prevalence of TG6 antibodies was 21 of 65 (32%) in idiopathic sporadic ataxia, 35 of 48 (73%) in GA, 16 of 50 (32%) in CD, and 2 of 57 (4%) in healthy controls.
42% of patients with GA had enteropathy.

Tissue transglutaminase 6 (TG6) is mostly expressed in a subset of neurons in the CNS.

55% of patients with CD tested positive for more than one type of transglutaminase.
After 1 year of GFD, TG6 antibody titers were significantly reduced or undetectable.

Antibodies against TG6 are gluten-dependent and appear to be a sensitive and specific marker of GA.

Postmortem analysis of brain tissue showed cerebellar IgA deposits contained TG6.
The deposition was most pronounced in the cerebellum, pons, and medulla.

Result: is immunological damage to the cerebellum, to the posterior columns of the spinal cord, and to peripheral nerves?
Antibodies against transglutaminase 6 can serve as a marker to identify a subgroup of patients with gluten sensitivity who may be at risk for development of neurological disease.
Gluten ataxia is characterized by positive AGA, changes in the cerebellum, and ataxic symptoms including upper or lower limb ataxia, gait ataxia, and dysarthria.

AGA is sensitive markers of gluten ataxia.
In addition to AGA, patients with gluten ataxia have oligoclonal bands in their CSF, inflammation at the cerebellum, and anti-Purkinje cell antibodies.

These studies suggest, we may have additional antibodies that react with Purkinje.

It seems likely that the Purkinje cells of the cerebellum share epitopes with gliadin proteins.
The humoral response in the pathogenesis of gluten ataxia (
*Neurology* April 23, 2002)

Using indirect immunocytochemistry on human cerebellar and CNS tissue, cross-reactivity of a commercial IgG antigliadin antibody with human cerebellar tissue also was studied.

Patients with gluten ataxia have antibodies against Purkinje cells. AGA cross-react with epitopes on Purkinje cells.
Other unknown antigens?

Research revealed AGA had a strong immunoreaction to synapsin I.

Synapsin I is a neuronal phosphoprotein found in most neurons of the central and peripheral nervous systems and plays a role in forming and sustaining the reserve pool of synaptic vesicles.
AGA may cross-react with synapsin I

In gluten sensitive patients, AGA could negatively affect synapsin I activity directly interfering with neurotransmitter release and possibly contributing to neurological impairments.
Antigliadin antibody in sporadic adult ataxia Iran J Neurol. 2012; Dr hamidian

- For 30 patients with idiopathic cerebellar ataxia, Serum AGA (IgA and IgG) and antiendomysial antibody (AEA) were assessed. Gluten ataxic patients underwent duodenal biopsy.

- Only 2 patients had a positive IgG AGA (6.7%) who both had a positive AEA while none of them showed changes of celiac disease in their duodenal biopsies.
Prevalence of gluten ataxia in Iranian patients with idiopathic ataxia seems to be lower than most of other regions.
Dietary treatment of gluten neuropathy

Gluten-free diet may thus be a useful therapeutic intervention for patients with gluten neuropathy. Muscle Nerve, 2006
Wheat allergy
wheat allergy

- IgE-mediated reactions to wheat affect about 0.5% of the worldwide population and can occur after ingestion (food allergy), inhalation (occupational asthma/rhinitis; e.g. baker’s asthma), contact (contact urticaria) or wheat-dependent exercise-induced anaphylaxis (WDEIA)

- Hypersensitivity to wheat accounts for most grain reactivity among patients with food allergies
Wheat Allergy

- Prevalence of and its clinical manifestations changes according to age

- Food-induced wheat allergy typically arises early in life and in most cases resolves by 3 to 5 years of age

- In birth cohort studies, the prevalence of wheat sensitization is about 4% in pre-school children and progressively increases with age from 2 to 9% from 2 to 10 years old, mainly due to the secondary sensitization with grass pollen allergy
Cross reaction

- Cross-reactivity between wheat flour and grass pollen has been proved and is due to the presence of common pan-allergens both in pollens and wheat:
- 65% of patients with grass pollen allergy show specific IgE (sIgE) against wheat
- Up to 40% of wheat allergic patients have sIgE against grass pollen
21 allergenic components have been identified in wheat grain and classified into two groups, according to their solubility:

- The water/dilute salt-soluble proteins [albumins and globulins]
- Gliadins (soluble in aqueous alcohol) and glutenins (soluble in dilute alkali or acid)
Gliadins are considered as markers of genuine wheat sensitization

Specific role of the different allergenic components of wheat as elicitors of different clinical reactions and the cross-reactivity with pollens still need to be clarified
little information is available on the most reliable wheat allergens for predicting clinical reactivity
Specific IgE

- Positive IgE responses to ≥5 different allergenic components improved diagnostic accuracy (LR+) of 5.10.

- Alpha-amylase inhibitors (AAI) (LR+ 6.12), alpha-, beta-, and gamma-gliadins (LR+ from 3.57 to 4.53), and high-molecular-weight (HMW) glutenin subunits (LR+ 4.37)
In one study dimeric AAI, known as a relevant allergen in clinically reactive patients.

The accuracy improved by measuring IgE responses to several components of wheat.
Clinical history is often unreliable

To date, there are no skin tests or other laboratory tests that will confirm or exclude food allergy with certainty
In infants under the age of 1 year, the tests suggest relevant food allergy because at this age the secondary development of tolerance has hardly taken place.

In older children, tests has to be confirmed by elimination challenge because of false positive.

Tests remain positive after tolerance.
Prick test

- Prick /puncture method of skin testing used for evaluation of IgE mediated food allergy in a patient with clinical history.

- Highly effective to exclude IgE mediated allergy particularly in a patient with low pre test probability and should not be used for screening.
High probability

- A clinical history of suspected immediate (within 1 hour) adverse reaction after wheat ingestion
- Symptoms suggestive of atopic dermatitis, food and respiratory allergy (asthma and/or rhinoconjunctivitis)
- Parental history of atopy
Atopy patch tests (APT) is a useful tool in the diagnostic work up of food-allergy-related GI symptoms.

Whereas SPT had a high sensitivity, but low specificity for predicting the outcome of oral food challenge, APT had a high specificity but low sensitivity.

Combining these two tests improves the overall predictive power.
Diagnosis

- Serum total IgE concentration and wheat-specific IgE should be measured.
- Skin prick and patch tests for wheat should be done.
Diagnosis

The diagnosis of wheat allergy was confirmed with an open oral food challenge.
food challenge

- wheat was given orally in increasing amounts in 15-minute intervals starting from a dose of 50 mg to reach the total of 18-20 g (3.24-3.6 g of wheat protein). If there was no reaction, wheat was administered daily (>20 g of wheat) at home for 7 days.

- If the adverse effects had been observed, WA was diagnosed.
In one study:

- Patients with positive food challenge (symptoms occurring within 2 hours after wheat consumption)
- GI symptoms (vomiting, loose stools, abdominal pains)
- All had positive SPT as well as the high levels of sIgE
Thirty-two children (≤12 years old) with suspected wheat allergy were evaluated for wheat allergy. The patients underwent wheat skin prick test (SPT), measurement of wheat-specific IgE and wheat challenge test.

Anaphylaxis was a dominant clinical feature, accounting for 54.1% of acute symptoms. Chronic allergy symptoms like asthma and eczema were noted in 50% of the patients.
If, at any time, the patient becomes unstable from pulmonary, cardiovascular, or renal complications, perform a necrosectomy, minimally invasive if possible to remove necrotic debris and pus. If there has been no improvement after one week of antibiotics perform a percutaneous CT-guided aspiration. If there is bacterial infection, we consider performing a necrosectomy.

Thanks for your attention.