ORIGINAL ARTICLE

Ataxia and the Role of Antigliadin Antibodies

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ABSTRACT: ***Background:*** Although it is acknowledged that patients with celiac disease can develop neurological complications such as ataxia, the association of antigliadin antibodies in the etiology of sporadic ataxia and the usefulness of this testing in diagnosis of ataxia is controversial. ***Methods:*** We investigated this association by testing for the presence of IgG and IgA antigliadin antibodies in 56 ataxic patients and 59 controls. The ataxia patients were subsequently classified into three groups: sporadic, hereditary and MSA. ***Results:*** Of the total ataxic patients, 6/56 (11%) were positive for either IgG or IGA antigliadin antibodies compared to the controls of which 5/59 (8%) were positive (p = 0.68). In a subgroup analysis, 4/29 (14%) of the samples in the sporadic ataxic subgroup were positive for antigliadin antibodies (IgG or IgA) compared to control (p = 0.44). Similar negative results were found in the remaining subgroup analyses. ***Conclusions:*** These results do not support an association between antigliadin antibodies and sporadic ataxias.

RÉSUMÉ: Rôle des anticorps antigliadine dans l'ataxie. ***Contexte :*** Bien qu'il soit connu que les patients atteints de la maladie c?liaque peuvent présenter des complications neurologiques comme de l'ataxie, le rôle des anticorps antigliadine dans l'étiologie de l'ataxie sporadique et l'utilité de ce test dans le diagnostic de l'ataxie demeurent controversés. ***Méthodes :*** Nous avons étudié cette association chez 56 sujets ataxiques et 59 témoins chez qui nous avons vérifié la présence d'anticorps antigliadine IgG et IgA. Les patients ataxiques ont ensuite été répartis en trois groupes, selon qu'ils étaient atteints d'ataxie sporadique, héréditaire ou d'atrophie multisystémique. ***Résultats :*** Six des 56 patients ataxiques (11%) et 5 des 59 témoins (8%) avaient des anticorps antigliadine IgG ou IgA (p = 0,68). Une analyse de sous-groupes a montré que 4 des 29 patients atteints d'ataxie sporadique avaient des anticorps antigliadine (IgG ou IgA) par rapport aux témoins, p = 0,44. Des résultats négatifs ont également été obtenus lors de l'analyse des données des autres sous-groupes. ***Conclusions :*** Ces résultats ne sont pas en faveur d'une association entre les anticorps antigliadine et les ataxies sporadiques.

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Celiac disease is a chronic immune mediated disorder and manifests as a hypersensitivity to dietary gluten in some genetically predisposed individuals.[1] Clinically these patients may develop an enteropathy associated with bloating, diarrhea and sequelae of malabsorption. Celiac disease has been associated with a variety of neurological symptoms including ataxia, dementia and peripheral neuropathy.[2]

An early study demonstrated that gluten sensitivity was common in patients with a variety of neurological disorders of unknown etiology.[3] The majority of these patients lacked the histological evidence of celiac disease, however, ataxia was the most common neurological manifestation. A number of studies have since reported an association between gluten sensitivity and sporadic cerebellar ataxia in the absence of gastrointestinal symptoms, commonly referred as 'gluten ataxia'. These gluten ataxia patients do not have any distinct neurological features that

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help differentiate them from patients with sporadic ataxia nor from patients with celiac disease with ataxic symptoms.[4] Additionally, there has been a report of clinical improvement in patients with gluten ataxia who adhere to a strict gluten free diet.[5]

In a genetically predisposed individual, the consumption of gluten exposes the bowel to immunoreactive epitopes that initiate a maladapative immune response.[6] In patients with biopsy confirmed celiac disease IgA antigliadin antibodies (AGA) have a sensitivity of (81%-83%)[7] and a specificity of (82%-89%)[7] where as the sensitivity of IgG AGA is (82-99%)[7] and the specificity is (76%-92%).[7] It has been proposed that antigliadin antibody testing, a marker of gluten sensitivity, is an essential investigation for patients with sporadic ataxia[4,8] and antigliadin antibodies of the IgG type are the best marker for neurological manifestations of gluten sensitivity.[9] Some groups have reported antigliadin antibodies in as much as 12 to 68% of patients with sporadic ataxias.[3-4,8,10-13] Unfortunately, when these studies are scrutinized this association does not appear as robust as initially reported. Many of the studies that reported an association investigated a small population of sporadic ataxic patients[3,4,11] and the authors failed to report the prevalence of antigliadin positivity in a control population.[4,7,13,14] Other studies have failed to find an association.[11,14] Although one study found did find positive antigliadin antibodies in 19% of sporadic ataxia patients tested, this was not found to be statistically different from the prevalence of these antibodies in the control population.[11]

In light of the conflicting results surrounding the significance of elevation of antigliadin antibody in the literature, we examined the prevalence of the positivity of IgG and IgA antigliadin antibodies in a population of ataxic patients identified through a neurology outpatient clinic. The importance of such an association may lead to treatment in a population where such options are limited.

Methods

Patient selection

Ataxia patients were identified through a systematic review of the charts at a neurological outpatient clinic. The study included all adult patients (ie. older than 18 years old) identified with a clear diagnosis of adult onset ataxia. Patients were excluded if a symptomatic cause for their ataxia was identified (ie. stroke, hemmorhage, MS, tumor, alcohol, toxin, malignancy, vitamin B 12 or E deficiency, thyroid dysfunction, structural lesion).

A total of 86 adult patients with a clinically confirmed diagnosis of ataxia were identified. Patients were classified into three subgroups: hereditary ataxia, multiple system atrophy (MSA-C) or sporadic ataxia. Hereditary ataxia patients had either a positive genetic testing (autosomal dominant spino-cerebellar ataxia, Fredreich's ataxia, episodic ataxia type 2, or others) or at least one first degree relative with ataxia. Patients were diagnosed with clinically probable MSA-C according to the criteria published in the Consensus statement on the diagnosis of multiple system atrophy.[15] Patients were classified into the sporadic ataxia subgroup if the etiology of the ataxia was unknown, and they did not meet the diagnostic criteria for MSA-C. None of the patients enrolled in the study had a diagnosis of celiac disease.

Letters were sent to the 86-ataxia patients identified, to inform them of the study and solicit their participation. They were subsequently contacted by phone. Fifty-six patients agreed to participate in the study and serum samples were collected from them. Control samples were obtained from 59 unaffected individuals (spouses also recruited through the clinic). The University of British Columbia (UBC) Clinical Ethics Board approved the study protocol.

Antigliadin antibody estimation

Samples were tested for IgG and IgA antigliadin using the QUANTA LiteTM Gliadin IgG kit (INOVA Diagnostics Inc, San Diego, USA) according to the manufacturers' instructions. Briefly, 96 well microwell plates precoated with purified gliadin were used. Horseradish peroxidase (HRP) concentrate was diluted (1:40) and added to the study serum (affected and unaffected samples), negative controls and positive celiac disease controls, (diluted to 1:101) and incubated at room temperature for 30 min. Unbound samples were washed away and enzyme labeled human IgG conjugate was added to each well and incubated for 30 min. Subsequently, unbound enzyme labeled anti-human IgG was washed away and tetra-methyl benzidine (TMB) added and incubated in the dark for 30 min. A stop solution was added to each well after incubation. The absorbance of each well was measured within one hour of stopping the reaction. Sample optical density units were converted to INOVA arbitrary units using the precalibrated standards. Results were reported as either positive (> 30 units) or negative.

A chi-square with continuity correction was used for the subsequent statistical analysis.

Results

A total of 56 patients with ataxia participated in the study. Of those patients, 31 were men (55%) and 25 were women with a median age of 55. Twenty-nine patients had sporadic ataxia, 9 had MSA-C, and 18 patients were diagnosed with a hereditary ataxia. This latter group consisted of 4 SCA3, 1 SCA6, 3 EA2, patients and 10 patients with a hereditary ataxia not yet determined.

Table 1 shows that 4/56 (7%) of the group of ataxic patients group were positive for IgG antigliadin antibodies compared to control of which 3/59 (5%) were positive (p = 0.94). Testing for IgA antigliadin antibodies identified 2/56 (4%) positive results in

Table 1: Antigliadin antibody results for all ataxia patients and controls

	IgG		IgA		IgG or IgA	IgG&IgA
	+	-	+	-	+	+
Total Ataxia	4	52	2	54	6	0
Control	3	56	2	57	5	0

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Table 2: Antigliadin antibody results for ataxia subgroups and controls

	IgG		IgA		IgG or IgA	IgG&IgA
	+	-	+	-	+	+
Sporadic	2	27	2	27	4	0
MSA-C	1	8	0	9	1	0
Hereditary	1	17	0	18	1	0
Control	3	56	2	57	5	0

the ataxia group compared to 2/59 (3%) positive results in the control group (p = 0.65). None of the patients or control samples was positive for both IgG and IgA antigliadin antibodies. Therefore, samples from 6/56 (11%) of the ataxia cases and 5/59 (8%) of the control cases were positive for either IgG or IgA antigliadin antibodies (chi-square = 0.1667, p = 0.68).

Subsequent subgroup analysis is illustrated in Table 2; the antigliadin antibody testing results for each identified subgroup are compared to the results for the normal controls. Of the patients with sporadic ataxia, a total of 4/29 (14%) was positive for either IgG or IgA antigliadin antibodies (sporadic vs. control, chi-square = 0.599, p = 0.44). Further subgroup analysis revealed that of those with hereditary ataxia, 1/18 (6%), were positive for either IgG or IgA (hereditary vs. control, chi-square = 0.1636, p= 0.69). Lastly of the patients with probable MSA-C, 1/9 (11%) was positive for either antigliadin antibody (MSA-C vs. control, chi-square = 0.1636, p= 0.80). None of the ataxic patients or controls who tested positive for either AGA had gastrointestinal complaints.

Discussion

In contrast to initial studies,[3,4,8,10,12] the results of this study do not support an association between clinically diagnosed ataxia and the increased prevalence of serum antigliadin antibodies when compared to the prevalence in an appropriately matched control group. A number of the previous studies did not include control groups.[4,10,13,14] In this study, gluten sensitivity was determined by the presence of positive IgG and IgA antigliadin antibodies in serum. It has been previously suggested that these antibodies appear to be a useful diagnostic test for gluten ataxia.[8,9] Of the sporadic ataxia population 14% were positive for either IgG or IgA, as opposed to 8% (p=0.44) in a control population.

Previous studies have reported a wide range of antigliadin antibody prevalences in a sporadic ataxia populations. The small number of patients studied in many of those publications can account for much of the variation observed. However, even among the two largest studies that have examined this issue with 132 and 104 sporadic ataxia patients, prevalences vary considerably from 41%[6] to 11.5%[9] respectively. One could therefore consider other intervening factors including the lack of a standard commercial assay used to measure antigliadin antibodies and genetic variation between the populations studied, such as racial groups.

Another point, is that association does not prove causation. A study of 54 Huntington Disease (HD) patients found high antigliadin antibody titers in 44% of the HD patients[16] and another study identified high AGA prevalence in patients with multiple system atrophy.[17] Antigliadin antibodies may be an epiphenomena of neurodegenerative disease.

The prevalence of antigliadin antibodies within our sporadic ataxia population falls within the range that has been previously reported. Furthermore, the prevalence of gluten sensitivity measured in our control population is consistent with the prevalence reported in large-population based studies.[8] Based on these findings, testing for the presence of serum antigliadin antibodies does not appear to be a useful diagnostic tool in ataxia. This is the second study that has included a well-matched control population which did not find an association between antigliadin antibodies and sporadic ataxia. The relationship between the presence of serum antigliadin antibodies and sporadic ataxia still remains unclear. Large studies are warranted to better address this question.

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