

# Antigliadin antibody in sporadic adult ataxia

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## Keywords

Celiac Disease-Idiopathic Ataxia-Gluten Ataxia-Prevalence

## Abstract

**Background:** The most common neurologic manifestation of gluten sensitivity is ataxia, which accounts for up to 40% of idiopathic sporadic ataxia. Timing of diagnosis of gluten ataxia is vital as it is one of the very few treatable causes of sporadic ataxia and causes irreversible loss of Purkinje cells. Antigliadin antibody (AGA) of the IgG type is the best marker for neurological manifestations of gluten sensitivity. This study was conducted to measure the prevalence of gluten ataxia in a group of Iranian patients with idiopathic ataxia.

**Methods:** For 30 patients with idiopathic cerebellar ataxia, a questionnaire about clinical and demographic data was completed. Serum AGA (IgA and IgG) and antiendomysial antibody (AEA) were assessed. Gluten ataxic patients

underwent duodenal biopsy. Magnetic resonance imaging was done for all patients to see if cerebellar atrophy is present.

**Results:** 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. Only presence of gastrointestinal symptoms and pursuit eye movement disorders were higher in patients with gluten ataxia.

**Conclusion:** Prevalence of gluten ataxia in Iranian patients with idiopathic ataxia seems to be lower than most of other regions. This could be explained by small sample size, differences in genetics and nutritional habits and also effect of serologic tests in clinical versus research setting. Further researches with larger sample size are recommended.

## Introduction

Celiac disease, also known as gluten-sensitive enteropathy, is an immune mediated disorder in

some genetically predisposed individuals and is determined by a chronic inflammatory intestinal disease induced by an environmental precipitant, gluten.<sup>1-4</sup> The term "gluten" refers to the entire protein component of wheat.<sup>5</sup> The diagnosis of celiac disease requires both a duodenal biopsy that shows the characteristic findings of intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy and a positive response to a gluten-free diet.<sup>5</sup>

However, serological tests have an important role in the management of patients with celiac disease and provide the greatest chance of establishing the diagnosis of celiac disease.<sup>2</sup> These tests include antigliadin antibody (AGA), antiendomysial antibodies (EMA) and tissue transglutaminase (Ttg). IgA Ttg antibody test has a greater than 90% sensitivity and specificity for celiac disease. Antigliadin IgG and IgA antibodies have a poor specificity and a poor sensitivity, respectively, while endomysial IgA antibodies are highly specific markers for celiac disease, approaching 100% accuracy. So the gold standard in celiac serologic tests is the IgA AEA.<sup>5,6</sup>

Diarrhea, the main classic presentation of celiac in adults, is the presenting symptom in less than 50% of cases.<sup>5</sup> Approximately 8% to 12% of patients who have celiac disease show neurologic symptoms, including cerebellar ataxia, peripheral neuropathy, seizures, and myelopathy.<sup>3,7,8</sup> The most common neurologic manifestation of gluten sensitivity is ataxia, the so-called gluten ataxia (GA).<sup>9,10</sup> Gluten ataxia is characterized by progressive cerebellar ataxia affecting mainly lower limbs<sup>11</sup> and is commonly presented in the absence of gastrointestinal symptoms.<sup>3</sup> In fact, gluten ataxia is the single most common cause of sporadic idiopathic ataxia<sup>9,12</sup> and accounts for up to 40% of cases of idiopathic sporadic ataxia.<sup>13</sup>

Due to the marked cerebellar cortical atrophy with cell loss in dentate and olivary nuclei<sup>14</sup> and also antibodies against Purkinje cells in patients with gluten ataxia, it is suggested that the likely mechanism of gluten ataxia is cross-reaction of antigliadin antibodies with epitopes on cerebellar Purkinje fibers.<sup>7,9,15,16</sup>

In addition, GA with or without classical celiac disease symptoms and enteropathy, responds to a strict gluten-free diet.<sup>3,9,12,17</sup> Considering that loss of Purkinje cells is irreversible, timing of diagnosis of gluten ataxia is vital as it is one of the very few treatable causes of sporadic ataxia.<sup>9,13</sup>

Among the described autoantibodies, gluten ataxia is associated with high AGA titers<sup>7</sup> so that antigliadin antibody of the IgG type is the best marker for neurological manifestations of gluten sensitivity.<sup>18,19</sup> Therefore, in populations which gluten ataxia accounts for a high percent of idiopathic ataxia, AGA should be measured for all patients with idiopathic ataxia.<sup>3,9</sup>

Celiac is not uncommon in Iran. Therefore, we measured prevalence of gluten ataxia in group of Iranian patients with idiopathic ataxia to see if it is rationale to measure AGA for all Iranian patients with idiopathic ataxia.

## Materials and Methods

### *Patient selection*

Over a period of 18 months from April 2006 to October 2007, 30 patients with idiopathic cerebellar ataxia were enrolled in a case-series study. Patients were identified through a review of the charts at neurology wards of four hospitals (Sina Hospital, Imam Khomeyni Hospital, Imam Hoseyn Hospital and Shariati Hospital) in Tehran.

Presence of progressive cerebellar ataxia without a definite diagnosis was the prerequisite for enrollment in the study. Patients with a malignancy, mass or ischemia or hemorrhage in posterior fossa, a positive VDRL test, abnormal thyroid function test, a positive family history of ataxia, long use of anti-epileptic drugs, a history of alcohol abuse, and Wilson disease if less than 40 years old were excluded.

After obtaining informed consent, questionnaire about clinical and demographic data was filled. All patients were tested for antigliadin antibody (IgA and IgG). If one of two types of antigliadin was positive, patient was considered as suffering "gluten ataxia". In gluten ataxic patients, antiendomysial antibody was measured and a biopsy of duodenum was performed to detect patients with celiac disease. The study was approved by Ethics Committee of Tehran University of Medical Sciences. In addition, to see if cerebellar atrophy is present, magnetic resonance imaging (MRI) was done for all patients.

### *Antibody assays*

Antigliadin antibody titers (IgG and IgA) were measured using a commercially available enzyme-linked immunoassay (ELISA) kit (ORG 534A and ORG 534G, ORGENTEC Diagnostica GmbH, Mainz, Germany).

According to the manufacturer's instructions, an IgA value >15 U/ml and also IgG value > 15 U/ml were considered positive. On serum samples (dilution of 1:10), AEA was assessed using a commercially available immunofluorescence assay kit (FA 1911AG-A, EUROIMMUN Medizinische Labordiagnostika A G, Lübeck, Germany)

### *Statistical analysis*

Differences in demographic and clinical data were assessed between AGA positive and negative patients using the chi-square test (with fisher exact test) for categorical variables and the Mann-Whitney U test for continuous variables.

## Results

Among 30 patients, 18 were men (60%) and mean age was 42 years. Mean of duration of ataxia was 5 years. Only one patient did not have gate ataxia. Upper and lower limb ataxia was detected in 7 and 14 patients, respectively. MRI study showed a mild cerebellar atrophy in 7 patients (23.3%) and a severe atrophy in 10 patients (33.3%). Eight patients had ocular signs [all had a nystagmus and 7 had problems in pursuit of eye movement (PMD)] and 19 patients suffered dysarthria. Other neurologic signs included left hand paresthesia (one patient), abnormal position sense (one patient), sustained clonus on ankle joints (one patient), mild psychomotor retardation and bradykinesia (one patient), reduced blinking (one patient) and hyperreflexia in another patient. Gastrointestinal symptoms were present in three patients. One was constipated, another patient suffered from abdominal bloating. Diarrhea and weight loss was present in the other one. Average duration of gastrointestinal symptom in these three patients was 2.6 years. IgA AGA of none of patients was positive while IgG AGA was positive in 2 patients (6.7%) who were considered gluten ataxic. AEA of these two patients was positive and none of them showed changes of celiac disease in their duodenal biopsies. As it is shown in table 1, only presence of gastrointestinal symptoms and pursuit eye movement disorders were higher in patients with gluten ataxia.

## Discussion

While serological screening in healthy volunteers around the world has estimated the prevalence of celiac to be about 0.5-1.0%,<sup>2,5-7</sup> in a study from Italy celiac disease was found in 12.5% of patients with idiopathic ataxic group and 0% in other ataxic patients.<sup>8</sup> In another study from Finland which was done on 44 patients it

was 16%.<sup>9</sup> Overall, in different studies celiac disease was found in 16% (4 of 25), 16.7% (4 of 24), 12.5% (3 of 24), and 1.9% (2 of 104) in sporadic ataxia.<sup>12</sup>

Regarding serologic tests, gluten ataxia was found to be 12 out of 104 (11.5%) amongst idiopathic ataxias in a study in Germany.<sup>9</sup> In USA, it was found in 27% of idiopathic ataxic patients<sup>9</sup> while it was 14% in Canada.<sup>3</sup> In summary, prevalence of antigliadin antibodies has been reported as much as 11.5 to 68% of patients with sporadic ataxias as opposed to 4-12% in a control population.<sup>3,9,20-22</sup>

Consequently, antigliadin antibodies and celiac disease seem to be more prevalent in ataxic patients than in general population. But although initial studies found a significant and strong association between ataxia and gluten sensitivity<sup>12</sup> this association does not appear as robust as initially reported. Recently, the association was seen in many studies<sup>3,20</sup> while other studies have failed to find an association. For example, although antibodies were positive in 8% of the controls and 19% of patients with sporadic ataxia in a study, no statistically significant differences between the groups was observed.<sup>22</sup> In another study, none of 20 patients with idiopathic ataxia showed serologic evidence of celiac disease.<sup>23</sup> Moreover, a report from Spain describes 32 patients with idiopathic ataxia who were screened for gluten ataxia but none of them found to have antigliadin antibodies and they reported prevalence of 0% for gluten ataxia in their idiopathic ataxic patients.<sup>9</sup>

In our study, AGA and AEA were positive in 6.7% of patients and none of them showed celiac disease in duodenal biopsy which is lower than most of other studies. However, there are reports which found lower prevalence of gluten ataxia and celiac disease than our study. In addition to small sample size,

**Table 1.** Univariate analysis of IgG antigliadin antibody

Qualitative variable	Positive IgG (n = 2)		Negative IgG (n = 28)		P-value
	Frequency	Percent	Frequency	Percent	
Male	1	50	17	56	1
GI disorder	2	100	1	33.3	0.007
Nystagmus	2	100	6	20	0.064
Pursuit of eye movement	2	100	5	16	0.048
Ocular problem	2	100	6	20	0.064
Dysarthria	1	50	18	60	1
Upper limb ataxia	1	50	6	20	0.418
Lower limb ataxia	1	50	13	43	1
Gate ataxia	2	100	27	90	1
Atrophy	2	100	15(8,7)	50	0.117
Quantitative	Mean	SD	Mean	SD	P-value
Age (year)	43.2	15.7	26.5	4.9	0.96
Ataxia duration (year)	5.0	4.1	5.0	2.8	0.900
GI disorder duration (year)	3.5	2.1	1.0	-	0.221

genetics and geographic differences could account for low prevalence in our study.<sup>3</sup> In Iran, minimum prevalence of gluten sensitivity has been reported as 1:166 in healthy blood donors and 1:104 in general population of northern and southern Iran and the estimated prevalence of celiac disease was 1:700.<sup>4,16,24,25</sup> Although not rare, it is lower than 1% prevalence of celiac disease in these regions. In addition, according to information from the Iran Ministry of Agriculture, the per capita consumption of wheat by Iranian people is 160 kg per year, which seems much more than the world average and this will rank Iranian as one of the top wheat consuming populations in the world.<sup>24</sup> It may be argued that the continuous and high level of exposure to wheat proteins has induced some degree of immune tolerance, leading to milder symptoms and negative serologic tests.<sup>26,27</sup>

The prevalence of gluten sensitivity amongst familial ataxias did not differ from what was found in the normal population, suggesting no etiological link between these types of ataxia and gluten sensitivity.<sup>9</sup> Due to the lack of genetic study and HLA-typing in our study, some cases were probably of familial type which decreased the prevalence of gluten ataxia in our patients.

Role of serologic tests must be considered in interpreting results of this study. The lower sensitivity of serologic tests in the diagnosis of gluten sensitivity in the clinical practice compared to the research setting has been described previously. Lack of standard commercial assay used to measure antigliadin was a problem in assessing prevalence of gluten ataxia and causes a wide range of it among different studies.<sup>2,3,5-6</sup> In addition, IgG antigliadin antibody titer in patients with gluten ataxia was lower than that in patients with celiac disease without neurological illness.<sup>9</sup> Therefore, if antigliadin assay is set so as to have high specificity for celiac disease, it

might cause lower sensitivity by itself.<sup>9</sup>

In our study in both patients with positive AGA, IgG was positive but IgA was absent. In fact, IgA AGA and antiendomysial antibodies lack sensitivity and specificity when used in a neurological population and IgG AGA is a better marker of the whole spectrum of gluten sensitivity irrespective of the organ involved.<sup>9</sup> However, results of IgG AGA should be interpreted cautiously because the specificity of IgG AGA is lower than that of IgA AGA in diagnosis of gluten sensitivity.<sup>20</sup>

In this study, only PMD and gastrointestinal symptoms were significantly higher in patients with gluten ataxia when compared to other idiopathic ataxic patients, but other neurologic features were not significantly different. The absence of distinctive neurological features in ataxic patients with celiac disease suggests that in populations which gluten ataxia accounts for a high percent of idiopathic ataxia, AGA should be measured for all patients with idiopathic ataxia.<sup>3,8</sup>

## Conclusion

Prevalence of gluten ataxia in Iranian patients with idiopathic ataxia (6.7%), seems to be lower than most of other regions. This could be explained by small sample size, differences in genetics and nutritional habits and also the effect of serologic tests in clinical versus research setting. Therefore, it is needed to perform further researches with larger samples to measure prevalence of gluten ataxia in Iranian patients.

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