



Anti-gliadin Antibodies and Gluten Neuropathies: A Borderline Link

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Authors' contributions

This work was carried out in collaboration between all authors. Author MRB managed the patients and control's medical reports, led the literature searches, and wrote the first draft of the manuscript. Authors NL and NK managed the recruitment of patients and accomplished the clinical investigations. Author IB performed the laboratory testing. Author MA performed the statistical analysis of the study. Author BA designed the study, wrote the protocol, supervised the all process of the study and settled the final version of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

The aim of this research was to estimate the prevalence of gluten sensitivity in neurologic diseases of unknown etiology and to determine their clinical and biological characteristics in a Moroccan population.

Patients and Methods: A prospective case-control study was performed on 60 patients and 57 controls. Patients and controls underwent a screening for IgG and IgA anti-gliadin antibodies (ELISA anti-Gliadin, Orgentec, threshold: 12 IU/ml), and IgA anti-tissue transglutaminase antibodies (ELISA IgA-tGTA, DRG, threshold: 10 IU/m).

Results: The median age of patients was 43±13.91 years (ranges: 13-67), versus 39.4±9.12 (ranges: 19-58) for controls. Male to female sexe-ratio was 0.7 for patients vs 2.1 for controls. IgG

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and/or IgA anti-gliadin antibodies (AGA) were positive in 26.7% of cases (n=16) vs 15.8% (n=9) in controls (p=0.15), while IgA-tTGA was negative in all patients, but positive in 1 control. Positive AGA cases corresponded to peripheral neuropathy (n=4), ataxia (n=3), ischemic stroke (n=3), myopathy (n=2), and 1 case for each of the following conditions: multiple sclerosis, epilepsy, cerebral thrombophlebitis and myelopathy. Among the positive AGA cases, IgA isotype was more prevalent, but IgG AGA titers were higher and clinically more relevant.

Conclusion: Gluten Sensitivity is a potential cause of unknown etiological neurologic diseases in young adults, particularly peripheral neuropathy, ataxia and ischemic stroke. AGA testing especially IgG isotype might be a suitable marker to screen for gluten neuropathies.

Keywords: Gluten sensitivity; neuropathies; anti-gliadin antibodies.

1. INTRODUCTION

Gluten sensitivity (GS) is a systemic autoimmune disease, characterized by abnormal immunological responsiveness to ingested gluten in genetically susceptible individuals [1]. It represents a spectrum of diverse manifestations [1]. The term celiac disease (CD) should now be restricted to describe gluten-sensitive enteropathy (triad of villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes on histological examination of small-bowel mucosa). When the first comprehensive report of neurological manifestations in the context of histological confirmed CD was published in 1966 [2], the assumption was that such manifestations were caused by vitamin deficiencies, secondary to malabsorption, as a result of the enteropathy. Detailed post-mortem data from the same report, however, showed an inflammatory process that affected the cerebellum, and also involved other parts of the central and peripheral nervous systems. This finding favored an immune-mediated pathogenesis [1]. Later, some authors investigated the prevalence of GS in patients with neurological dysfunction of unknown etiology [3-5]. Actually, the neurological manifestations can present even in the absence of an enteropathy, and the most common neurological dysfunctions encountered are ataxia (gluten ataxia) and peripheral axonal neuropathy [1,3,6]. Indeed, many authors found that anti-gliadin antibodies (AGA) in these patients was common, compared to controls [1,3,7]. Also, some reports demonstrated an association between peripheral neuropathies and anti-tissue transglutaminase-2 (tTG2) antibodies [8]. Moreover, rare cases of ischemic stroke and epilepsy of young adults revealing GS have been published [9-11].

The main aim of this study was to estimate the prevalence of gluten sensitivity in neurologic diseases of unknown etiology, using an anti-

gliadin antibody testing, and to determine their clinical and biological characteristics in a Moroccan population.

2. PATIENTS AND METHODS

2.1 Patients and Controls' Selection

We prospectively recruited patients (inpatients and outpatients) presenting clinical data of neuropathies of unknown etiology, from the department of neurology. Those with known etiological neuropathies or with confirmed CD undergoing gluten free diet (GFD) were excluded from the study.

Patients were matched to healthy controls that were selected among volunteer donors from the regional blood transfusion center.

2.2 Clinical Examination and Investigations

The clinical data of patients were collected using a preset questionnaire, which included:

- Socio-demographic characteristics: gender, age, origin, education level and occupation;
- Medical history: diabetes, high blood pressure (HBP), smoking, alcohol intake, nutrition deficiency, known gluten sensitive enteropathy (GSE), age of gluten introduction, digestive symptoms, or other clinical conditions, and the mode of onset and progression of the neurologic symptoms;
- Neurological and general physical examination, indicating the neuropathy's clinical characteristics (Table 1).

2.3 Immunological Testing

All the patients and controls were screened for both IgG and IgA AGA, using an immuno-

enzymatic method (ELISA IgG and IgA-Gliadin, Orgentec Diagnostika, GmbH, Germany, threshold: 12 IU/ml), followed by anti-IgA tissue-transglutaminase antibodies using the ELISA system (tGTA-IgA, DRG instruments, USA, threshold 10 IU/mL).

2.4 Statistical Analysis

The statistical analysis was performed, using SPSS and Epiinfo6 applications. The Chi-Square test was used to determine whether there is a significant difference between patients and controls. If the p-value is under .05, results are considered statistically significant.

2.5 Ethical Aspects

According to the declaration of Helsinki-Ethical Principles for Medical Research, patients have been informed about the objectives of the study, and the required testing. After their consent, the enrolled patients were asked to approve the clinical questionnaire and sign the informed consent. Selected controls have also been informed about the intended AGA and tTGA testing on their samples.

3. RESULTS

3.1 Socio-Demographic Characteristics of the Population

Sixty patients were enrolled, the patients' median of age was 43 years (± 13.91 , ranges: 13-67), with a female predominance (male to female sex-ratio =0.7). Regarding the social status of the population, as reported in Table 1, the standard of living was medium for most of the patients (n=33, 55%), and about half of patients (n=29, 48.33%) had a primary school education level, and the majority of females (77.7%, n=28) were housewives.

Fifty seven healthy controls were included. Their mean of age was 39.4 (± 9.12 , ranges: 19-58) years, with a male predominance (male to female sex-ratio =2.1).

3.2 Clinical Data and Investigations' Findings

Ischemic stroke was the most common clinical condition (30%, n=18), related to the middle cerebral artery (MCA) area in 9 cases, and associated with cerebral atrophy in 2 cases. The biological testing showed 6 cases of inflammatory syndrome, 4 cases of

hypocholesterolemia and 1 case of increased rate of homocysteinemia. Haemostasis testing was normal in all patients. Sixteen patients had different forms of neuropathies including polyneuropathy (n=10), mononeuropathy multiplex (n=3), polyradiculoneuropathy (n=2), and undefined form (n=1). Their electrophysiological testing showed combined motor-sensitive, motor, and sensitive neuropathies in 7, 2 and 2 cases respectively. In addition, among these patients, 9 had increased inflammatory markers.

Furthermore, 5 patients had gait and limb cerebellar ataxia and 2 others had sensory ataxia. Among ataxic patients, increased inflammatory markers were detected in 5 cases, and 1 patient had a hypocholesterolemia. Also, MRI showed a global atrophy in 4 cases.

The epilepsy group included 5 cases of generalized tonico-clonic seizures and 2 cases of partial seizures in which 1 had partial status epilepticus. The electro-encephalogram showed generalized spikes and waves in 4 cases, and localized ones to the left parietal lobe in 2 cases, while, this exam was normal in 1 case. Only 4 patients underwent neuro-imaging (MRI or scanner), without abnormalities. Four patients had increased inflammation markers.

All the 3 myopathy cases had bilateral and symmetric myogenic syndrome, associated to partial muscular atrophy in 1 case and to global handicap in 1 case. Inflammation markers and CPK (Creatine phosphokinase) were increased in 2 cases. The muscle biopsy revealed a mitochondriopathy in 1 case and dermatomyositis features in the other case. In addition, 2 patients had myelopathy with non specific medullar imaging's findings. The only patient with cerebral thrombophlebitis in this series had neither clinical nor biological pro-thrombotic conditions. One patient had multiple sclerosis with several recurring attacks.

On the other hand, 8 (13.3%) of the patients had gluten sensitivity risk factors, such as, consanguinity status (2 cases), diabetes mellitus (4 cases), and autoimmune conditions such as rheumatoid arthritis (1 case) and Raynaud syndrome (1 case).

3.3 Immunological Analysis

The AGA detection showed positive IgA and/or IgG isotypes in 26.7% (n=16), versus 15.8% (n=9) in controls ($p=.15$). The associated clinical

forms of neuropathies with a positive AGA status were as follow: peripheral neuropathies (25%, n=4); ataxia (18.75%, n=3); ischemic stroke (18.75%; n=3); myopathy (15.5%, n=2); and 1 positive case for each of the following conditions: epilepsy, cerebral thrombo-phlebitis, myelopathy and multiple sclerosis. The Neurologic clinical forms are listed in Table 2 according to AGA isotype results.

As mentioned in Table 2 and Figure 1, IgA AGA was the common positive isotype in peripheral neuropathies (4/4 cases) and ataxia (2/3 cases with 1 case of combined IgA and IgG AGA). The IgG AGA isotype was predominant in stroke (2/3 cases) and in myopathy (2/2 cases) (Figure 1).

Regarding the AGA titers, 25% of all positive cases (n=4) had levels greater than 30 IU/mL, while the titers were including 14.18 IU/mL and 30 IU/mL in 75% of positive cases (n=12). These high AGA titers corresponded to IgG isotypes (Figure 2). In the patient's group, the IgA tTGA testing was negative in all cases.

Among the control group, 9 (15.8%) cases were positive for AGA, in which 5 were positive for

only IgA AGA, with high titers (>30 IU/mL) and 2 were positive for only IgG AGA, while 2 patients were positive for both IgG and IgA AGA. The only double positive case (IgA and IgG AGA) was also highly positive for IgA anti-tTGA (titer =200 IU/ml).

4. DISCUSSION

Our study shows a high prevalence (26.7%) of AGA in patients with neuropathies of unknown etiology, versus 15.8% in the control group. This association is not statistically significant, but the presence of highly positive cases (Figure 2), and the absence of anti-tTGA in all patients support the fact that GS may represent a potential etiology for these neuropathies; which have been stated by many authors [7,12-15]. Compared to similar studies, the general prevalence of AGA in our series is amongst the highest ones, while large discrepancy rates are reported according to neuropathy categories and AGA isotypes (Tables 3 and 4).

The positive cases in our series are mostly noticed in young population (median of age= 43 years), fact observed in many studies [3,7,13].

Table 1. Socio-demographic characteristics and clinical categories of the patients

Socio-demographic characteristics		Neurological forms	
	n (%)		n (%)
- Median of age	43 years (± 13.91)	- Ischemic stroke	18 (30%)
- Age range	13-76 years	- Peripheral neuropathy	16 (26.7%)
- Male to female sex-ratio	0.7	- Ataxia	7 (11.6%)
Standard of living	n (%)	- Epilepsy	7 (11.6%)
- Medium	33 (55%)	- Myopathy	3 (5%)
- Low	22 (36.6%)	- Anterior horn disease	2 (3.3%)
- High	2 (3.3%)	- Multiple sclerosis	1 (1.6%)
- Not defined	3 (5%)	- Myelopathy	2 (3.3%)
Education level	n (%)	- Dystonia	1 (1.6%)
- Primary school	29 (48.3%)	- Parkinson disease	1 (1.6%)
- Illiteracy	16 (26.6%)	- Cerebral thrombophlebitis	1 (1.6%)
- High school	9 (15%)	- Lymphocytic meningitis	1 (1.6%)
- University	1 (1.6%)		
- Not defined	5 (8.3%)		
Occupation	n (%)	Total of patients	60
- Housewives	28 (46.6%)		
- Laborers	7 (11.6%)		
- Employees	5 (8.3%)		
- Traders	5 (8.3%)		
- Students	4 (6.6%)		
- Hairdressers	2 (3.3%)		
- Others	8 (13.3%)		

Table 2. IgG and IgA AGA profiles according to clinical categories in patients, and controls

Neuropathy categories	IgG AGA		IgA AGA		Total of positive AGA n (%)
	Pos n (%)	Neg n (%)	Pos n (%)	Neg n (%)	
Peripheral neuropathy, n=16	-	16 (100)	4 (25)	12 (75)	4 (25)
Stroke, n=18	2 (11.1)	16 (88.8)	1 (5.5)	17 (94.4)	3 (16.6)
Myopathy, n=3	2 (66.6)	1 (33.3)	-	3 (100)	2 (66.6)
Ataxia, n=7	1 (14.3)	6 (85.7)	3 (42.8)	4 (57.1)	3 (42.8)***
Epilepsy, n=7	-	7 (100)	1(14.3)	6 (85.7)	1 (14.3)
Myelopathy, n=2	1 (50)	1 (50)	-	2 (100)	1 (50)
M.S*, n=1	1 (100)	-	-	1 (100)	1 (100)
T.P**, n=1	-	1 (100)	1 (100)	-	1 (100)
Other conditions, n=5	-	5 (100)	-	5 (100)	-
Total of patients	7 (11.6)	53 (88.3)	10 (16.6)	50 (83.3)	16 (26.7%)***
Healthy controls	4 (7)	53 (93)	5 (8.7)	50 (87.7)	9 (15.8%)

*Multiple sclerosis, **Thrombophlebitis, *** including 1 positive patient for both IgA and IgG AGA

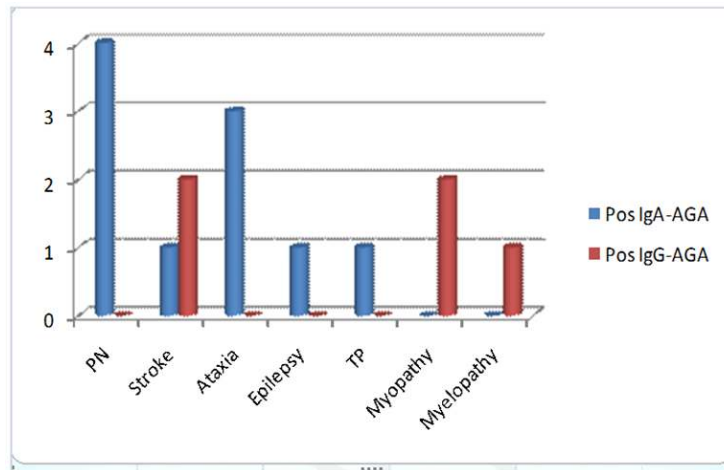


Figure 1. AGA positive cases according to neuropathy categories

PN: Peripheral neuropathy; TP: Thrombophlebitis; AGA: Anti-gliadin antibody; Pos: Positive

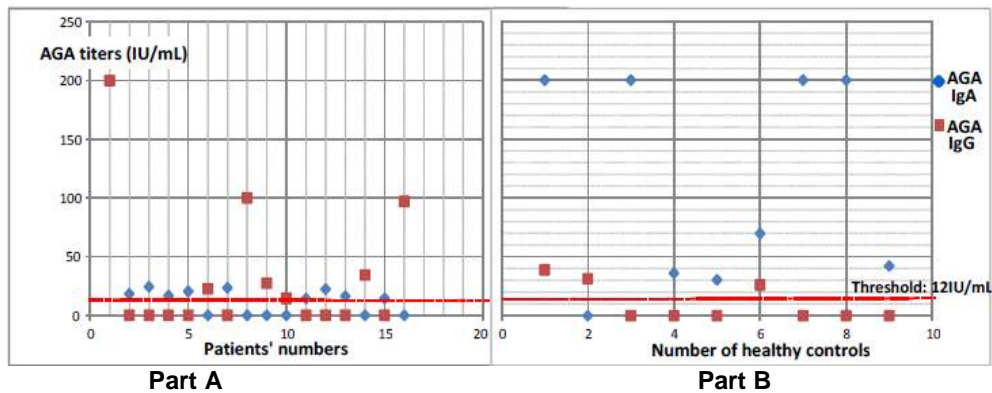


Figure 2. Comparison of AGA isotype titers in patients and healthy controls

Part A: AGA isotype titers in patients. Part B: AGA isotype titers in controls.

Table 3. Prevalence of AGA in idiopathic neuropathies according to studies

Studies	Idiopathic neuropathies with positive AGA n (%)	Controls n (%)	P-value	Ref
Hadjivassiliou, 2006 (n=140)	47 (34)	149/1200 (12)	< 0.001	[7]
Pellecchia, 1999 (n=24)	3 (13)	0	=.05	[14]
Wong, 2007 (n=56)	6 (11)	5/59 (8)	= .68	[15]
Our study (n=60)	16 (26.7)	9/57 (15.8)	= .15	-

Table 4. Positive AGA profile in idiopathic ataxia and peripheral neuropathies

Studies	Ataxia			Peripheral neuropathy		
	IgG AGA n (%)	IgA AGA n (%)	IgA+IgG AGA n (%)	IgG AGA n (%)	IgA AGA n (%)	IgA+IgG AGA n (%)
Ihara, 2005 (n=14), [16]	3(21.4)	2(14.3)	-	-	-	-
Hadjivassiliou,2003 (n=176) [13]	62(35.2)	6(3.4)	-	-	-	-
Pellecchia,1999 (n=24) [14]	2(8.3)	0	1(4.1)	-	-	-
Burk, 2001 (n=104) [17]	2(2)	6(5.7)	2(2)	-	-	-
Hadjivassiliou,2006 (n=140) [7]	-	-	-	80(57)	22(1)	37(27)
Chin, 2003 (n=20) [18]	-	-	-	12(60)	10(50)	7(35)
Our study (n=60)	0	2(3.3)	1(1.7)	0	4(6.7)	0

Globally, peripheral neuropathy and ataxia are the most common neurological manifestations of GS [1,11,14] which is in line with our results (25% and 18.7% respectively). The ischemic stroke is also highly prevalent (18.75%) among the positive AGA patients, and this association was described especially by some case report studies [9,11,19].

4.1 Gluten Ataxia

The most common neurologic manifestation of gluten sensitivity is ataxia [20], the so called gluten ataxia is commonly presented in the absence of gastrointestinal symptoms [21,22]. In fact, gluten ataxia is the single most common cause of sporadic idiopathic ataxia [20], and accounts for up to 40% of cases of idiopathic sporadic ataxia [21].

Clinically, gluten ataxia usually presents with a cerebellar form, associated to dysarthria [1], and cerebellar atrophy on MRI [13]. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are seen in up to 80% of cases [23]. The association with axonal neuropathy was also reported [23]. The ataxic patients with evidence of GS in our series correspond to idiopathic

forms, and none of them had associated axonal neuropathy. Moreover, no combination of clinical features is specific enough to enable a clinical diagnosis of gluten ataxia, except maybe in patients with an established GSE [14]. A high frequency of AGA was reported in patients with idiopathic sporadic ataxia [1] (Table 4). These findings are similar to our data in which 3 of 7 (42.8%) ataxia cases were positive for AGA.

Many authors consider that IgG AGA is a reliable marker for the whole spectrum of GS, irrespective of the involved organ, and remains the best diagnostic marker for gluten ataxia [13,22]. However, IgA AGA seems to be the most frequent isotype in other similar studies [17]. In addition, the coexistence of both IgA and IgG AGA isotypes have been described by many authors (Table 4), but in a lower proportion, compared to only IgA AGA or IgG AGA profiles. Furthermore, the sensitivity of anti-tTGA as a marker of gluten ataxia is by definition low [6].

4.2 Peripheral Neuropathy

Peripheral neuropathy (PN) is the other most common manifestation of GS [7], and gluten

peripheral neuropathy (GPN) is a slowly progressive disease, affecting young patients in general [7]. PN syndrome is often associated with sensory abnormalities (tactile, thermo-algic and vibratory hypoesthesia) [24]. Symmetrical sensori-motor axonal neuropathy remains the prominent electrophysiological aspect of GPN [1]. Other features have also been reported such as asymmetrical neuropathy, sensory ganglionopathy, small fiber neuropathy, pure motor neuropathy, and autonomic neuropathy [1]; however, approximately 8% of GPN patients have a normal electro-physiological exploration (EMG) [24]. This clinical category is mostly associated with IgG AGA [7], which contrasts with our results, showing 4 cases of positive IgA-AGA.

4.3 Ischemic Stroke

According to literature, the association of ischemic stroke with GS seems less frequently than other neuropathies [3,9]. Actually, stroke is rarely associated to non celiac gluten sensitivity, and many authors described mainly case reports revealing or accompanying CD [25,26]. The majority of gluten stroke patients are young [9,11,19], which is consistent with our results (median of age at the onset: 40 years). They usually have normal etiological investigations [9,11,19]. The middle cerebral artery's area is mostly affected with uncommonly cerebral or cerebellar atrophy [9]. In such pathology, AGA usually coexists with decreased folate levels and hyper-homocysteinemia; the later parameter is a known risk factor of ischemic stroke [9].

4.4 Myopathy

Myopathy is a rare neurological manifestation of GS, mainly an idiopathic inflammatory clinical form [12,27]. In fact, AGA have been detected in various forms of myopathies, including proximal myopathy due to vitamin E deficiency, osteomalacia due to vitamin D deficiency, polymyositis and sporadic inclusion body myositis (s-IBM) and also in the juvenile form of dermatomyositis (DM). Patients generally have a bilateral and symmetric myogenic syndrome with progressive muscular atrophy [1]. Moreover, inflammatory infiltration on muscle biopsy was the common pathological feature in our series. Normal or increased CPK rate are possible in Gluten myopathy [27]. Furthermore, Hadjivassiliou reported a clinical improvement in many patients undergoing GFD [1].

4.5 Epilepsy

Several reports suggested a link between epilepsy and GSE [1,28]; it also belongs to a variety of non celiac gluten neuropathies described even in low prevalence [29].

It has a tendency to affect young individuals, and the seizures are mostly resistant to antiepileptic drugs [1,28]. Different clinical forms are described, such as the occipital lobe epilepsy and the generalized tonico-clonic status epilepticus. On neuro-imaging, an association with cerebral calcifications, especially of the temporal and occipital lobes has been reported [1,30]. According to some studies, either gluten sensitive epilepsy or celiac epilepsy improves after a GFD [1,30].

4.6 Thrombophlebitis

This entity usually affects young patients with no pro-thrombotic risk factors [31], and involves different vascular territories: central cerebral thrombophlebitis, deep venous proximal thrombosis of the leg, portal vein thrombosis, and non-ischemic central retinal vein occlusion [31]. Saibeni and al found that hyper-homocysteinemia is more frequent in patients with GSE compared to the control group [31]. A clinical case of gluten-sensitivity celiac disease (GSCD) and recurrent lower extremity vein thrombosis has been described by, who consider that GSCD may be associated with antiphospholipid syndrome, with an increased risk for thrombosis [32]. Similar to a Turkish study [31], our only cerebral thrombophlebitis case had positive IgA AGA, while IgG AGA and tTGA testing were negative. Thus, regarding these observations, the priority should be given to rule out an authentic celiac disease facing such condition, especially in front of the positivity of IgA AGA isotype.

4.7 Myelopathy

Myelopathy seems to be a rare GS linked clinical condition [1,33]. Clinical evidence of myelopathy with absence of vitamin or other deficiencies, particularly copper deficiency can be a rare manifestation of GS [1].

Some authors suggest that occult celiac disease should be considered in patients found to have copper deficiency, even in patients without gastrointestinal symptoms [34].

Myelopathy may show a progressive medullar syndrome in contrast with normal spinal cord on imaging [1], which is similar to our results. On the other hand, one of the two cases of our series displays a positive IgG AGA, which ought to consideration in further studies.

4.8 Multiple Sclerosis

There is some contradictory data in literature displaying either a significant link between GS and multiple sclerosis illustrated by an increasing frequency of mainly IgG or IgA AGA [35,36], or a lack of any association between these auto-antibodies and such clinical condition [37,38]. We registered 1 case of multiple sclerosis that was highly positive for IgG AGA. Therefore, we inquire whether if our solely observation corresponds to a fortuitous or to a real etiological association.

4.9 IgG AGA or IgA AGA?

Currently there are no specific biomarkers for non celiac GS, and the diagnosis is based on exclusion criteria [28].

Regarding the immunological status, many authors found that IgG AGA was more common in neurologic diseases than IgA AGA class [6,13,24]. Also, the high titers of IgG AGA in our neuropathy cases make it more substantial in such conditions. On the other hand, IgA AGA seem to be more linked to the gluten enteropathy forms according to literature [1,39,40], and their high frequency in our patients and controls explains the lack of sensitivity of this marker. Such observation connects with the data of Volta et al. who reported a serological pattern of a large spectrum of non celiac gluten sensitivity manifestations, characterized by IgG AGA positivity in 56.4% of cases associated to IgA AGA in 7.7% of patients, but without anti-EMA (Endomysium), anti-tTGA, and anti-DGP (deamidated gliadin peptide) antibodies, which are the specific markers of celiac disease [41].

Finally, our study gives evidence of original and promising results that emphasize the usefulness of anti-gliadin antibodies as a potential marker of various neuropathies of unknown etiology. However, the main pitfall of this study is the low number of patients and the possible selection bias in both patients and controls, which may have an impact either on increased or decreased prevalence rate of AGA in each clinical condition. Also, we could not perform intestinal biopsy in order to exclude CD.

5. CONCLUSION

Our data showed that peripheral neuropathy and ataxia and even ischemic stroke of young adults are commonly associated with GS. Face to neurological diseases of unknown etiology, the serological evidence of GS should be taken into consideration in daily clinical practice. A diagnosis approach based on IgA and IgG AGA testing might be suitable to screen for gluten neuropathies, with a necessity of ruling out atypical celiac disease on basis of the anti-transglutaminase antibodies and the intestinal biopsy. Besides, to strengthen our findings, further studies with larger sampling of patients as well as experiments on the effectiveness of the GFD should be carried out.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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