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Potential Biomarker of Gluten Related Neurological Disorders

Brahim Admou[1,2*], Abir Fguirouch[1], Ikram Brahim[1], Mohamed-Reda Bouroumane[2], Raja Haime[1], Imane Brahim[1], Nisrine Louhab[3] and Najib Kissani[3]

Abstract

Context: Gluten sensitivity corresponds to a broad spectrum of clinical manifestations including celiac disease and non-enteropathic based disorders. Among the latter conditions, neurologic disorders of unknown etiology seem frequently associated to anti-gliadin antibodies (AGA), usually called gluten neuropathies.

Objectives: We aimed to determine the clinical significance of AGA in neurologic diseases of unknown etiology.

Patients and methods: We prospectively enrolled 60 patients with following conditions: peripheral neuropathy (n=16), Ischemic Stroke (n=18), ataxia (n=7), epilepsy (n=7), myopathy (n=3), Myelopathy (n=2), Multiple Sclerosis (n=1), Thrombophlebitis (n=1) and undefined clinical conditions (n=5), matched to 57 healthy controls. Patients and controls underwent a screening for IgG and IgA AGA using an immunoenzymatic method (ELISA-Gliadin, Orgentec®, threshold: 12IU/ml). In order to rule out an authentic celiac disease, IgA anti-tissue transglutaminase antibodies (tTGA) were performed in both patients and controls, using an ELISA method (DRG®, IgA-tTGA, Inc. USA, threshold: 10 IU/ml).

Results: The mean age of the patients was 43 ± 13.91 years (ranges: 13-67), versus 39.4 ± 9.12 (ranges: 19-58) for controls. Male to female sex-ratio was 0.7 for patients versus 2.1 for controls. IgG and/or IgA AGA were positive in 26.7% of cases (n=16) vs 15.8% (n=9) in controls, while IgA-tTGA was negative in all patients, but positive in one case among controls. Positive AGA cases corresponded to peripheral neuropathy (n=4), ataxia (n=3), ischemic stroke (n=3), myopathy (n=2), and one 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: Our data give evidence that Gluten Sensitivity represents a potential cause of idiopathic neurologic diseases in young adults, particularly peripheral neuropathy, ataxia and ischemic stroke, and lesser in myopathy. AGA testing might be a suitable marker to screen for gluten neuropathies provided ruling out an atypical celiac disease. Further studies on bigger sample size are recommended, using additional relevant markers of gluten neurologic disorders.

Keywords

Neurologic disorders; Anti-gliadin antibodies; Gluten sensitivity

***Corresponding author:** Brahim Admou, Laboratory of Immunology, Center of Clinical Research, University Hospital Mohamed VI, Av Ibn Sina, Marrakech, 40080, Morocco, E-mail: br.admou@uca.ac.ma

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Introduction

Gluten Sensitivity (GS) is an autoimmune disease, characterized by abnormal immunological reaction triggered by ingested gluten in genetically predisposed individuals [1]. Patients with GS present with a broad spectrum of manifestations that ranges from an asymptomatic status to the disabling disorders linked to Celiac Disease (CD) also known as gluten-sensitive enteropathy and non-celiac gluten sensitivity (NCGS) [1-3]. The diagnosis of the whole spectrum of Gluten-Related Disorders (GRDs) is problematic. This is particularly the case for the NCGS, a relatively new entity belonging to the spectrum of GRDs, currently defined by clinical evidence of improvement of symptoms following the introduction of Gluten-Free Diet (GFD) in the absence of enteropathy [4]. A part from classical common symptoms, CD is frequently associated to diverse extra intestinal manifestations among which neurologic disorders are the most encountered conditions [5-7].

Neurologic diseases are also commonly reported in the context of GS without celiac enteropathy. Actually, since 1996, Hadjivassiliou and many other authors have demonstrated that patients with a variety of cryptogenic neurological disorders including ataxia, neuropathy, myelopathy, and myopathy had high prevalence of Anti-Gliadin Antibodies (AGA) [8-10]. Similar findings were also displayed in epilepsy, in cerebral vasculitis or dementia, in Huntington's disease and multiple system atrophy as well as in healthy controls.

Moreover, rare cases of ischemic stroke and epilepsy of young adults revealing GS were published [11-13]. Therefore, the importance and relevance of AGA in the absence of intestinal damage in such conditions is questionable, thus need to be more enlightened. The objective of this study was to determine the clinical significance of AGA in neurologic diseases of unknown etiology and their contribution to the diagnosis.

Patients and Methods

Population selection and clinical investigations

We prospectively enrolled 60 patients with neuropathies of unknown etiology, from the department of neurology. Those with known etiological neuropathies or with confirmed CD were excluded from the study. Patients were matched to 57 healthy controls selected among volunteer donors from the regional blood transfusion center. The clinical data of patients were collected using a preset questionnaire, which includes:

- Demographic characteristics: gender, age, origin
- 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, to define the clinical characteristics of the neuropathy

Immunological testing

Patients and controls underwent a screening 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 (tTGA), using the ELISA system (tGTA-IgA, DRG® instruments, USA, threshold: 10 IU/mL).

Statistical analysis

The data acquisition and statistical analysis were performed using SPSS and Epiinfo6 applications. The Chi-square test was used to find out a potential difference between patients and controls. Results are considered statistically significant if the p-value is under 0.05

Ethical aspects

According to the declaration of Helsinki-ethical principles for medical research, patients have been informed about the objectives of the study. An informed consent was obtained from both patients and selected controls mentioning the intended testing on the collected samples.

Results

Socio-demographic characteristics of the population

The mean age of patients was 43 years (±13.91, ranges: 13-67), with a female predominance (male to female sex-ratio =0.7). The mean age of controls was 39.4 (±9.12, ranges: 19-58) years, with a male predominance (male to female sex-ratio =2.1).

Clinical conditions and investigations' findings

The distribution of the neurologic disorder categories as recorded through the preset questionnaire and the physical clinical investigations is shown in Table 1.

Among these categories, ischemic stroke was the most frequent clinical condition (30%, n=18), affecting the middle cerebral artery (MCA) area in 9 cases, with 2 cases of cerebral atrophy. 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 for all patients. Sixteen (26.7%) patients had different forms of neuropathies including polyneuropathy (n=10), mononeuropathy (n=3), polyradiculoneuropathy (n=2), and undefined form (n=1). Their electro-physiological testing showed combined motor-sensitive, motor, and sensitive neuropathies in 7, 2 and 2 cases respectively and 9 cases of them had increased inflammatory markers.

Table 1: Demographic characteristics and neurologic disorder categories of our series.

Demographic characteristics	
Median of age	43 years (± 13.91)
Age range	13-76 years
Male to female sex-ratio	0.7
Neurological disorders n (%)	
Ischemic stroke	18 (30%)
Peripheral neuropathy	16 (26.7%)
Ataxia	7 (11.6%)
Epilepsy	7 (11.6%)
Myopathy	3 (5%)
Myelopathy	2 (3.3%)
Anterior horn disease	2 (3.3%)
Multiple sclerosis	1 (1.6%)
Dystonia	1 (1.6%)
Parkinson disease	1 (1.6%)
Cerebral thrombophlebitis	1 (1.6%)
Lymphocytic meningitis	1 (1.6%)
Total of patients	**60**

Ataxic cases represented 11.6% (n=7), 5 of patients had gait and limb cerebellar ataxia and 2 others had sensory ataxia. Increased inflammatory markers were detected in 5 cases, and 1 patient had a hypocholesterolemia. MRI imaging showed a global atrophy in 4 cases.

Seven cases of epilepsy 11.6% were noticed in our series, including 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 spikes in the left parietal lobe for other 2 cases, while this exam was normal in 1 case. Only 4 patients underwent neuro-imaging with no abnormalities. Four epileptic 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 a 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 dermato-myositis 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 our study 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).

Immunological results

The AGA detection showed positive IgA and/or IgG isotypes in 26.7% (n=16) of cases, versus 15.8% (n=9) in controls (p=0.15). The distribution of positive AGA according to clinical forms of neuropathies was as follow: Peripheral neuropathies (25%, n=4); Ataxia (18.75%, n=3); Ischemic stroke (18.75%; n=3); Myopathy (15.5%, n=2); and one positive case for each of the following conditions: epilepsy, myelopathy, multiple sclerosis and cerebral thrombo-phlebitis. The Neurologic conditions are listed in Table 2 according to AGA isotype results.

As mentioned in Table 2, 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).

Regarding the AGA titers, 25% of all positive cases (n=4) had levels greater than 30 IU/mL, while the titers were between 14.18 IU/mL and 30 IU/mL in 75% of positive cases (n=12). The high AGA titers corresponded to IgG isotypes (Figure-1). 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, and 2 were positive for only IgG AGA, while 2 patients were positive for both IgG and IgA

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)
Ataxia, n=7	1 (14.3)	6 (85.7)	3 (42.8)	4 (57.1)	3 (42.8)[c]
Epilepsy, n=7	-	7 (100)	1(14.3)	6 (85.7)	1 (14.3)
Myopathy, n=3	2 (66.6)	1 (33.3)	-	3 (100)	2 (66.6)
Myelopathy, n=2	1 (50)	1 (50)	-	2 (100)	1 (50)
MS[a], n=1	1 (100)	-	-	1 (100)	1 (100)
TP[b], 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%)[c]
Controls	4 (7)	53 (93)	5 (8.7)	50 (87.7)	9 (15.8%)

a) Multiple sclerosis; b) Thrombophlebitis, c) including 1 positive patient for both IgA and IgG AGA

Table 3: Prevalence of AGA in idiopathic neurologic disorders according to different studies.

Studies	Neurologic disorders with positive AGA n (%)	Control n (%)	P-value
Hadjivassiliou, 2006 (n=140)	47 (34)	149/1200 (12)	<0.001
Pellecchia, 1999 (n=24)	3 (13)	0	0.05
Wong, 2007 (n=56)	6 (11)	5/59 (8)	0.68
Our study (n=60)	16 (26.7)	9/57 (15.8)	0.15

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)	3(21.4)	2(14.3)	-	-	-	-
Hadjivassiliou, 2003 (n=176)	62(35.2)	6(3.4)	-	-	-	-
Pellecchia, 1999 (n=24)	2(8.3)	0	1(4.1)	-	-	-
Burk, 2001 (n=104)	2(2)	6(5.7)	2(2)	-	-	-
Hadjivassiliou, 2006 (n=140)	-	-	-	80(57)	22(1)	37(27)
Chin, 2003 (n=20)	-	-	-	12(60)	10(50)	7(35)
Our study (n=60)	1 (1.7)	2(3.3)	1(1.7)	0	4(6.7)	0

AGA. One of the double positive cases (IgA and IgG AGA) was also highly positive for IgA anti-tTGA (titer=200 IU/ml).

Discussion

Our study displays a relatively high frequency (26.7%) of AGA in patients presenting neuropathies of unknown etiology. This association was not statistically significant, but the presence of highly positive cases and the absence of anti-tTGA in all patients support the fact that GS may represent a potential etiology for these neuropathies. An intriguing high prevalence has been described in a variety of cryptogenic neurological disorders by many authors [4, 8,9,14-16]. Compared to similar studies, the global 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 patients, fact observed in many studies [4,8,17]. Globally, peripheral neuropathy and ataxia are the most common neurological manifestations of GS [13,15,18] which is in line with our results with 25% and 18.7% respectively. The ischemic stroke is also highly prevalent (18.75%) among the positive AGA patients, and this association was reported mainly as case report studies [11,13,19].

Gluten ataxia

Ataxia represents the most frequent neurologic manifestation of gluten sensitivity [20], the so called gluten ataxia is commonly existing in the absence of gastrointestinal symptoms [8,21]. In fact, gluten ataxia is one of the main cause of sporadic idiopathic [10,20], and accounts for up to 40% of its etiology. Clinically, gluten ataxia usually exhibits with a cerebellar form associated to dysarthria [18], with cerebellar atrophy on MRI [8,10]. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are seen in up to 80% of cases [16]. The association with axonal neuropathy was also reported [16]. 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 symptoms is specific enough to enable the clinical diagnosis of gluten ataxia, except maybe in patients with an established GSE [15]. Gluten ataxia cases are known to be highly positive for anti-gliadin antibodies [22]. These Abs cross-react with epitopes on Purkinje cells from human and rat cerebellum, and in doing so strengthens the impact of circulating antibodies against cerebellar Purkinje cells [22,23].

Many authors gave evidence of a high frequency of AGA in sporadic ataxia (Table 4). These findings are similar to our data in which 42.8% of ataxia cases were positive for AGA. Actually, IgG AGA is considered as the best diagnostic marker of gluten ataxia [8, 21]. However, IgA AGA seems more frequent in other similar studies [24]. In addition, the coexistence of IgA and IgG AGA isotypes has also been reported by many authors (Table 4), but in a lower proportion,

compared to only IgA or IgG AGA profiles. Furthermore, the sensitivity of anti-tTGA for gluten ataxia is by definition low [25].

Peripheral neuropathy

Peripheral Neuropathy (PN) is the other most common manifestation of GS [4] , and Gluten Peripheral Neuropathy (GPN) is a slowly progressive disease, affecting young patients in general [4]. PN syndrome is often associated with sensory abnormalities including tactile, thermo-algic and vibratory hypoesthesia [19]. Symmetrical sensori-motor axonal neuropathy remains the prominent electrophysiological aspect of GPN [18]. Other features have also been reported such as asymmetrical neuropathy, sensory ganglionopathy, small fiber neuropathy, pure motor neuropathy, and autonomic neuropathy [18]; however, approximately 8% of GPN patients have a normal electro-physiological exploration (EMG) [19]. This clinical category is mostly associated with IgG AGA [4], which contrasts with our results, showing 4 cases of positive IgA-AGA.

Ischemic stroke

According to literature, the association of ischemic stroke with GS seems less frequent than other neuropathies [11,17]. Actually, stroke is rarely related to NCGS, and many authors described mainly case reports revealing or accompanying CD [20,26]. On the other hand, the majority of gluten stroke patients are young [11,13,19], which is consistent with our results (mean age: 40 years). They usually have normal etiological investigations [11,13,19], and the middle cerebral artery's area is mostly affected with uncommonly cerebral or cerebellar atrophy [11]. In such pathology, AGA usually coexists with decreased folate levels and hyper-homocysteinemia. The later parameter is considered as a risk factor of ischemic stroke [11].

Myopathy

The myopathy, particularly the idiopathic inflammatory form is a rare neurological manifestation of GS [14,27]. 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). In the context of GS, patients generally have a bilateral and symmetric myogenic syndrome with progressive muscular atrophy [18]. Normal or increased CPK rate are possible in Gluten myopathy [27]. The GS linked patients of our series had an inflammatory infiltration on muscle biopsy was. On the other hand, Hadjivassiliou reported a clinical improvement in many patients undergoing GFD [18].

Epilepsy

Several reports suggested a link between epilepsy and GSE [18,28]. It also belongs to a variety of non-celiac gluten neuropathies described even with low prevalence. Related gluten epilepsy has a tendency to affect young individuals, and the seizures are mostly resistant to antiepileptic drugs [18,28]. 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 those of the temporal and occipital lobes has been reported. According to some studies, either gluten sensitive epilepsy or celiac epilepsy improves after GFD [18,29].

Thrombophlebitis

This entity usually affects young patients with no pro-thrombotic risk factors [30], and may have different anatomo-clinical forms according to the vascular territories: central cerebral thrombophlebitis, deep venous proximal thrombosis of the leg, portal vein thrombosis, and non-ischemic central retinal vein occlusion [30]. Actually, Saibeni et al consider that hyper-homocysteinemia is more frequent in patients with GSE compared to the control group [30]. Similarly, Baryshnikov et al reports a clinical case of Gluten-Sensitivity Celiac Disease (GSCD) with recurrent lower extremity vein, and then consider that GSCD may be associated with antiphospholipid syndrome, with an increased risk for thrombosis [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, especially in front of the positivity of IgA isotype.

Myelopathy

Myelopathy seems to be a rare GS linked condition [18,32]. Clinical evidence of myelopathy with absence of vitamin or other deficiencies, particularly copper deficiency can be a rare manifestation of GS [18]. Some authors suggest that occult celiac disease should be considered in patients with copper deficiency, even without gastrointestinal symptom [33]. Myelopathy may show a progressive medullar syndrome in contrast with normal spinal cord on imaging [18], 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.

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, or a lack of any association between these auto-antibodies and such clinical condition [33-36]. We registered 1 case of multiple sclerosis that was highly positive for IgG AGA. Therefore, we inquire whether if our solely observation is fortuitous or corresponds to a real etiological association, thing that needs to be enlightened by relevant studies.

IgG AGA or IgA AGA

IgG AGA is thought as a reliable marker for the whole spectrum of GS, irrespective of the involved organ [8,21]. Indeed, many authors demonstrated that IgG AGA is more common in neurologic diseases than IgA AGA class [8,19,25]. However, till now there is no specific biomarker for NCGS, and the diagnosis is mainly based on exclusion criteria [28].

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 [18,37,38], 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 NCGS manifestations, characterized by IgG AGA positivity in 56.4% of cases associated to IgA AGA in 7.7% of patients, but without anti-endomysium, anti-tTG, and anti-DGP (deamidated gliadin peptide) antibodies, which are the specific markers of CD [39].

On the other hand, many recent studies have given evidence of a significant association of IgA anti-transglutaminase 6 antibodies with diverse categories of gluten neuropathies, mainly sporadic

ataxia, compared to healthy controls [40-44]. These findings deserve importance in opening up new perspectives for the immunologic diagnosis of suspected gluten neuropathies.

To sum up, despite the relatively limited number of investigated cases, our study displayed original and promising results that emphasize the usefulness of AGA as a marker that may facilitate the diagnosis of neuropathies of unknown etiology. Additional testing based on other potential relevant marker such as anti-TG6 antibodies, with the assessing of the GFD effectiveness are required.

Conclusion

The results of our study strengthen previous data relating a substantial frequency of gluten sensitivity in peripheral neuropathy and ataxia, with a particular note for ischemic stroke of young adults. Face to neurological diseases of unknown etiology, serological evidence of GS is required, based on IgG and IgA AGA testing. Nevertheless, atypical celiac disease with neurologic manifestations must be ruled out using anti-tTGA testing followed if positive by an intestinal biopsy. To make stronger our findings, additional investigations on larger size of cases with additional relevant markers would be recommended.

Competing Interests

The authors declare that no competing interests exist for this study.

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References

1. Watkins RD, Zawahir S (2017) Celiac disease and nonceliac gluten sensitivity. Pediatr Clin North Am 64: 563-576.
2. Rashtak S, Snyder MR, Pittock SJ, Wu TT, Gandhi MJ, et al. (2011) Serology of celiac disease in gluten-sensitive ataxia or neuropathy: Role of deamidated gliadin antibody. J Neuroimmunol 230: 130-134.
3. Valenti S, Corica D, Ricciardi L, Romano C (2017) Gluten-related disorders: Certainties, questions and doubts. Ann Med 49: 569-581.
4. Barton SH, Murray JA (2008) Celiac disease and autoimmunity in the gut and elsewhere. Gastroenterol Clin North Am 37**:** 411-428.
5. Hadjivassiliou M, Grunewald RA, Kandler RH, Chattopadhyay AK, Jarratt A, et al (2006) Neuropathy associated with gluten sensitivity. J Neurol Neurosurg Psychiatry 77: 1262-1266.
6. Bushara KO (2005) Neurologic presentation of celiac disease. Gastroenterology 128: S92-S97.
7. Green PH, Alaedini A, Sander HW, Brannagan TH, Latov N, et al. (2005) Mechanisms underlying celiac disease and its neurologic manifestations. Cell Mol Life Sci 62: 791-799.
8. Hadjivassiliou M, Grunewald R, Sharrack B, Sanders D, Lobo A, et al. (2003) Gluten ataxia in perspective: Epidemiology, genetic susceptibility and clinical characteristics. Brain 126: 685-691.
9. Lock RJ, Pengiran DS, Unsworth DJ, Ward JJ, Wills AJ (2005) Ataxia, peripheral neuropathy, and anti-gliadin antibody. Guilt by association? J Neurol Neurosurg Psychiatry 76: 1601-1613.
10. Ihara M, Makino F, Sawada H, Mezaki T, Mizutani K, et al. (2006) Gluten sensitivity in japanese patients with adult-onset cerebellar ataxia. Intern Med 45: 135-140.
11. Audia S, Duchene C, Samson M, Muller G, Bielefeld P, et al. (2008) Stroke in young adults with celiac disease. Rev Med Interne 29**:** 228-231.
12. Peltola M, Kaukinen K, Dastidar P, Haimila K, Partanen J, et al. (2009) Hippocampal sclerosis in refractory temporal lobe epilepsy is associated with gluten sensitivity. J Neurol Neurosurg Psychiatry 80: 626-630.
13. Rachid B, Zouhayr S, Chtaou N, Messouak O, Belahsen F (2010) Ischemic stroke revealing celiac disease. Pan Afr Med J 5**:** 2.
14. Hadjivassiliou M, Chattopadhyay AK, Grunewald RA, Jarratt JA, Kandler RH, et al. (2007) Myopathy associated with gluten sensitivity. Muscle Nerve 35: 443-450.
15. Pellecchia MT, Scala R, Filla A, De Michele G, Ciacci, et al (1999) Idiopathic cerebellar ataxia associated with celiac disease: Lack of distinctive neurological features. J Neurol Neurosurg Psychiatry 66: 32-35.
16. Wong D, Dwinnel M, Schulzer M, Nimmo M, Leavitt BR, et al. (2007) Ataxia and the role of antigliadin antibodies. Can J Neurol Sci 34: 193-196.
17. Hadjivassiliou M, Gibson A, Davies-Jones GA, Lobo AJ, Stephenson TJ, et al. (1996) Does cryptic gluten sensitivity play a part in neurological illness? Lancet 347: 369-371.
18. Hadjivassiliou M, Sanders DS, Grunewald RA, Woodroofe N, Boscolo S, et al. (2010) Gluten sensitivity: From gut to brain. Lancet Neurol 9: 318-330.
19. Chin RL, Sander HW, Brannagan TH, Green PH, Hays AP, et al. (2003) Celiac neuropathy. Neurology 60: 1581-1585.
20. El Moutawakil B, Chourkani N, Sibai M, Moutaouakil F, Rafai M, et al. (2009) Celiac disease and ischemic stroke. Rev Neurol (Paris) 165: 962-966.
21. Hamidian Y, Togha M, Nafisi S, Dowlatshahi S, Jahromi SR, et al. (2012) Anti-gliadin antibody in sporadic adult ataxia. Iran J Neurol 11: 16-20.
22. Hadjivassiliou M, Boscolo S, Davies-Jones GA, Grunewald RA, Not T, et al. (2002) The humoral response in the pathogenesis of gluten ataxia. Neurology 58: 1221-1226.
23. Nanri K, Shibuya M, Taguchi T, Hasegawa A, Tanaka N (2011) Selective loss of purkinje cells in a patient with anti-gliadin-antibody-positive autoimmune cerebellar ataxia. Diagn Pathol 6: 14.
24. Burk K, Bosch S, Muller CA, Melms A, Zuhlke C, et al. (2001) Sporadic cerebellar ataxia associated with gluten sensitivity. Brain 124: 1013-1019.
25. Hadjivassiliou M, Grunewald RA, Chattopadhyay AK, Davies-Jones GA, Gibson A, et al. (1998) Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. Lancet 352: 1582-1585.
26. Fabbri E, Rustignoli L, Muscari A, Puddu GM, Guarino M, et al. (2012) Recurrent ischemic strokes in a young celiac woman with MTHFR gene mutation. World J Gastroenterol 18: 3472-3476.
27. Selva-O'Callaghan A, Casellas F, de Torres I, Palou E, Grau-Junyent JM, et al. (2007) Celiac disease and antibodies associated with celiac disease in patients with inflammatory myopathy. Muscle Nerve 35**:** 49-54.
28. Bruni O, Dosi C, Luchetti A, Della Corte M, Riccioni A, et al. (2014) An unusual case of drug-resistant epilepsy in a child with non-celiac gluten sensitivity. Seizure 23**:** 674-676.
29. Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL (2012) Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. Psychiatr Q 83: 91-102.
30. Beyan E, Pamukcuoglu M, Beyan C (2009) Deep vein thrombosis associated with celiac disease. Bratisl Lek Listy 110: 263-264.
31. Baryshnikov EN, Krums LM, Vorob'eva NN, Parfenov AI (2010) Lower extremity deep vein thrombosis associated with gluten-sensitivity celiac disease. Ter Arkh 82**:** 52-54.
32. Hadjivassiliou M, Grunewald RA, Davies-Jones GA (2002) Gluten sensitivity as a neurological illness. J Neurol Neurosurg Psychiatry 72: 560-563.
33. Reichelt KL, Jensen D (2004) IgA antibodies against gliadin and gluten in multiple sclerosis. Acta Neurol Scand 110: 239-241.
34. Shor DB, Barzilai O, Ram M, Izhaky D, Porat-Katz BS, et al (2009) Gluten sensitivity in multiple sclerosis: Experimental myth or clinical truth? Ann N Y Acad Sci 1173: 343-349.
35. Borhani Haghighi A, Ansari N, Mokhtari M, Geramizadeh B, Lankarani KB (2007) Multiple sclerosis and gluten sensitivity. Clin Neurol Neurosurg 109**:** 651-653.
36. Nicoletti A, Patti F, Lo Fermo S, Sciacca A, Laisa P, et al. (2008) Frequency of

celiac disease is not increased among multiple sclerosis patients. Mult Scler 14: 698-700.

37. Hadjivassiliou M, Williamson CA, Woodroofe N (2004) The immunology of gluten sensitivity: Beyond the gut. Trends Immunol 25**:** 578-582.

38. Marzari R, Sblattero D, Florian F, Tongiorgi E, Not T, et al. (2001) Molecular dissection of the tissue transglutaminase autoantibody response in celiac disease. J Immunol 166: 4170-4176.

39. Volta U, Tovoli F, Cicola R, Parisi C, Fabbri A, et al. (2012) Serological tests in gluten sensitivity (nonceliac gluten intolerance). J Clin Gastroenterol 46**:** 680-685.

40. Zis P, Rao DG, Sarrigiannis PG, Aeschlimann P, Aeschlimann DP, et al. (2017) Transglutaminase 6 antibodies in gluten neuropathy. Dig Liver Dis 49: 1196-1200.

41. Sato K, Nanri K (2017) Gluten ataxia: Anti-transglutaminase-6 antibody as a new biomarker. Brain Nerve 69: 933-940.

42. Gadoth A, Nefussy B, Bleiberg M, Klein T, Artman I, et al. (2015 Jun) Transglutaminase 6 antibodies in the serum of patients with amyotrophic lateral sclerosis. JAMA Neurol 72: 676-681.

43. Goodman BP, Mistry DH, Pasha SF, Bosch PE (2009) Copper deficiency myeloneuropathy due to occult celiac disease. Neurologist 15: 355-356.

44. Ruggieri M, Incorpora G, Polizzi A, Parano E, Spina M, et al. (2008) Low prevalence of neurologic and psychiatric manifestations in children with gluten sensitivity. J Pediatr 152: 244-249.

Author Affiliation Top

[1]Laboratory of Immunology, Center of Clinical Research, University Hospital Mohamed VI, Av Ibn Sina, Marrakech, Morocco
[2]B2S Research Laboratory, Faculty of Medicine, Cadi Ayyad University, Marrakech, Morocco
[3]Department of Neurology, University Hospital of Marrakech, Morocco Marico Research and Development Center, Morocco