Gluten sensitivity and neuropathies
A Moroccan Case-Control Study

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الملخص

الحساسية المفرطة للغلوتين هي استجابة مناعية مبالغة ضد الغلوتين و مشتقاته عند أشخاص ذو استعداد وراثي. و قد بينت الأبحاث الطبية الحديثة أن هذا المرض يمكن أن يظهر بأعراض عصبية فقط دونما عوارض هضمية. و لهذا تأتي هذه الدراسة الاستباقية من أجل تحديد معدل انتشار هذه الحساسية المفرطة في الأمراض العصبية المجهولة السبب و تبيان خواصها السريرية، الإشعاعية، الفيزيولوجية و الإحيائية. تم انجاز هذا البحث على 60 مريضا (متوسط العمر 43 سنة محصورة بين 13 و 76 سنة و نسبة الذكور للإناث: 0,7) في مقابل 57 شاهدا سليما تم انتقاؤهم من بين المتبرعين بالدم. استفاد المشاركون من فحص بدني وفحص بالأشعة و تحاليل مخبرية ضمت قياس تركيز مضادات الأجسام ضد الغليادين من نوع "أ" و "ج" إضافة إلى مضادات الأجسام ضد ناقلات الغليادين من نوع "أ".أسفرت هذه الفحوصات عن 18 حالة جلطة دماغية (28,3%)، 16 حالة من مرض اعتلال الأعصاب (26,7 %)، 7 حالات من الصرع (11,7%)،7 حالات من الرنح (11,7%)، 3 حالات من الاعتلال العضلي (6,7%)،حالتان من مرض القرن النخاعي الأمامي، حالتان من مرض اعتلال النخاع الشوكي و حالة واحدة لكل من متلازمة باركنسون، التهاب السحايا، التصلب اللويحي، و مرض خلل التوتر العضلي و التهاب الوريد الخثاري. أما التحليل المناعي فأسفر عن تسجيل 16 مريضا (26,7%) و 9 شهود (15,7%) ذو تركيز موجب لمضادات الأجسام ضد الغليادين (الرقم الاستدلالي =0,151) في حين أن مضادات ناقلات الغلوتامين كانت ذات تركيز موجب عند شاهد واحد. يتوزع المصابون بالحساسية الزائدة للغلوتين على الشكل الآتي: 4 حالات من مرض اعتلال الأعصاب، 3 حالات لكل من الرنح المخيخي و الجلطة الدماغية، حالتين للاعتلال العضلي إضافة الى حالة واحدة لكل من التصلب اللويحي و الصرع و التهاب الأوردة الدماغية الخثاري و مرض اعتلال النخاع الشوكي. و قد أثبتت التحاليل المخبرية أن مضادات الغليادين من نوع "أ" هي الأكثر ترددا لكن تركيزها يبقى أقل من مضادات الغليادين من نوع "ج". نستنتج من كل ما سبق ان معدل الانتشار المهم للحساسية المفرطة للغلوتين تجعلها سببا محتملا للأمراض العصبية المجهولة المصدر و خصوصا مرض اعتلال الأعصاب و الرنح المخيخي إضافة إلى الجلطة الدماغية.

الكلمات الأساسية: الحساسية المفرطة للغلوتين، الأمراض العصبية، مضادات الأجسام ضد الغليادين، معدل الانتشار

Abstract: Gluten sensitivity GS) is a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals. Recently, it became accepted that GS can present only with neurological manifestations. In order to estimate prospectively the prevalence of GS among idiopathic neurologic diseases and to study their clinical, radiological, electrophysiological, immunological and biological characteristics, we performed a prospective screening (using IgA and IgG antigliadin (AGA) and IgA-anti-tissue transglutaminase antibodies using ELISA system) on 60 patients (mean age: 43 years, ranging between 13 and 76 years and male to female ratio: 0,7) with different idiopathic neuropathies compared to 57 controls. Patients were recruited from Neurology Department (University Hospital of Marrakesh) and controls corresponded to healthy blood donors from the blood transfusion center (Ibn-Sina Military Hospital, Marrakesh). According to physical examination and specific investigations of the patients, the study included 18 cases of ischemic stroke (28,33%), 16 cases of peripheral neuropathy (PN) (26,7%), 7 cases of epilepsy (11,7%), 7 patients with ataxia (11,7%), 3 with myopathy (6,7%) and 9 had other neuropathies (15%) corresponding to 2 cases of myelopathy, 2 cases of anterior horn disease together with 1 case for each of the followings: Parkinson disease, lymphocytic meningitis, multiple sclerosis, cerebral thrombophlebitis, dystonia. After immunological testing, 26.7% of patients (n=16) had positive AGA versus 15.7% in the healthy controls *(p=0,151)* while IgA-tTG was negative for all patients, and positive in only one control. The positive AGA cases corresponded to peripheral neuropathy (n=4), ataxia (n=3), ischemic stroke (n=3) and myopathy (n=2) followed by one case for each of the following conditions: multiple sclerosis, epilepsy, cerebral thrombophlebitis and myelopathy. Among the positive AGA, IgA isotype is more frequent than IgG; however, IgG-AGA titres are higher than IgA-AGA ones. In summary, regarding the high prevalence of AGA in our series, GS may be considered as potential cause for neurologic diseases of unknown aetiology, particularly peripheral neuropathy and ataxia and ischemic stroke of young adults. Moreover, the AGA testing might represent the best marker for gluten neuropathies.
Key words: gluten sensitivity, neuropathies, antigliadin antibodies, prevalence.

Résumé : La sensibilité au gluten (SaG) est un état de réponse immunologique excessive aux protéines ingérées du gluten, chez un individu génétiquement prédisposé. Récemment, il est apparu que la SaG peut se manifester uniquement par des troubles neurologiques en dehors de tout symptôme digestif. Notre étude a pour objectif de mesurer la prévalence de la SaG au cours des neuropathies idiopathiques et de déterminer leurs caractéristiques cliniques, radiologiques, électro-physiologiques et biologiques. Ceci dit, nous avons recherché des marqueurs de la SaG, représentés par les anticorps anti-gliadine (AGA, IgA et IgG) couplés aux anticorps anti-transglutaminase tissulaire (Ac anti-tTG), chez 60 patients (âge moyen: 43 ans, allant de 13 à 76 ans, sexe-ratio M/F: 0,7) émanant du service de neurologie du Centre Hospitalier Universitaire de Marrakech et 57 témoins sélectionnés parmi des donneurs de sang sains (Centre de transfusion de l'Hôpital Militaire Avicenne-Marrakech). Selon les données cliniques et para-cliniques, les patients correspondaient à 18 cas d'accident vasculaire cérébral ischémique (AVCi) (28,33%), 16 cas de neuropathies périphériques (NP) (26,7%), 7 cas d'épilepsie (11,7%), 7 cas d'ataxie (11,7%), 3 cas de myopathies (6,7%), 2 cas de maladie de la corne antérieure,2 cas de myélopathie et 1 cas pour chacune des pathologies suivantes : maladie de Parkinson, méningite lymphocytaire, sclérose en plaques (SEP), la thrombophlébite cérébrale et la dystonie. Les AGA étaient positifs chez 26,7% des patients contre 15,7% chez les témoins *(p=0,151),* alors que le dosage des anti-tTG était négatif pour tous les patients et positif chez un témoin. Les patients AGA positifs correspondaient à 4 cas de NP, 3 cas d'ataxie, 3 cas d'AVCi, 2 cas de myopathie suivi d'un cas pour chacune des neuropathies suivantes : la SEP, l'épilepsie, la thrombophlébite cérébrale et la myélopathie.
En conclusion, les données de notre série, confrontées à celles de la littérature, permettraient d'attribuer l'étiologie des neuropathies idiopathiques à une SaG, essentiellement la NP, l'ataxie et l'AVCi du sujet jeune. En plus, le dosage des AGA constituerait un meilleur marqueur pour les neuropathies au gluten.
Mots clés : Sensibilité au gluten, neuropathies, anticorps antigliadin, prévalence

Introduction

Gluten sensitivity (GS) is a systemic autoimmune disease with diverse manifestations[1]. This disorder is characterised by abnormal immunological responsiveness to ingested gluten in genetically susceptible individuals. It represents a spectrum of diverse manifestations, one of which is gluten-sensitive enteropathy (GSE). 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). The neurological

manifestations can present even in the absence of an enteropathy and the most common neurological dysfunction encountered is ataxia (gluten ataxia) and peripheral axonal neuropathy[1-3].

When the first comprehensive report of neurological manifestations in the context of histologically confirmed celiac disease was published in 1966[4], 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 CNS and peripheral nervous system. This finding favoured an immune-mediated pathogenesis[1]. In 1996, Hadjivassiliou and colleagues investigated the prevalence of GS in patients with neurological dysfunction of unknown aetiology; most patients had ataxia either with or without neuropathy and the presence of antigliadin antibodies (AGA) in these patients was common compared with controls[3].

Several studies showed significant prevalence of GS in neurologic diseases that varied between 34% and 47%[1, 3, 5]; also, some reports demonstrated an association between neuropathies and anti-tTG2 antibodies[6]. Moreover, rare cases of ischemic stroke and epilepsy of young adults revealing GS have been published [7-9].

The main aim of this study was to estimate the prevalence of gluten sensitivity in patients with idiopathic neuropathies, using antigliadin and transglutaminase antibodies. The second aim was to determine the clinical characteristics of these gluten neuropathies.

Patients and methods

Patients' selection

We performed a prospective study about 60 patients with different categories of idiopathic neuropathies and 57 controls. The patients were recruited at the department of neurology in the University Hospital of Marrakesh over a period of one year (from June 2010 to June 2011). Patients with known CD undergoing gluten free diet and those with etiological established diagnosis of the neuropathy were excluded from the study.

The control individuals were selected from blood transfusion center affiliated to Ibn-Sina Military Hospital of Marrakesh.

Clinical examination and investigations

Using a preset questionnaire, the clinical data of the population were picked up, including:

- Socio-demographic characteristics: sex, age, origin, education level and occupation;
- Medical history: diabetes, HBP, smoking, alcohol intake, nutrition deficiency, known GSE, gluten introduction age, digestive symptoms, tuberculosis, and the type of onset and progression;
- All the patients had neurological and general physical examination, permitting to characterize the type of the neurological disorder.

Immunologic testing

All the patients and controls were screened for both IgG and IgA antigliadin antibodies, using an immuno-enzymological method (ELISA IgG, IgA Gliadin, Diagnostic system, Germany, threshold: 12 IU/ml), followed by the anti-IgA tissue-transglutaminase antibodies using the ELISA system (tGT IgA, DRG instruments, GmbH, Germany, threshold 10 IU/mL).

Statistical analysis

All statistical analysis was performed in the laboratory of epidemiology, Faculty of Medicine, Marrakesh.

Results

Socio-demographic characteristics

The study concerned 60 patients and 57 controls. The patients' median of age was 43 years (+/- 13,9 years), ranging between 13 and 76 years old, with a female predominance (male to female sex-ratio = 0,7). The standard of living was medium for 55 % (n=33) of patients, low for 36,7% (n=22) , and high for 3,3% (n=2), and not defined for 3 other patients. About half of patients (n=29, 48,33%) had primary school level, 26,66% (n=16) of them were illiterate, 15% (n=9) had high school level, while only one patient (1,6%) reached college.

Regarding the social status of patients, 77,77% (n=28) of females were housewives, 11,6% (n=7) were labourers, 8,33% (n= 5) were employees, 8,33% (n= 5) were traders, 6,6% (n= 4) were students and others. The socio-demographic characteristics of the population including the social status and the standard of living and the occupation are reported in table-1.

Clinical data and investigations' results:

Among our patients, 8 had gluten sensitivity risk factors, corresponding to 2 cases of consanguinity status, 4 cases of diabetes and 2 cases of autoimmune conditions (rheumatoid arthritis in 1 patient, livedo and Raynaud disease in 1 patient). Minor gastrointestinal symptoms were reported by 6 patients such as diarrhoea or dyspepsia while one patient had nutrition deficiency. No patient had excluded the gluten or its derived components from his diet. The clinical neurologic categories are listed in table-1.

The Ischemic stroke was the major clinical category in our series (30%, n=18), affecting mostly the middle cerebral artery (MCA) area (n=9) and was associated to cerebral atrophy in 2 cases. Three patients were positive for AGA abs corresponding to 1 case of IgA-AGA and 2 cases of IgG-AGA. The biological testing showed 6 cases of hypochromic microcytic anaemia and 6 cases of inflammatory syndrome, also, 4 patients had hypocholesterolemia and 1 had intermediate rate of serum Homocysteine (1,37 mg/l) while haemostasis testing was normal for all.

Table I: Socio-demographic characteristics and clinical categories of the patients

Socio-demographic characteristics	
Median of age	43 years (+/- 13,9)
Age range	13-76 years
Male to female sex ratio	0,7
Neurologic forms	**n (%)**
Ischemic stroke	18 (30%)
Peripheral neuropathy	16 (26,7%)
ataxia	7 (11,7%)
Epilepsy	7 (11,7%)
Myopathy	3
Anterior horn disease	2
Multiple sclerosis	1
Myelopathy	2
Dystonia	1
Parkinson disease	1
Cerebral thrombophlebitis	1
Lymphocytic meningitis	1
Total of patients	60

The 16 cases of neuropathy corresponded to 10 cases (58,8%) of polyneuropathy, 3 cases of mononeuropathy multiplex and 2 cases of polyradiculoneuropathy. The electro-physiological testing showed combined motor and sensitive, motor, and sensitive neuropathies in respectively 7 and 2 and 2 cases. Moreover, 4 patients were positive for AGA and all of them had the IgA-AGA isotype; anaemia was found in 8 patients and 9 had increased inflammatory markers.

Seven of our patients had ataxia related to gait and limb cerebellar form in 5 cases and sensory ataxia in 2 cases. Among the first group, the biologic testing found 1 had increased AGA levels (combined IgG and IgA) and 1 another had increased IgA-AGA isotype; 3 cases of anaemia and increased inflammatory markers were detected and 1 patient had hypocholesterolemia, also, MRI detected global atrophy in 4 patients; meanwhile, 2 cases of anaemia and 1 case of positive inflammatory markers were detected in the second group.

The epilepsy group comprised 5 cases of generalized tonico-clonic seizures and 2 cases of partial seizures wherein 1 patient had partial status epilepticus. On the electro-encephalogram, 6 patients had spikes and waves; they were generalized in 4 cases and localized in the left parietal lobe in 2 other cases; and normal in 1 case. Besides, Only 1 patient was positive for IgA-AGA antibodies. Also, 3 patients had microcytic hypochromic anaemia and 4 had increased inflammation markers while 4 patients had neuro-imaging (MRI or scanner) that was normal for all of them.

All the 3 myopathy cases had bilateral and symmetric myogenic syndrome, associated to partial muscular atrophy in one case and to global handicap in another case. CPK was increased in 2 cases (1067 and 5213 U/L), IgG-AGA was positive in 2 patients, hypochromic microcytic anaemia was found in 2 cases and increased inflammation markers in 2 cases. The muscle biopsy revealed mitochondriopathy in 1 case and inflammatory changes in the other, which was later diagnosed as dermato-myositis.

Two patients presented with myelopathy and one of them had increased IgG-AGA antibodies. Furthermore, the only patient with cerebral thrombophlebitis had no clinical or biological pro-thrombotic conditions and was positive for IgA-AGA antibodies. One of our patients corresponded to multiple sclerosis condition characterised by several and recurring attacks, on immunological testing, IgG-AGA was positive.

Immunologic findings are detailed in table 2 and 3 and in figure 1.

Immunologic analysis

Positive serology for gluten sensitivity (IgA and/or IgG antigliadin) was found in 26,7% of the patients (n=16) versus 15,78% (n=9) in the control group (p value: 0.151) (Table 2); however; all the patients were negative for anti-IgA-tTG.

The neurological forms associated with positive AGA status are respectively: peripheral neuropathies (25%, n=4), followed by ataxia (18,75%, 3), ischemic stroke (18,75%; n= 3), myopathy (15,5%, n=2) and 1 positive case either IgA or IgG-AGA for each of the following diseases: epilepsy, cerebral thrombo-phlebitis, myelopathy and multiple sclerosis (table 2).

Table-II: **Immunologic profile of positive serologic tests in patients and controls**

Neuropathy categories	AGA IgG		AGA IgA		Total of positive AGA
	Pos n(%)	Neg n(%)	Pos n(%)	Neg n(%)	
Peripheral neuropathy	-	16 (100)	4 (25)	12 (75)	4
Stroke	2	16 (88,8)	1	17(94,4)	3
Myopathy	2	1	-	3	2
Ataxia	-	6	3	4	3
Epilepsy	-	7	1	6	1
Myelopathy	1	-	-	1	1
M.S*	1	1	1	-	1
T.P**	-	1	1	-	1
Total of Patients	6	54 (90)	9	52 (86,66)	***16 (26,7%)***
Healthy donors	4	53 (93%)	7	50(87,7)	***16 (15,8%)***

*Multiple sclerosis **Thrombophlebitis

Among the positive IgA-AGA, 4 patients had peripheral neuropathy and 1 had stroke and 3 had cerebellar ataxias and 1 had epilepsy and 1 patient had thrombophlebitis (figure 1). Meanwhile the positive IgG-AGA was associated to 2 cases of stroke, to 2 cases of myopathy and to one case of medullar compression syndrome and one case of multiple sclerosis (table2).

Globally, for all positive cases, IgG-AGA isotype titers are found to be higher than IgA-AGA ones (table-3).

Regarding the immunological profile of the positive cases, IgA AGA isotype was the predominant isotype in peripheral neuropathy (the 4 positive cases) and in ataxia (2 IgA-AGA vs 1 combined IgA and IgG AGA), and in cerebral thrombophlebitis and epilepsy where iwas the only positive isotype; however, IgG-AGA isotype was common in stroke (2 IgG-AGA vs. 1 with IgA-AGA) and in myopathy (2 IgG-AGA vs. no IgA-AGA isotype) and in medullar compression syndrome (the

patient was positive for IgG-AGA only) (figure 1; table 2 and 3).

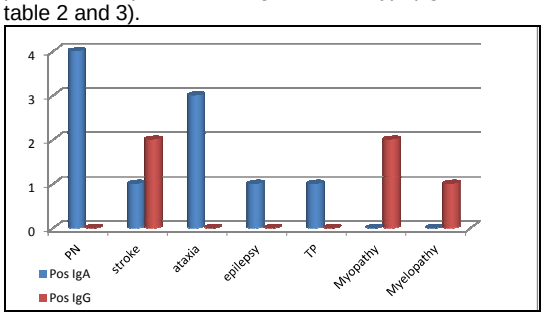

Fig I: The profile of positive AGA cases according to neuropathy categories and AGA isotypes.
PN: peripheral neuropathy; TP: thrombophlebitis; AGA: antigliadin antibody; pos: positive

Among the 57 healthy donors, 9 (15,78%) were positive for AGA in which 6 were positive for IgA-AGA and 3 were positive for IgG-AGA. For the IgG-AGA isotype, the titers varied between 26,14 IU/mL to more than 200IU/mL, and between 30,38 IU/mL and more than 200IU/mL for IgA-AGA isotype. The only double positive case (IgA and IgG AGA) was positive for IgA-anti-tTG with a high titer (>200 IU/ml).

Discussion

Our study found a high prevalence (26,7%) of antigliadin antibodies in patients with neuropathies of unknown cause, versus 15,78% in the control group. Even if this association is not significant (p=0,151), these findings support the fact that GS may represent a potential aetiology of these neuropathies. Compared to similar studies, this prevalence is amongst the highest ones, ranging between 34%, and 57% (table-4), while lower prevalence is reported by other authors (table-4).

The patients of our series are predominantly young (median of age: 45, 5 +/- 11,9 years old) and masculine (male to female ratio among the AGA positive individuals : 1,6) and many studies support this fact[3].

Globally, peripheral neuropathy and ataxia are the most common neurological manifestations of GS which is in line with our findings (25 % and 18,7% respectively). The ischemic stroke is also highly prevalent (18,75%) among the positive AGA patients and this is established by many authors [7].

Table IV: Summary of studies on the Prevalence of AGA abs in idiopathic neuropathies

	Idiopathic neuropathy with positive AGA abs n(%)	Healthy controls n(%)	p value	Ref
Hadjivassiliou, 2003(n =53)	57 %	12%	< 0,0001	[10]
Hadjivassiliou et al, UK (n=140)	34%	12%	< 0,001	[5]
Pellecchia et al, Italy (n=24)	13%	0%	<0,05	[11]
D.Wong *and al,* Canada (n=56)	11%	8%	=0,68	[12]
Our study	16 (26,7%)	9(15.7)	= 0,151	-

Clinically, gluten ataxia usually presents with a cerebellar form associated with dysarthria [1], and commonly cerebellar atrophy on MRI, [10]. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are seen in up to 80% of cases[13]. Also, the association with axonal neuropathy was reported by several authors [13]. All our patients with evidence of GS correspond to idiopathic form of ataxia. but none of them had axonal neuropathies.

No combination of clinical features is specific enough to enable a clinical diagnosis of gluten ataxia to be made with confidence, except perhaps in patients with established GSE[11].

In many studies, patients with idiopathic sporadic ataxias were found to have frequent occurrence of AGA antibodies compared with healthy controls[1] (table-6) which goes with our results; actually, we found 3 cases of gluten ataxia among the 7 ataxic patients we include.

Table V: **Immunologic profile of positive AGA in idiopathic ataxia and peripheral neuropathies**

	Ataxia			Peripheral neuropathy		
	IgG only n(%)	IgA only n(%)	IgA and IgG n(%)	IgG only n(%)	IgA only n(%)	IgA and IgG n(%)
Ihara, 2005, (n=14), [14]	3 (21,4)	2 (14,3)	-	-	-	-
Hadji-vassiliou, 2003, (n=176)[10]	62 (35,2)	6 (3,4)	-	-	-	-
Pellecchia, 1999, (n=24) [11]	8,3%	0	4,1%	-	-	-
Burk, 2001, (n=104) [15]	2%	5,7%	2%	-	-	-
Hadji-vassiliou, 2006, (n=140) [5]	-	-	-	57%	16%	27%
Chin, 2003, (n= 20) [16]	-	-	-	0%	25%	45%
Hadji-vassiliou, 1996, (n=53) [3]	3	8	6	1	3	3
Our study (n=60)	0	3 (5)	1 (1,6)	0	4 (6,7)	0

Many authors found that IgG-AGA is a better marker of the whole spectrum of GS irrespective of the organ involved and remains the best diagnostic marker for gluten ataxia; they supported their contention by HLA studies[10]. However, others ones found that IgA-AGA

was the most frequent isotype among gluten ataxia patients which is similar to our findings[15]. In addition, combined IgA and IgG-AGA abs is possible (table-3), but at a lower proportion compared with the other immunological features; however, such association wasn't detected in our group of ataxic patients (table-2). The sensitivity of anti-tTG antibodies as markers of gluten ataxia (where the bowel is not affected) is by definition, low which is in line with our results (all our patients are negative for anti-tTG) [2].

Peripheral neuropathy (PN) is the other most common manifestation of gluten sensitivity[5]. Gluten neuropathy is a slowly progressive disease affecting mostly young patients [5]. PN syndrome is often associated with sensory abnormalities (tactile, thermo-algic and vibratory hypoesthesia[17], which is consistent with our findings. Symmetrical sensori-motor axonal neuropathy remains the prominent electrophysiological aspect of gluten peripheral neuropathies (GPN) [1]. Other features have also been reported such as asymmetrical neuropathy, and sensory ganglionopathy, and small fiber neuropathy, and pure motor neuropathy, and autonomic neuropathy[1]; however, Chin *and al* related a normal electro-physiologic exploration (EMG) in approximately 8% of GPN patients [17]. This clinical category is mostly associated with IgG-AGA Abs, but, the IgA-AGA isotype can also be positive [5]; which is coherent with our results showing 9/16 cases of IgA-AGA and 6/16 cases of IgG-AGA. Besides, anti-TG2 IgA antibodies are rarely detectable in patients with neurological manifestations.

According to literature, the association of ischemic stroke with GS seems less frequent than other neuropathies, and mostly concerns young subjects [7]. In our series, 3 of 18 ischemic stroke cases had positive AGA which is important. The majority of gluten stroke patients are young (median of age: 45 years), with normal biological, and radiological and cardiovascular investigations. The major clinical presentation of our patients corresponded to pure and proportional pyramidal syndrome, which has been reported by various studies [7]. On neuro-imaging, the middle cerebral artery's area is mostly affected with seldom cerebral or cerebellar atrophy[7]. In such pathology, AGA frequently coexists with hyper-homocysteinemia and decreased folates' levels [7]; this hyper-homocysteinemia is a known risk factor of ischemic strokes and demonstrated by many studies[7].

Myopathy is a rare neurological manifestation of GS and idiopathic inflammatory myopathy remains the most common form[18]. In fact, AGA antibodies have been detected in various clinical forms of myopathies including proximal myopathy due to vitamin E deficiency, and osteomalacia due to vitamin D deficiency, and polymyositis and sporadic inclusion body myositis (s-IBM) and also in the juvenile form of dermatomyositis (DM). Also, many patients under gluten free diet showed improvement[1]. Patients usually have bilateral and symmetric myogenic syndrome with progressive muscular atrophy [1]. Besides, inflammatory infiltration on muscle biopsy was the common pathology finding. Gluten myopathy is combined to normal or increased CPK rate[18].

Several reports have suggested a link between epilepsy and GSE[1]. It tends to affect young patients, and the seizures are resistant to antiepileptic drugs in most patients[1]. Different forms are described such as occipital lobe epilepsy and generalized tonico-clonic status epilepticus; also, authors reported an association with cerebral calcifications, especially of the temporal and occipital lobe, on neuro-imaging[1]. An improvement of GSE linked epilepsy, after the introduction of gluten-free diet, has been reported by many case-reports studies [1].

The cases of thrombophlebitis associated with GSE have been rarely published; it affects usually young patients with no pro-thrombotic risk factors[19], involving different vascular territories: cerebral vascular thrombophlebitis, deep venous proximal thrombosis of the leg , portal vein thrombosis, and non-ischemic central retinal vein occlusion[19]. Saibeni and al found that hyper-homocysteinemia is more frequent in patients with GSE compared with the control group[19]. Similar to a Turkish study[19], our cerebral thrombo-phlebitis case had positive IgA-AGA Abs, while IgG AGA and tTG were negative.

Clinical evidence of myelopathy in the absence of vitamin and other deficiencies (particularly copper) can be a rare manifestation of GS[1]. Besides, it can present with progressive medullar syndrome and is usually associated with normal imaging of the spinal cord[1].

Our series revealed one case of positive AGA in multiple sclerosis; however, this association hasn't been described by the literature till now [20]. Therefore we raise the question: is it a fortuitous or an aetiological association? That's why further studies are needed in order to get an answer.

Otherwise, we found no case-reports suggesting an association between dystonia[21], and amyotrophic lateral sclerosis [22], and meningitis[23], also, all of the patients having such pathologies in our series were negative for AGA.

Regarding the limited number of the included patients, our findings should be completed by further studies including large-based populations.

Conclusion

We conclude that serological evidence of gluten sensitivity is commonly found in neurological diseases of unknown cause and may be aetiologically linked. The diagnosis is based on AGA testing which might be the best marker for gluten neuropathies.

The clinical assessment showed that peripheral neuropathy and ataxia and even ischemic stroke of young adults are commonly associated with GS. Otherwise, the effect of gluten free diet on the neuropathy will be an additional argument for this association and, therefore, offers the prospect of a realistic therapeutic possibility for some untreatable neuropathies.

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