PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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• BRIEF REPORTS •

Assessment of autonomic function in untreated adult coeliac disease

Gian Marco Giorgetti, Antonio Tursi, Cesare Iani, Flavio Arciprete, Giovanni Brandimarte, Ambrogio Capria, Luigi Fontana

Gian Marco Giorgetti, Department of Internal Medicine, Clinical Nutrition Unit, "S. Eugenio" Hospital, Rome, Italy
Antonio Tursi, Digestive Endoscopy Unit, "Lorenzo Bonomo" Hospital, Andria (BA), Italy
Cesare Iani, Flavio Arciprete, Division of Neurology, "S. Eugenio" Hospital, Rome, Italy
Giovanni Brandimarte, Department of Internal Medicine, Division of Gastroenterology, "Cristo Re" Hospital, Rome, Italy
Ambrogio Capria, Luigi Fontana, Department of Internal Medicine and Immunology, "Tor Vergata" University, Rome, Italy
Correspondence to: Dr. Antonio Tursi, Galleria Pisani, 4, 70031 Andria (BA), Italy. antotursi@tiscali.it
Fax: +39-883-290225
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Abstract

AIM: Some recent studies showed that alteration of upper-gut motility in coeliac disease may be related to dysfunction of autonomic nervous system. The aim of our study was to investigate whether autonomic nervous system was altered in untreated and unselected coeliac disease patients.

METHODS: We studied 8 untreated and consecutive coeliac disease patients (2 males and 6 females, age range 37±14.5 years). Histological evaluation of duodenal mucosa, anti-gliadin antibodies (AGA), antiendomysial antibodies (EMA) and anti-tTG antibodies and sorbitol H2 breath test were performed in all patients. Extrinsic autonomic neuropathy was assessed by the standardized measurement of cardiovascular reflexes (lying-to-standing, Valsalva manoeuvre, deep breathing, sustained handgrip). The results obtained were compared with a healthy, asymptomatic control group (6 males and 7females, age range 42.3±13.5 years).

RESULTS: Coeliac patients exhibited a lower increase of PAS as a response to isometric effort, a reduction of spectral power LF as a response to clinostatic position, but without statistical significance. Also they showed a lower tolerance to orthostatic position, associated with a latent disequilibrium of sympathetic-vagal balance, a relative prevalence of parasympathetic component of the autonomic function. However, these results were not statistically significant when compared with control group (P = n.s.). And they were unchanged after 6 and 12 mo of gluten-free diet.

CONCLUSION: This study failed to confirm a significant correlation between autonomic dysfunction and coeliac disease, yet we could not exclude a role of autonomic dysfunction in the genesis of systemic symptoms in some coeliacs.

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INTRODUCTION

Coeliac disease (CD) is the most common severe food intolerance in the Western world[1]. It is a clinical syndrome of intestinal malabsorption, a characteristic though not specific histological lesion involving total, subtotal or partial small bowel villous atrophy (predominating in its proximal segments). It is the result of sensitiveness to ingested gluten in genetically susceptible people with the subsequent immune reaction leading to small bowel inflammation[2]. The classical malabsorptive symptoms of diarrhoea and weight loss are only one aspect of the spectrum of manifestations of this relatively common disease[3,4], since symptoms may be subtle and many patients have subclinical or silent disease[5,6]. A proper gluten-free diet (GFD) would lead to a clinical and histological improvement[7-9]. In particular, GFD played a key role in preventing nutritional deficiency, especially of micronutrients, and in reducing the risk of the development of intestinal malignancies[10].

It is quite frequently seen in clinical practice that coeliac patients present gastrointestinal motor abnormalities[11]. It has been recently shown that alteration of upper-gut motility may be related to dysfunction of autonomic nervous system[12]. The aim of our study was to investigate whether autonomic nervous system (ANS) was altered even in untreated and unselected coeliac patients and to assess the effect of GFD on ANS dysfunctions.

MATERIALS AND METHODS

Patients

We studied 8 untreated, consecutive and unselected coeliac disease patients (2 males and 6 females, age range 37±14.5 years). Both the original[13] and revised[14] criteria for the diagnosis of CD were used in this study. CD was defined as a permanent gluten-sensitive enteropathy, primarily manifested by the presence of characteristic small intestinal lesions[15]. Small-bowel biopsy was performed in all patients, as well as esophagogastroduodenoscopy (Fujinon EG300 videogastroscope; Fujinon, Omiya, Japan). At least six small-bowel biopsies were obtained from the second part of the duodenum using a disposable biopsy forceps with spike (U.S. Endoscopy Inc., Mentor, Ohio, U.S.A.) and evaluated by haematoxylin/eosin staining. Histopathology was expressed according to the Marsh classification of 1992[16]: "infiltrative" lesions with >30 lymphocytes/100 epithelial cells were defined as Marsh type I, "infiltrative/hyperplastic" lesions as Marsh II and "partial (sub)total villous atrophy (VA) as type III. We subdivided the Marsh III type into partial VA (Marsh IIIa), subtotal VA (Marsh IIIb) and total VA (Marsh IIIc), according to Oberhuber's modified classification[17].

Other possible causes of villous atrophy or duodenal damage, such as *Giardia Lamblia* infection, tropical sprue, collagenous sprue, food protein hypersensitiveness (cow's milks, eggs, fish, rice, chicken) were excluded, as well as other causes of inflammatory infiltration of duodenum, such as peptic duodenitis[17].

Methods

IgA and IgG anti-gliadin antibodies (AGA) were measured in all patients by enzyme-linked immunosorbent assay (kit Alfa-gliatest, Eurospital, Trieste - Italy); the lower limit of positivity

of IgA-class was 0.2 EU/mL and of IgG-class 10.0 EU/mL. IgA antiendomysial antibodies (EMA) were screened by the indirect immunofluorescent method on monkey oesophagus (kit Antiendomysium, Eurospital, Trieste - Italy). IgA anti-tissue transglutaminase antibodies were also screened by enzyme-linked immunosorbent assay using human recombinant tTG (kit Eu-tTG, Eurospital, Trieste - Italy); the lower limit of positivity of these antibodies was 7 UA/mL.

Also sorbitol H2 breath test (H2-BT) was performed. All patients were studied after an overnight fasting having been instructed to consume a meal of rice and meat; they were also requested not to smoke on the morning of the test day. End expiratory samples were collected before the patients drank the test solution (5 g of sorbitol in 150 mL of tap water) and every 30 min for 4 h. Hydrogen concentrations in each collected sample were measured with a breath-hydrogen analyzer (EC60 Gastrolyzer Breath Hydrogen Monitor, Bedfont Scientific Ltd, Upchurch - Kent, England [U.K.]). An increase in H2 concentration of at least 20 ppm over fasting baseline was considered positive for sorbitol malabsorption. The cut-off for calculating the validity of the test was shifted every 30 min, and a response operating characteristics (ROC) curve was plotted on the basis of the obtained results.

The clinical, endoscopic, histological and serological pattern of the studied coeliacs are described in Tables 1, 2.

Table 2 Non- invasive tests in the studied coeliac population

Patient No.	AGA IgA	AGA IgG	EMA	Anti-tTG	Sorbitol H2-BT
1	+	+	+	+	+
2	+	+	+	+	+
3	+	+	+	+	+
4	+	+	-	-	+
5	+	+	+	+	+
6	+	+	-	+	+
7	-	-	+	-	+
8	+	-	-	+	+

Abbreviations: AGA: Anti-gliadin antibodies; EMA: anti-endomysium antibodies; anti-tTG: anti-tissue transglutaminase; H2-BT: Hydrogen2-breath test.

No patient had other associated organic (such as hereditary, toxic, infectious, inflammatory) or metabolic diseases.

Extrinsic autonomic neuropathy was assessed by the standardized measurement of cardiovascular reflexes. Tests were performed in the morning and at constant temperatures. Autonomic function was evaluated by means of electrocardiograph Personal 120 (Esaote Biomedica, Firenze, Italy) and a Finapress set (Ohmeda, Louisville, Colorado, USA). We evaluated the heart rate variation (R-R interval) and systolic (SBP) and diastolic (DBP) blood pressures in response to a variety of stimuli: lying-to-standing (evaluation of R-R variation with a 30.15 ratio); Valsalva manoeuvre (forced expiration for 15 s with a 40 mm Hg pressure); deep breathing (6 expiratory cycles throughout one minute, evaluating the average of differences between the maximal and minimal duration of R-R interval during three subsequent deep breath [DB3]); sustained handgrip (performing isometric sub-maximal work for 3 min and evaluating blood pressure and heart rate variations); and tilt tests. The results of each test were scored according to Ewing's modified criteria[18,19].

The results obtained were compared with a healthy, asymptomatic control group (13 people, 6 males and 7 females, age range 42.3±13.5 years). All coeliac patients were re-evaluated about the autonomic function 6 and 12 mo after GFD has started.

Statistical analysis

The Student's *t*-test for unpaired data was used, and data are presented as mean±SD. $P<0.05$ was considered as statistically significant.

RESULTS

We noted that coeliac patients showed a lower increase of PAS in response to isometric effort. Moreover, they showed a reduction of spectral power LF in response to clinostatic position, but without statistical significance (Tables 3, 4).

Only one female patient (Table 5, patient number 8) showed symptomatic orthostatic hypotension (defined as SBP decrease >/= 20 mm Hg and DBP >/= 10 mmHg within 3 min in orthostatic position) as responsiveness to orthostatic position.

The overall results of ANS in coeliacs showed a tendency

Table 1 Demographic, clinical, endoscopic and histological data of the coeliac patients

Patient No.	Sex	Age (yr)	Clinical finding	Endoscopic finding	Histology
1	F	71	Weakness, diarrhoea	Absence of Kerckring's folds	Marsh IIIc
2	M	58	Diarrhoea, weight loss	Absence of Kerckring's folds	Marsh IIIb
3	F	31	Aphtous stomatitis, IDA	Reduction of Kerckring's folds	Marsh IIIb
4	F	31	IDA	"Scalloping" of duodenal folds	Marsh IIIa
5	F	38	Diarrhoea, abdominal pain, weight loss	Reduction of Kerckring's folds, micronodular mucosa	Marsh IIIc
6	M	33	IDA	Reduction of Kerckring's folds	Marsh IIIa
7	F	24	IDA, Grave's disease	Reduction of Kerckring's folds	Marsh IIIa
8	F	32	IDA, weakness	Reduction of Kerckring's folds	Marsh IIIa

Abbreviations: IDA: iron-deficiency anaemia.

Table 3 Evaluation of autonomic function in coeliac patients and control group

Group	LS	VR	DB	△PAS Handgrip	△PAD Handgrip
Coeliac disease	1.22±0.1	1.73±0.38	35.5±16.4	35.7±16.4	24.6±13.2
Control group	1.24±0.19	1.62±0.25	32.5±7.67	55.5±24.2	27.1±11.1
P	NS	NS	NS	NS	NS

LS: Lying-to-standing; VR: Valsalva reaction; DB: Deep breathing.

Table 4 Evaluation of Heart rate variance in coeliac patients and control group

Group	LF Clino	LF Ortho	HF Clino	HF Ortho	LF/HF Clino	LF/HF Ortho
Coeliac disease	35.9±18.1	73.5±15.3	35.7±18.9	13.21±9.3	1.56±1.85	8.63±6.34
Control group	52.8±21.0	67.1±25.9	31.1±15.6	17.90±12.9	2.35±1.65	6.94±5.5
P	NS	NS	NS	NS	NS	NS

Table 5 Overall results of autonomic tests in coeliac patients

Patient No.	Basal SBP	Basal DBP	Ortho SBP	Ortho DBP	Clino. LF	Ortho. LF	Clino. HF	Ortho. HF	Clino. LF/HF	Ortho. LF/HF	LS	VR	DB	Syst. SH	Diast. SH	Syst. Tilt Test	Diast. Tilt Test
1	127	82	120	82	40.99	61.65	48.00	32.82	0.85	1.88	1.03	1.46	19.2	54	27	-9	7.00
2	130	87	135	87	21.41	60.74	30.09	10.73	0.71	5.66	1.37	1.90	35.9	36	14	-9	5.00
3	130	80	125	80	77.04	92.52	12.89	5.96	5.98	15.52	1.20	1.40	33.3	35	25	19	14.00
4	105	70	105	85	38.26	63.87	20.19	17.85	1.9	3.58	1.20	2.30	40.1	39	36	3	7.00
5	115	80	120	82	31.15	58.43	62.16	16.49	0.5	3.54	1.20	1.40	39.3	48	28	7	14.00
6	120	80	108	75	27.16	87.79	27.33	11.00	0.99	7.98	1.18	1.50	40.2	50	47	2	12.00
7	105	70	115	75	20.30	94.00	61.00	4.79	0.3	19.6	1.30	2.30	44.3	7	6	-7	15.00
8	115	70	80	60	30.93	68.81	23.81	6.06	1.3	11.35	1.30	1.60	31.8	17	14	-10	2.00
Mean	118.38	77.38	113.50	78.25	35.91	73.48	35.68	13.21	1.57	8.64	1.22	1.73	35.51	35.75	24.63	-0.50	9.50
SD	10.20	6.52	16.50	8.51	18.13	15.27	18.88	9.28	1.85	6.34	0.10	0.39	7.74	16.37	13.20	10.23	4.87

to lower systolic-diastolic values of blood pressure both in clinostatic position and in active and passive orthostatic positions. However, these results had no statistical difference compared with those of control group (Table 4).

The spectral analysis of heart rate variance (HRV), performed with autoregressive method, confirmed these findings. The autoregressive analysis of HRV showed an important, but not significant, reduction of the power LF according to a considerable reductive activity of sympathetic tone at rest with a relative prevalence of parasympathetic tone. Passive orthostatic, evaluated by tilt tests, induced a marked sympathetic response (with increase of spectral power LF) (Table 5).

All patients were re-evaluated about the autonomic function 6 and 12 mo after GFD has started. In none of them we noted change of the results, and the symptomatic orthostatic hypotension persisted in patient number 8 despite strict adherence to GFD.

DISCUSSION

In recent years a discrete frequency of autonomic neuropathy has been disclosed in coeliac patients[12,20], similar to that reported in other functional gastrointestinal disorders, but lower than that described in diabetic subjects[21]. Pathogenetic factors involved in autonomic dysfunction in coeliac disease were unknown, and autoimmune damage or metabolic derangement have been hypothesized[22-24].

We investigated our coeliac patients, exploring their autonomic function using the cardiovascular tests because they were easily available reproducible, and not very expensive[25,26]. Our study showed quite different results from those recent studies about autonomic function in coeliacs. In particular, they differed from Usai's study, which reported ANS abnormalities in 45% of coeliacs affected by upper gastrointestinal symptoms[12]. Thus, we can hypothesize that ANS abnormalities may play a role in upper gastrointestinal symptoms rather than in systemic symptoms. In fact we recorded ANS abnormalities only in 1/5 patient without gastrointestinal symptoms. On the other hand, it is noteworthy that we did not find ANS abnormalities in any of the 3 patients complaining about gastrointestinal symptoms (Table 5). However, a role of ANS dysfunction in some coeliac patients cannot be excluded, since the patient No. 8 of our studied population (a 32-year-old female), the only one with ANS dysfunction, did not show dyspeptic symptoms but only systemic symptoms.

What a role could then the autonomic neuropathy play? Can it really play a role in the systemic symptoms in coeliac disease? We knew that several coeliac patients experienced weakness or chronic fatigue in clinical practice. In most cases it was related to malabsorption (such as iron-deficiency anaemia or folic acid deficiency), but in some cases autonomic neuropathy might be suspected. Our study unfortunately failed to demonstrate a significant autonomic dysfunction in CD; however, we cannot exclude that in some patients ANS dysfunction might play a role in the genesis of some systemic symptoms, such as weakness or chronic fatigue. In fact we noted that coeliac patients showed a lower tolerance to orthostatism, associated with a latent disequilibrium of sympathetic-vagal balance, ie, a relative prevalence of the parasympathetic component of the autonomic function. These alterations, and in particular the reduced tolerance to orthostatism, may explain the above mentioned symptoms in some cases, as we noted in patient No. 8 (Table 5).

But another very finding was that ANS dysfunction did not improve in this patient after GFD. It is difficult to explain why ANS did not improve after gluten withdrawal. We speculate that ANS dysfunction may be a two step process. In the first phase it may be gluten-related, and may improve after GFD. This phase may have a variable length, probably related to age, gender and time to gluten exposure. In the second phase it may be gluten - independent, probably related to autoimmune axonal aggression to autonomic nervous system, in which autoimmunity may perpetuate the neurological damage. Recent studies of Luostarinen *et al*.[27] may in part confirm this hypothesis. They showed that axonal neuropathy in CD might be also subclinical without any sign of malabsorption and it often persisted despite good compliance to GFD[27]. This hypothesis may justify the persistence of the orthostatic hypotension in patient 8 after six and twelve months of GFD, and it may also explain why some coeliacs experienced persistence or recurrence of chronic fatigue despite GFD. We consider that the recurrence of systemic symptoms is related to incidental gluten ingestion from unknown sources: the autonomic neuropathy, with consequent disequilibrium of sympathetic-vagal balance may be the cause of these systemic symptoms.

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