JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2014, 65, 6, 833-841
www.jpp.krakow.pl

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DISTURBANCES OF AUTONOMIC NERVOUS SYSTEM ACTIVITY AND DIMINISHED RESPONSE TO STRESS IN PATIENTS WITH CELIAC DISEASE

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Celiac disease (CED) is immune-mediated enteropathy caused by gluten intolerance affecting genetically predisposed individuals. CED may exert a number of various symptoms, including extra intestinal manifestations. Neurological symptoms can be the first sign of gluten intolerance. However, affected autonomic nervous system (ANS) activity may be linked to other symptoms. We evaluated the frequency of ANS impairment and resting ANS response to several stimuli in CED patients without neurological manifestations. Twenty five neurologically asymptomatic patients with CED were studied. The medical history was taken and ANS activity was determined. ANS tests included heart rate variability (HRV) at rest and after stimulation (sympathetic - stress, and parasympathetic - deep breathing). The results were compared with those of the control group comprising of 30 healthy asymptomatic volunteers. Both the resting HRV parameters and the HRV indices recorded after deep breathing (parasympathetic stimulation) were significantly lower in patients with CED than in the controls ($P<0.05$). Also the stress-induced increase in normalized low frequency parameter (LFnu) was significantly lower in the CED group than in the control group ($P<0.05$). Overall, about 20% of CED patients presented with parasympathetic dominancy but 36% with sympathetic dominancy, and 44% of patients did not show changes in sympathetic-vagal balance of the autonomic nervous system. We conclude that sympathetic-parasympathetic imbalance, in favour of more often sympathetic than parasympathetic overactivity occurs among neurologically asymptomatic CED patients. The ANS impairment observed in the course of CED may result from prolonged intestinal inflammation. Therefore, routine ANS testing might be considered in patients presenting with this condition.

Key words: *celiac disease, heart rate variability, autonomic nervous system activity, stress, body mass index, Valsalva maneuver, visceral sensitivity*

INTRODUCTION

Celiac disease (CED) is an autoimmune disorder occurring in genetically predisposed individuals (1, 2). CED is triggered by gluten peptide present in wheat proteins (1, 2). Up to 10% of patients with CED can be associated with neurological signs, such as ataxia, peripheral neuropathy, cognitive disorders and dementia (3, 4). The available sources rarely refer to the prevalence of autonomic nervous system (ANS) impairment among CED patients. The ANS impairment observed in CED might be related to chronic fatigue, orthostatic hypotonia and other systemic symptoms (5). So far, only few publications, based on small groups of patients or case series, referred to ANS impairment in CED-affected individuals (5-10). Gibbons *et al*. reported on four patients with confirmed CED and concomitant dysautonomia (8). According to other authors, up to 45% of patients with CED exhibit ANS impairment (6). Usai *et al*. (6) documented subclinical abnormalities of cardiovascular reflexes in 19% of CED patients with esophageal dysmotility; up to 20% of the patients with CED and dysautonomia were asymptomatic. However, the latter study included small number of subjects. Nevertheless, the frequency of CED dysautonomia seems to be underestimated (6).

Multiple pathogenic factors can be involved in the autonomic dysfunction associated with CED. ANS dysfunction may reflect various pathomechanisms of CED. Autoimmune damage and metabolic derangements have been hypothesized (7, 8, 10-13). Cooke and Smith postulated the role of clinical or subclinical malabsorption of microelements and/or vitamins including folic acid, vitamin E and cobalamin, which are indispensable for the maintenance of proper neurological functions (14). Other proposed pathomechanisms include gluten toxicity and immunological reactions, such as the presence of both, neuron-specific and non-specific antibodies or cross reactions with neuronal compounds (7, 15).

CED results from hypersensitivity to ingested gluten in genetically susceptible individuals, and subsequent immune reaction that may lead to small bowel inflammation. The

inflammation of the intestine induces changes in visceral perception, hyperreaction and local and/or central sensitizations (16). These changes could contribute to ANS dysfunction and alter motility of the upper gut, known to be the most sensitive (17). Inflammation can affect the functioning of ANS and modulate other visceral functions due to increased visceral sensory inflow (5-7), however, the exact pathomechanism of these dysfunctions has not been fully elucidated. The aim of this study was to analyze the frequency of ANS impairment, resting ANS activity and response of ANS to sympathetic and parasympathetic stimulations, and to recognize the pathomechanisms underlying possible ANS dysfunctions in CED patients.

MATERIAL AND METHODS

The protocol of the study was approved by the Local Bioethics Committee at the Jagiellonian University (decision no. KBET/148/B/2012). All the participants gave their written informed consent confirming their participation in the study.

The study included 25 neurologically asymptomatic patients with CED and 30 healthy volunteers without history of either gastrointestinal (GI) or neurological disorders; all subjects were subjected to clinical and laboratory investigation.

Histological examination of the duodenal biopsy specimens (Marsh grading) and testing for anti-endomysial antibodies (EMA) and anti-tissue transglutaminase (anti tTG) antibodies in blood serum were conducted in all the patients in order to determine CED severity and adherence to a gluten free diet. Typical endoscopic changes and histological features are presented in *Fig. 1A-1C*. The detailed characteristics of the studied individuals are presented in *Table 1*.

Biochemical analyses included determination of serum concentration of thyroid-stimulating hormone, the markers of nutritional status (hemoglobin concentration, mean corpuscular volume, lymphocyte count, red blood cell distribution width, serum concentrations of calcium and albumin), international normalized ratio (INR) and C-reactive protein (CRP) as a marker of inflammation (18) (*Table 2*).

A total of 55 subjects were divided into two groups:

- Group CED - 25 patients with celiac disease (8 men, 17 women, mean age 42.4 ± 15.8 years) and
- Group CG (control group) - 30 healthy volunteers (9 men, 21 women, mean age 42.1 ± 9.2 years).

The exclusion criteria for his study were: diabetes mellitus, obesity (BMI ≥30 kg/m^2), cardiovascular diseases (hypertension, coronary artery disease, valvular heart disease, cardiac arrhythmias), tobacco smoking, use of medications that may interfere with gastric myoelectric activity, history of surgeries, as well as any pathologies of the GI tract (e.g. inflammatory bowel disease), gynecological conditions or other chronic diseases.

The study protocol

All subjects were asked to fast for at least 12 hours prior to the examination and to discontinue any medications with a known effect on ANS three days before the study. As several stimuli can affect the function of cardiovascular autonomic system, the patients were requested to remain in a stable clinical status for at least 48 hours prior to the testing. The examination took place at room temperature, in a quiet relaxed atmosphere.

The evaluation of ANS activity comprised of:

- 30-min heart rate variability (HRV) recording at rest;
- 5-min HRV recording during deep breathing (DB; breathing frequency 6 breaths/min, 5-s inspiration, 5-s expiration);
- HRV recording 10 min following exposure to a stressor (sound signal).

Assessment of the autonomic nervous system

ANS activity was assessed by the heart rate variability (HRV) determined with Task Force Monitor 3040 (CNSystems, Austria)

Table 1. Clinical characteristic of the studied groups.

PARAMETER	STUDIED GROUPS		p
	Celiac disease (CED) (N=25)	Control group (N=30)	
Age (years)	42.4 ± 15.8	42.1 ± 9.2	NS
Gender female male	17 (68%) 8 (32%)	21 (70%) 9 (30%)	NS
BMI (kg/m^2)	21.7 ± 2.7	23.8 ± 0.6	NS
HR (beat/min)	69.1 ± 11.1	69.1 ± 11.1	NS
$BP_{s\ (mmHg)}$	119.4 ± 7	126.5 ± 9	NS
$BP_{d\ (mmHg)}$	82 ± 9	84 ± 9	NS
Marsh classification of duodenal mucosa	Type I 10pts (40%) Type III 15pts (60%)	0	
Serum albumin (g/dl)	43.55 ± 5.1	58.7 ± 4.2	<0.05
Serum anti-tTG antibodies (U/ml)	138.5 ± 80.4	12.4 ± 6.2	<0.05
CED duration (years) minimum maximum	8.75 0 40	0	
CED newly diagnosed cases	8 (32%)	0	
CED non adhering to GFD	9 pts (36%)	0	
CED adhering to GFD	8 pts (32%)	0	

CED - celiac disease; HR - heart rate mean ± standard deviation; BMI -body mass index, BPs - systolic blood pressure mean ± standard deviation, BPd - diastolic blood pressure mean ± standard deviation, GFD - gluten free diet, anti-tTG - antibodies against tissue transglutaminase, NS - non-significant.

Table 2. Biochemical characteristics of patients with celiac disease.

Parameter	Mean	Minimum	Maximum	Norm
TSH (uIU/ml)	1.63	0.33	3.93	0.27–4.20
Lymphocytes x10^3 µl	1.49	0.32	3.90	0.80–4.00
MCV (fl)	86.36	78.00	102.00	82.00–92.00
RDW CV (%)	13.61	12.40	17.90	12.10–14.10
Calcium (mmol/l)	2.35	2.10	2.90	2.15–2.55
INR	1.16	0.90	1.59	0.80–1.20
CRP (mg/l)	<5.0	<5.0	<5.0	5.0–10.0

CED - celiac disease, TSH - thyroid-stimulating hormone, MCV - mean corpuscular volume, RDV CV- red blood cell distribution width, INR - international normalized ratio, CRP - C reactive protein.

and analyzed with Task Force V Monitor 2. 2 software. The ECG signals were registered during 30-minute rest, 5-minute deep breathing (DB; 6 breaths per minute, one full cycle every 10 seconds), and 10 minutes after exposure to a stressor (sound signal, acoustic startle, 1100 Hz frequency, duration 0.5 s, intensity of 100 dB). The following HRV parameters were evaluated: LF (component of the low-frequency range, 0.04–0.15 Hz, modulated by both the sympathetic and parasympathetic nervous system and associated with baroreceptor activity), HF (component of the high-frequency range, 0.15–0.4 Hz, modulated by the parasympathetic nervous system, associated with respiration and blood pressure changes) and LF/HF ratio, reflecting interactions of both types of autonomic modulation (19, 20).

Deep breathing test (DB)

The respiratory fluctuations and heart rate are likely to be primarily mediated by parasympathetic efferent pathways (20). The respiratory sinus arrhythmia can be used as a measure of cardiac vagal modulation (21). To quantify the test score, the difference between maximum and minimum heart rate for each of the six cycles is determined and averaged to obtain the inspiratory - expiratory (I-E) difference, expressed in beats/min. The other parameters that can be analyzed during DB test include: E/I ratio - mean ratio of the longest RR(1) interval during expiration to the shortest RR (2) interval during inspiration counted from 6 consecutive cycles, ΔI-E - the difference between maximal heart rate during inspiration and minimal during expiration, DBD - the deep breath difference, i.e. mean difference between RR1 interval and RR2 interval, and RSA - respiratory arrhythmia index ({DBD/(RR1+RR2)}/2) (20).

Statistical analysis

Statistica 10.0 PL package (StatSoft the Inc., the Tulusa, Oklahoma, USA) was used for database management and statistical analyses. All values were expressed as either percentages or mean ± S.D. Normal of distribution of the analyzed variables was verified with the Shapiro-Wilk test. The variables that did not fulfill the criteria of normality underwent a logarithmic transformation (to natural logarithms) prior to further analyses. Unpaired Student t-test (in the case of normally distributed variables) or Wilcoxon's signed rank test (if either distribution was not normal) were used for intergroup comparisons of quantitative variables. The effects of the deep breathing and exposure to stressor were tested with paired Student t-test or Mann-Whitney U-test. The associations between pairs of the HRV parameters were analyzed on the basis of the Spearman's coefficients of rank correlation. The threshold of statistical significance of all the tests was set at $P<0.05$.

RESULTS

Biochemical parameters

Mean serum level of anti-tissue transglutaminase antibodies (anti tTG) in CED group turned out to be higher than in the controls (138.5 U/ml vs. 12.4 U/ml, $P<0.05$). Moreover, the CED patients and the controls differed in terms of mean serum albumin concentrations (43.55 g/dl vs. 58.7 g/dl, $P<0.05$), but the results obtained in both the groups were within normal limit (*Table 1*).

All participants presented with low concentrations of C reactive protein (<5 mg/l) and were euthyroid. One patient had lymphopenia and microcytosis, and macrocytosis was documented in one case. Another patient showed slight coagulation abnormality (raised international normalized ratio of prothrombin time). Almost all the participants presented with normal values of iron metabolism markers, i.e. mean corpuscular volume and red blood cell distribution width (*Table 2*).

Autonomic system disturbances

The analysis of HRV at rest showed that some individuals with CED differed from the controls in terms of decreased TP, LF and HF, and/or increased LF/HF ratio. Therefore, we stratified the patients with CED according to LF/HF ratio, a spectral domain HRV parameter reflecting the interactions of both types of autonomic modulation. We identified the subjects with LF/HF ratio <0.6, corresponding to the evident parasympathetic predominance, and those with LF/HF ratio >1.5, i.e. with the evident sympathetic predominance. The cut-off values of LF/HF ratio were defined as the mean LF/HF ratio of the controls ± 1 S.D. (19).

A total of 5 (20%) CED patients presented with the parasympathetic predominance; another 9 (36%) subjects showed the sympathetic predominance, and 11 (44%) did not show alterations the in sympathetic-vagal balance.

Comparison of heart rate variability (HRV) at rest and in response to parasympathetic stimulation

The resting HRV parameters of the CED patients, LF and HF, were lower than in the controls (ln LF 5.65 ± 1.51 vs. 6.96 ± 0.83, $P=0.0002$; ln HF 5.58 ± 1.65 vs. 7.08 ± 1.11, $P=0.0002$); the only exception was normalized LF (LFnu), higher in the CED group. The abovementioned differences corresponded to disturbances of the parasympathetic-sympathetic balance, namely to sympathetic overactivity of the CED patients (*Fig. 2*).

The DB (parasympathetic stimulation) resulted in an increase in LFnu (51.76 ± 11.68 vs. 81.42 ± 13.91, $P=0.00002$) and LF/HF ratio (1.43 ± 0.84 vs. 15.98 ± 15.94, $P=0.0001$) of CED patients (*Fig. 3*).

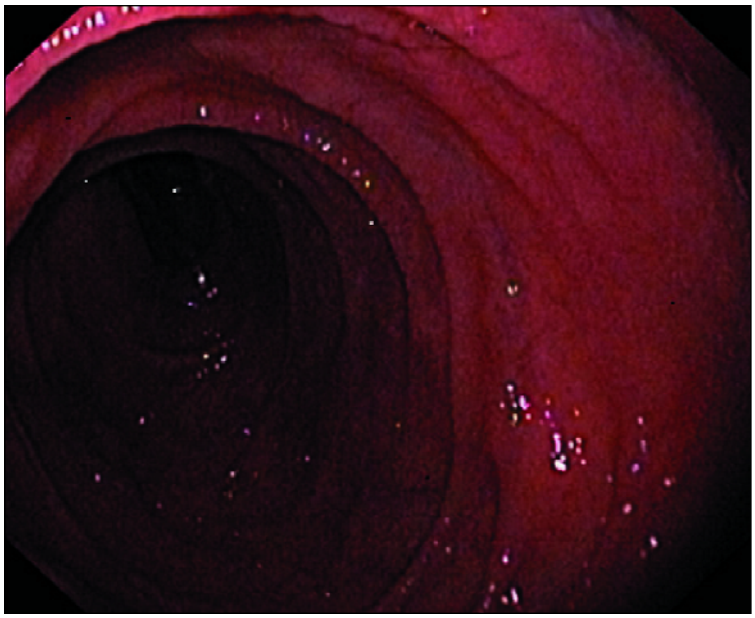

Fig. 1A. Celiac disease endoscopic view - reduced duodenal folds and fold scalloping in duodenum. (Source: Department of Gastroenterology, Hepatology, and Infectious Diseases Jagiellonian University, Medical College, Cracow, Poland).

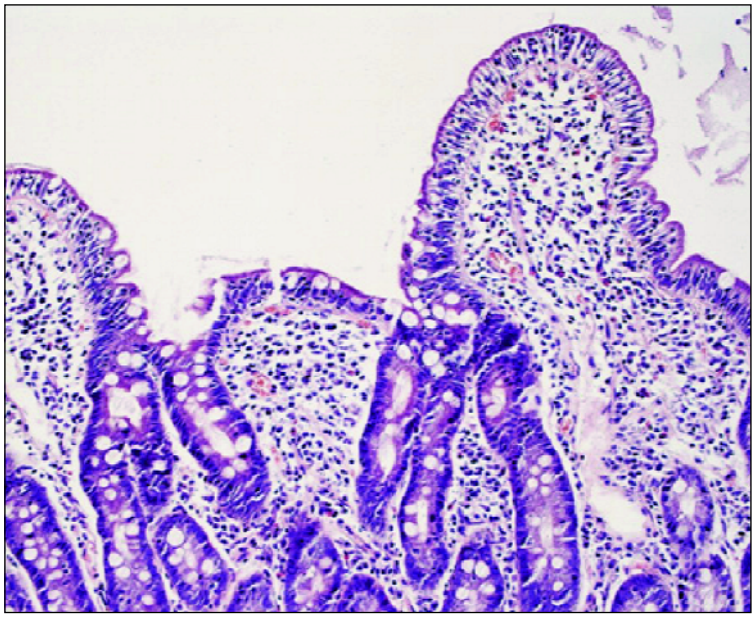

Fig. 1B. Celiac disease microscopic view - increased number of intraepithelial lymphocytes, crypt hyperplasia and subtotal villous atrophy (Marsh type 3b). Hematoxylin-eosin staining. (Source: Department of Pathomorphology, Jagiellonian University Medical College, Cracow, Poland).

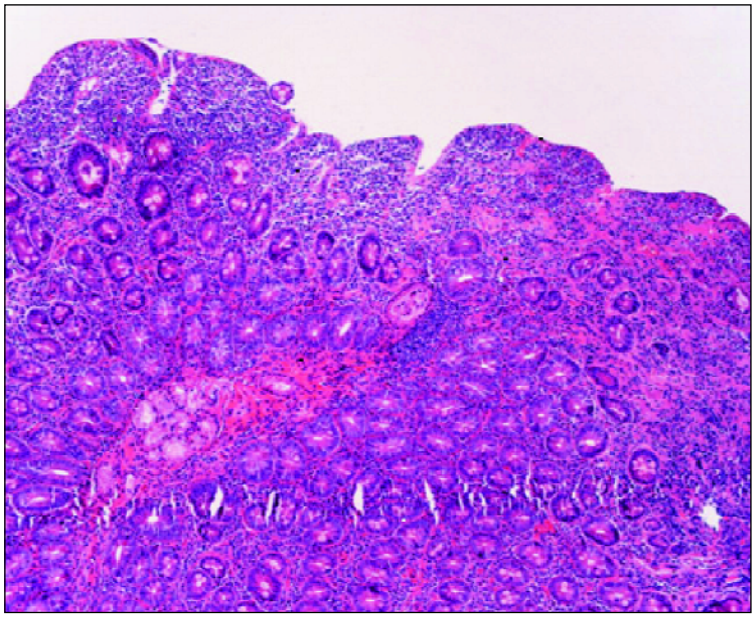

Fig. 1C. Celiac disease microscopic view - increased number of intraepithelial lymphocytes, crypt hyperplasia and total villous atrophy (Marsh type 3c). Hematoxylin-eosin staining. (Source: Department of Pathomorphology, Jagiellonian University, Medical College, Cracow, Poland).

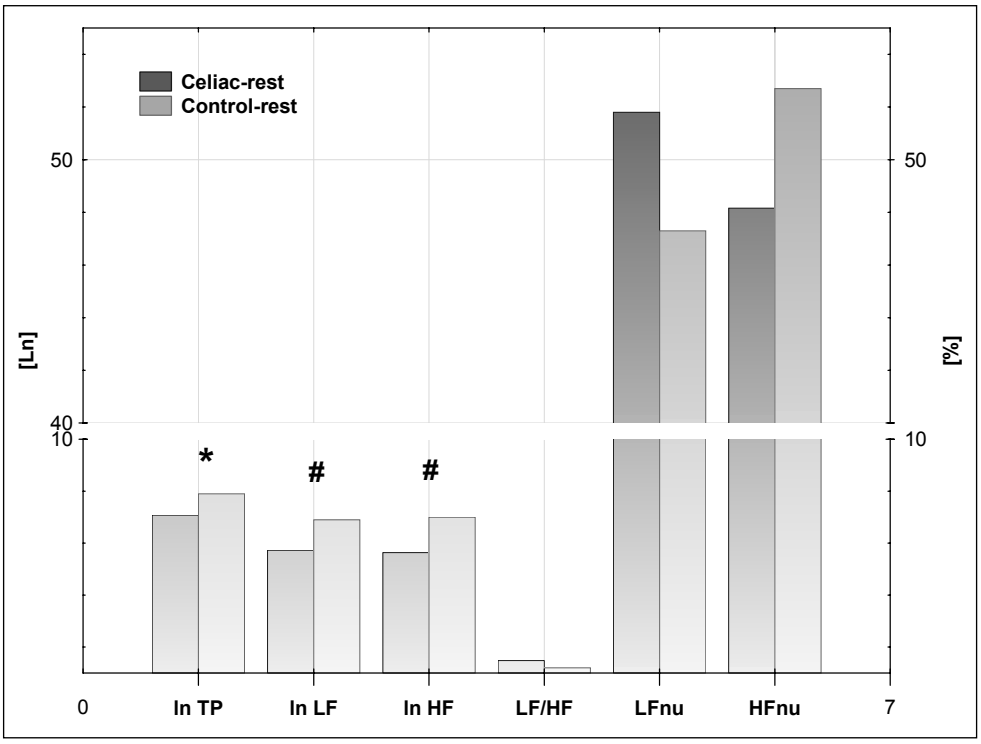

Fig. 2. Differences in resting values of spectral parameters of heart rate variability (HRV) of patients with celiac disease and the controls.* - significant difference between CED and CG; P=0.003; # - significant difference between CED and CG; P=0.0002.
TP - total power (ln), LF - low-frequency range (ln), HF - high-frequency range (ln), LF/HF - low-frequency to high-frequency ratio, LFnu - normalized low-frequency index (%), HFnu - normalized high-frequency index (%).

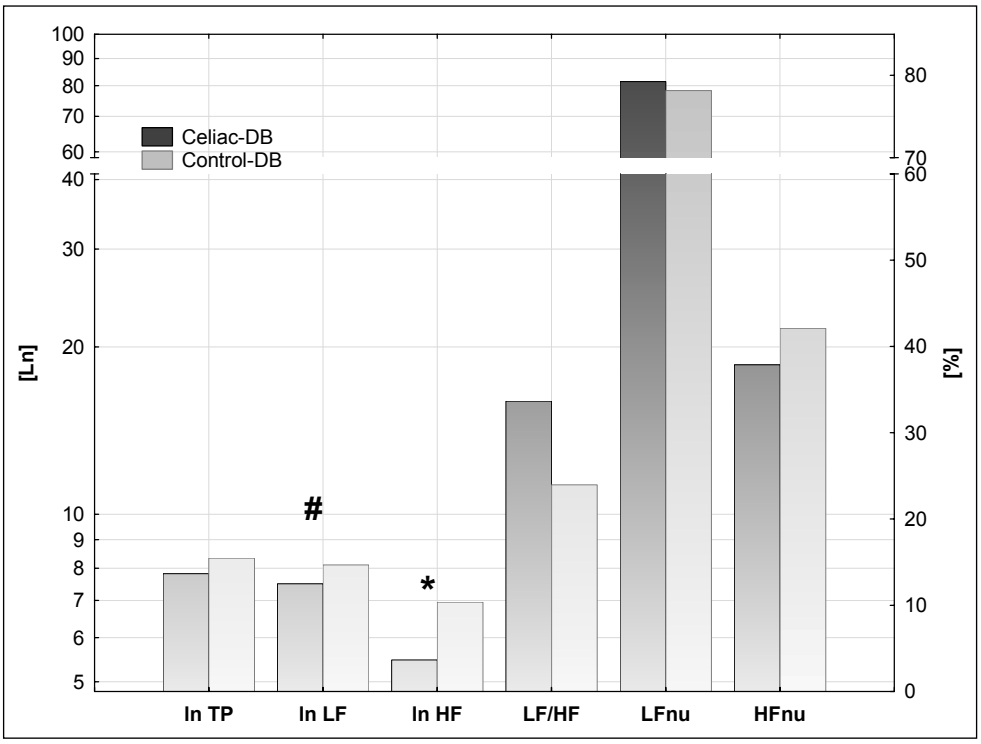

Fig. 3. Differences in values of spectral parameters of heart rate variability (HRV) of patients with celiac disease and the controls recorded during deep breathing (DB). * - significant difference between CED and CG; P=0.04; # - no significant difference between CED and CG; P=0.08.
TP - total power (ln), LF - low-frequency range (ln), HF - high-frequency range (ln), LF/HF - low-frequency to high-frequency ratio, LFnu - normalized low-frequency index (%), HFnu - normalized high-frequency index (%).

The direction of DB-induced changes in HRV of CED patients and the controls was generally similar. However, despite normal response to the DB test, the values of E/I, ΔI - E, DBD and RSA documented in patients with CED were significantly lower than in the controls (P<0.05; *Fig. 3*, *Table 3*).

Response of heart rate variability (HRV) to sympathetic stimulation

Exposure to the stressor (sound stimulation) was reflected by a significant increase in LFnu (51.76 ± 11.68 vs. 64.62 ± 8.75, P=0.000003) and LF/HF ratio (1.43 ± 0.84 vs. 2.21 ± 0.95, p=0.000015), and a significant decrease in HFnu (48.23 ± 11.68 vs. 35.42 ± 8.74, P=0.000004) of CED patients (*Fig. 4*). Although the effects of the exposure in CED patients and the controls were similar (*Fig. 5*), the former group showed significantly lower relative increase in LFnu (differences between rest and stress response 12.83% vs. 27.64%). Thus, compared to the controls, patients with CED showed blunted sympathetic response to the stressor in form of sound stimulation, all HRV parameters were lower in CED patients in comparison to the control in response to the stress (*Table 4*).

Table 3. Parameters of deep breathing test response in patients with celiac disease and in the controls.

Parameters		CED	CG	P value
DB test	E/I	1.22 ± 0.16	1.35 ± 0.15	0.0004*
	ΔI – E (beat/min)	13.92 ± 9.41	19.86 ± 6.72	0.0009*
	DBD (ms)	172.25 ± 111.67	272.30 ± 118.83	0.002*
	RSA	0.19 ± 0.12	0.29 ± 0.10	0.002*

CED - celiac disease, CG - control group, DB test - deep breathing test; * - significant difference between CD and CG, E/I ratio - mean ratio of the longest RR interval during expiration to the shortest RR interval during inspiration counted from 6 consecutive cycles, ΔI–E - difference between maximum heart rate during inspiration and minimum heart rate during expiration, DBD - deep breath difference, RSA - respiratory arrhythmia index. Data presented as arithmetic means ± S.D.

Table 4. Parameters of HRV in patients with celiac disease and in the controls in response to the stress.

Parameters HRV	CED	CG	P value
LFnu (%)	64.62 ± 8.75	74.06 ± 11.65	0.0016
HFnu (%)	35.42 ± 8.75	26.02 ± 11.63	0.0016
ln LF	5.88 ± 1.04	7.20 ± 0.91	0.000007
ln HF	5.46 ± 1.20	6.96 ± 1.08	0.00001
ln PSD	7.10 ± 1.19	8.06 ± 0.80	0.0008
LF/HF	2.21 ± 0.95	3.27 ± 1.12	0.0004

CED - celiac disease, CG - control group, TP - total power (ln), LF - low-frequency range (ln), HF - high-frequency range (ln), LF/HF - low-frequency to high-frequency ratio, LFnu - normalized low-frequency index (%), HFnu - normalized high-frequency index (%).

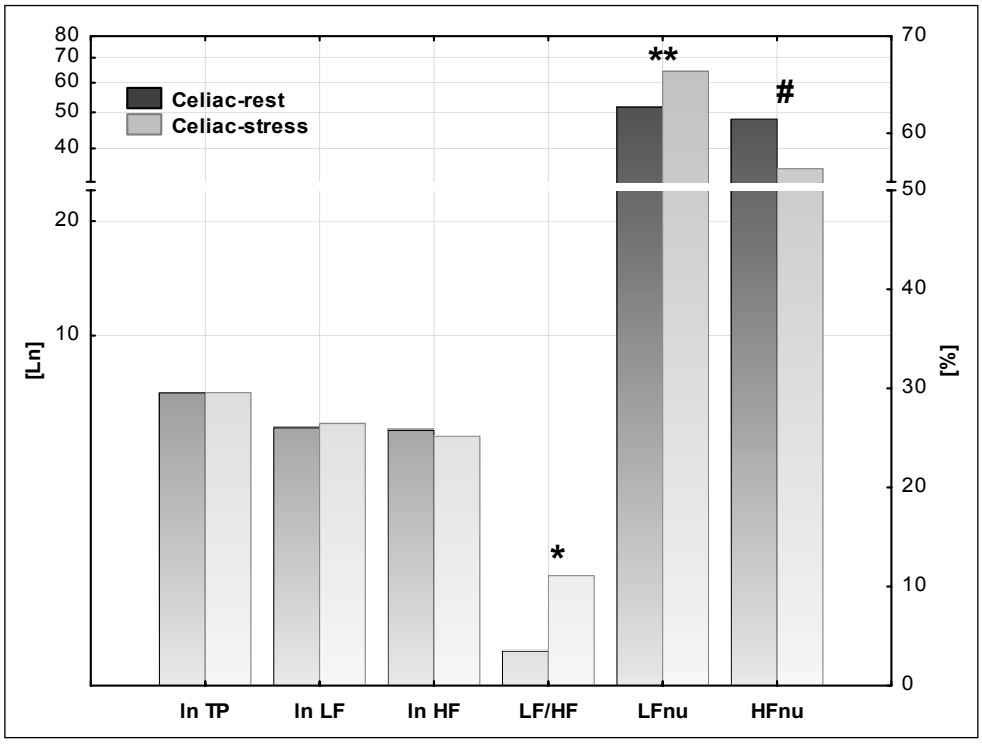

Fig. 4. Differences in values of spectral parameters of heart rate variability (HRV) of patients with celiac disease recorded at rest and following acoustic stimulation. * - significant difference between rest and stress; P=0.000015; ** - significant difference between rest and stress; P=0.000003; # - significant difference between rest and stress; P=0.000004.
TP - total power (ln), LF - low-frequency range (ln), HF - high-frequency range (ln), LF/HF - low-frequency to high-frequency ratio, LFnu - normalized low-frequency index (%), HFnu - normalized high-frequency index (%).

DISCUSSION

This study was undertaken to evaluate the pathophysiological role of changes in ANS activity in patients with CED. We analyzed HRV as a measure of ANS dysfunction at rest, after parasympathetic stimulation and following exposure to sympathetic stressor. In line with the previously presented hypotheses, we showed that the resting spectral HRV parameters of CED patients were lower than in the controls. Moreover, the CED patients showed blunted responses to parasympathetic stimulation during deep breathing and exposure to sympathetic stressor. The signs of ANS dysfunction were documented in 56% of our patients; 20% of the subjects presented the parasympathetic predominance, and 36% showed a shift towards the sympathetic predominance.

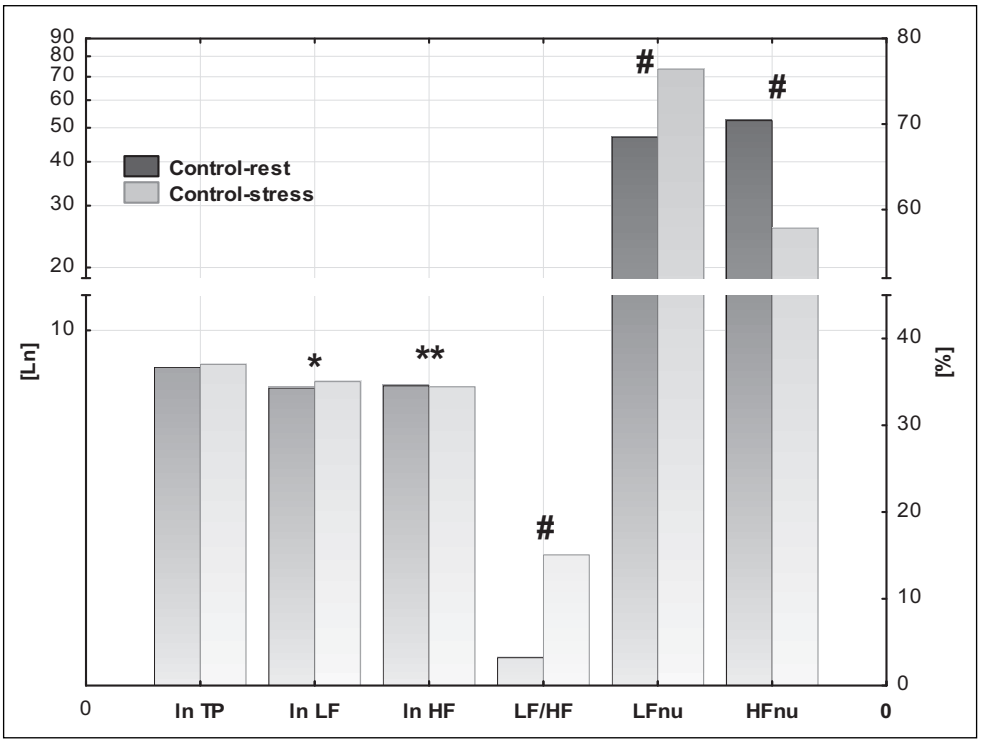

Fig. 5. Differences in values of spectral parameters of heart rate variability (HRV) of the controls recorded at rest and following acoustic stimulation. * - significant difference between rest and stress; P=0.001; ** - significant difference between rest and stress; P=0.01; # - significant difference between rest and stress; P=0.000001.
TP - total power (ln), LF - low-frequency range (ln), HF - high-frequency range (ln), LF/HF - low-frequency to high-frequency ratio, LFnu - normalized low-frequency index (%), HFnu - normalized high-frequency index (%).

Previous studies of ANS activity in CED were limited to small groups of patients with this condition. Gibbons *et al*. (8) analyzed ANS activity in only four CED patients presenting with the autonomic dysfunction of unknown etiology. The patients were referred for ANS testing due to body position-related nausea, lightheadedness and presyncopal or syncopal history (8). The ANS testing included determination of expiratory to inspiratory HRV, tilt test and Valsalva maneuver with heart rate and blood pressure analysis (8). Three out of four studied patients presented abnormal sympathetic and parasympathetic activity during heart rate and blood pressure responses to Valsalva maneuver and tilt testing. Orthostatic hypotension was detected in two of the patients, and the other two presented with postural tachycardia (8). Our findings are partially consistent with the above mentioned data. The resting HRV parameters of our CED patients were lower and normalized LF higher than in the controls. These changes corresponded to the disturbances of parasympathetic-sympathetic balance, namely to the sympathetic overdrive. Partial discrepancies between our findings and the results published by Gibbons *et al*. (8) may result from a different number of analyzed patients and the fact that the latter authors used neurological symptom-based inclusion criteria.

Usai *et al*. (6) used standardized cardiovascular reflexes, i.e. HRV and response of systolic and diastolic blood pressure to different stimuli: Valsalva maneuver, handgrip and DB, rather than spectral analysis of HRV, to detect autonomic neuropathies in CED patients. A total of 19% (5/27) of their CED patients presented with autonomic neuropathy and 44% (12/27) showed different degree of autonomic dysfunction. Moreover, they found up to 20% of CED patients with asymptomatic dysautonomia (6). However, the study included a small number of subjects, and thus likely underestimated the true prevalence of dysautonomia among CED patients (6). The latter statement seems to be supported by the results the hereby reported study, as we identified as many as 56% of CED patients with disturbed autonomic balance.

Giorgetti *et al*. (5) studied the prevalence of autonomic neuropathies in a group of eight celiac patients; the authors analyzed cardiovascular response (HRV, systolic and diastolic blood pressure) to several stimuli, including lying-to-standing test, Valsalva maneuver, deep breathing and sustained handgrip. The study revealed a tendency to lower systolic-diastolic blood pressure response in celiac patients. This finding was further confirmed by spectral analysis of HRV, in which the power of LF was reduced at rest, but increased during passive orthostatic testing (sympathetic response). The same authors reported a relative prevalence of the parasympathetic component in the ANS function of CED patients, but this difference did not prove to be significant when compared to the controls (5). In contrast, our CED patients presented with lower values of spectral HRV parameters (LF, HF), both at rest and during deep breathing. Furthermore, these patients showed an increase in the resting value of normalized LF. All these changes point to disturbances of sympathetic-parasympathetic balance in form of the sympathetic predominance. Therefore, our findings are consistent with the data published by Barbato *et al*. (9). These authors showed that also children with celiac disease may present an imbalance of the neurovegetative system with a prevailing sympathetic tone persisting after 24 months on gluten-free diet, despite the resolution of local and systemic signs of dysautonomia.

The response of our CED patients to deep breathing was significantly lower than in the control group. Contrary to Giorgetti *et al*. (5) and Usai *et al*. (6), we did not observe changes in response to DB. The discrepancies may reflect different number of tested patients: 25 in our study vs. 8 in Giorgetti *et al*.'s and 17 in Usai *et al*.'s studies (5, 6). Our findings point to the presence of high sympathetic drive and resultant decrease in parasympathetic activity of CED patients. These phenomena were also reflected by the lower response of CED patients to acoustic stress; probably the blunted transduction of the sympathetic impulse resulted from a down regulation of adrenergic receptors being a consequence of prolonged sympathetic stimulation (20). To the best of our knowledge, our study is the first one in which the ANS activity of CED patients was evaluated on the basis of a stress test. It is well known that acute symptoms of disease in patients with CED may

be sometimes triggered by severe emotional stress (22). Exposure to stress results in alterations of the brain-gut interactions ('brain-gut axis') and might lead to disturbances of neuromodulation (22-24). The stress augments colonic injury and promotes intestinal expression of several proinflammatory mediators which affect 'brain-gut axis' (24). Also an impact on effector cells of this axis (25) leading to dysregulation of gastrointestinal motility and visceral hypersensitivity as observed e.g. in irritable bowel syndrome (IBS) (23). Exposure to stress eventually is leading to an array of gastrointestinal disorders, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and other functional gastrointestinal conditions, food antigen-related adverse responses, peptic ulcers and gastroesophageal reflux disease (GERD) (22-24). The major effects of stress on gut physiology include: 1) alterations in gastrointestinal motility, 2) increase in visceral perception, 3) changes in gastrointestinal secretion, 4) increase in intestinal permeability, 5) decreased regenerative capacity of gastrointestinal mucosa and reduced mucosal blood flow, and 6) negative influence on intestinal microorganisms (22, 25).

The functional impairment of ANS in our CED patients was reflected by incorrect HRV response at rest, during deep breathing and following stress stimulation. Pathogenic factors involved in autonomic dysfunction observed in the course of CED remain unknown. The dysfunction of ANS may be related to various mechanisms involved in CED pathogenesis, such as the autoimmune damage or metabolic derangements, clinical or subclinical malabsorption of microelements and vitamins (folic acid, vitamin E, cobalamin), gluten toxicity or immunological reactions (presence of both neuron-specific and non-specific antibodies and cross reactions with neuronal compounds) (7, 14, 15). We speculated that hypersensitivity to ingested gluten and resultant small bowel inflammation lead to changes in visceral perception, inducing local or central sensitization and eventually affecting the brain-gut axis. These disturbances could alter ANS activity, which was manifested by abnormal sympathetic-parasympathetic balance at rest and during response to stimulation.

An assessment of the influence of CED on visceral perception in the gut could be vital for better understanding of the mechanisms of ANS changes and the involvement of the enteric nervous system in patients with CED.

We concluded that celiac disease causes disturbances of the autonomic activity. As a result, CED patients demonstrate diminished response to sympathetic and parasympathetic stimulation. This can result from involvement of many pathophysiological mechanisms, such as intestinal inflammation, visceral sensitivity and local or central sensitization. The prevalence of the autonomic dysfunction seems to be underestimated due to multiple, still unexplained, pathways in CED pathogenesis. The pathomechanisms of neural dysfunction observed in CED patients will not be understood without the knowledge of its prevalence and data on resultant metabolic and receptor changes.

The prevalence of autonomic neuropathy among patients with celiac disease constitutes a new challenge for both pathologists and clinicians, but points to potential use of the autonomic system therapy in some cases of CED.

Author contributions: M. Przybylska-Felus, A. Furgala, M. Mazur, and A. Widera performed the majority of experiments; M. Przybylska-Felus, A. Furgala, M. Zwolinska-Wcislo and P. Thor designed the study and wrote the manuscript; M. Zwolinska-Wcislo, T. Mach, P. Thor were involved in editing the manuscript; A. Furgala performed statistical analysis.

Acknowledgements: The study was supported by the grant number K/ZDS/002963 (specific subsidy for holding the research capacity of the Ministry of Science and Higher Education).

Conflict of interests: None declared.

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Received: May , 2014
Accepted: October 27, 2014

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