Assessment of autonomic function in untreated adult coeliac disease

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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 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 7 females, 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 ($P = \text{n.s.}$). 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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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 transglaminase 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 U/A/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 transglaminase; H2-BT: Hydrogen2-breath test.

### 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       | Aphthous 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.
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 a significant, reduction of the power LF according to a relative prevalence of parasympathetic 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, similar to that described in diabetic subjects. Pathogenetic factors involved in autonomic dysfunction in coeliac disease were unknown, and autoimmune damage or metabolic derangement have been hypothesized. 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. Recent studies of Luostarinen may in part confirm this hypothesis. They showed that axonal neuropathy in CD 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 dysfunction 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. 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. 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 coeliac patients 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.

### 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    |

### Table 5 Overall results of autonomic tests in coeliac patients

| Patient No. | Basal SBP | Basal DBP | Basal Ortho SBP | Basal Ortho 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 | Tilt Test | 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       | 35.5| 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    |
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