CELIAC DISEASE: 10- YEAR EXPERIENCE IN A ROMANIAN TERTIARY CENTER

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(Abstract) Aim: To evaluate the experience of a single coeliac center over a 10-year-observational period. Material and methods: Between January 2003 and December 2013 a total of 195 consecutive patients admitted with celiac disease were tested by multiple duodenal biopsies, anti-tissue transglutaminase and anti-gliadin antibodies, and baseline demographic, clinical, biological and immunological parameters. Results: Patients were divided into two major groups according to the clinical features and number of signs and symptoms present upon admission: gastrointestinal (131, 67.17%) and non-gastrointestinal (64, 32.8%). Anti-tissue transglutaminase and anti-gliadin antibodies showed seropositivity in 109/158. Histological samples were available in 152 cases, according to Marsh-Oberhuber classification 11.18% being type 0, 17.76%, type I–II, and 71.05% type III. Correlations between anti-tissue transglutaminase antibody titers and Marsh-Oberhuber classification were found to be statistically significant. Body mass index was available in 96 cases. We found that severe atrophy was predominant in patients with a BMI<18 kg/m². Conclusions: Celiac disease has an increasing prevalence and can be diagnosed at any age. Histology samples were indicative of different stages of villous atrophy. The disease prevalence is significantly higher among women. There was no statistically significant correlation between Marsh classification and BMI values. Keywords: CELIAC DISEASE, ANTI-TISSUE TRASGLUTAMINASE ANTIBODIES, ANTI-GLIADIN ANTIBODIES, MARSH–OBERHUBER CLASSIFICATION.

Celiac disease (CD) is a chronic multisystemic immune-mediated entero-pathy precipitated by exposure to dietary gluten in genetically predisposed individuals (1).

Until the 1970’s, the estimated global prevalence of celiac disease in the general population was just 0.03% (2). The risk for the development of celiac disease appears to increase as one lives longer. Celiac disease is being increasingly recognized in the elderly (3); 2.5 % of the elderly in Finland have celiac disease compared to 1 % in children (4, 5). It is unlikely that genes have changed, and there is evidence that gluten exposure has not either (6). In clinical and pathological terms, our understanding of the disease has considerably improved in recent decades, thus making an accurate diagnosis possible. Despite the huge interest for CD for both the general population, gastroenterologists and general practitioners according to current
knowledge there is still a lack of celiac patients cohort trials. In the past 5 years the size of CD patient population in our centre has been growing rapidly with a huge prevalence of CD among atypical nonspecific presentation and first degree relatives. We performed a retrospective review of the medical records of all patients diagnosed with CD and followed up at our hospital in the past 10 years in order to see if the trend is similar to that reported in the literature (7-10).

MATERIAL AND METHODS
The data for this retrospective cohort study were taken from a database of CD patients assessed at a Iasi town tertiary referral center between January 2003 to December 2013. The study is part of a single-center research aiming to investigate the true prevalence of celiac disease. We collected data from 147 female and 48 male patients (75.3% vs. 24.7%, respectively), with a mean age of 33 years, range 18 - 68 years. The yearly distribution of patients enrolled in this study is shown in figure 1.

The graph shows an increasing incidence of celiac disease due to increasing awareness and knowledge of pathophysiology, wide spectrum of clinical presentation, disease progression, and pathological mucosal intestinal features, which range from early and mild clinical forms of disease to severe villous atrophy.

Patients with serology (anti-gliadin or anti-transglutaminase) and histology (DII, DIII, bulb) performed within 3 to 6 months of each other were included in the study.

Patients were divided into two major groups categorized by their clinical features according to the number of signs and symptoms present upon admission: gastrointestinal (GI): non-specific abdominal pain, dyspepsia, bloating, flatulence, heartburn, chronic diarrhea, unintentional weight loss; and non-GI: iron deficiency anemia, dermatitis herpetiformis, osteoporosis, elevated liver enzymes, chronic fatigue, joint pain, headache, infertility, ataxia, epilepsy, aphthous stomatitis.

Patient consent was obtained before further examinations including quadrant biopsy specimens taken from the bulb, second or third part of the duodenum. Duodenal histology samples were taken in 152 (77.9%) cases. The mucosal specimens were
graded independently according to Marsh-Oberhuber classification as follows: type 0 - normal villi, type I-II - normal villi but intraepithelial lymphocytosis without (I) or with (II) hyperplastic crypts, type III a-c - varying degrees of villous atrophy with hyperplastic crypt (I). Immunohistochimical studies were performed and CD3+IELs were counted with a 100 x flat field light microscope objective. The histological evaluation was performed in the Department of Pathology of the hospital.

Serological results were based on measuring tissue transglutaminase antibody (anti-TTG) IgA and IgG (normal range: 0–30 U/ml) and anti-gliadin (anti-gl) antibodies (normal range: 0-12U/ml). The IgG antibody tests were applied for cases of selective IgA-deficiency. Baseline serology data of 158 patients were available.

Positive diagnosis was made using a combination of findings from the medical history, physical examination, serology, and upper endoscopy with histological analysis of multiple biopsies of the duodenum. A positive CD-specific serology in patients with villous atrophy confirmed the diagnosis of celiac disease.

Data were analyzed with the SPSS Software for Windows Version 17.0 (SPSS Inc., Chicago, Illinois). Quantitative data were expressed as the number of subjects and percentages, or as medians and ranges. When appropriate, the Pearson correlation coefficients were used to assess correlations between different variables. A p-value <0.05 was considered statistically significant.

RESULTS
Celiac disease was found in 131 (67.17%) patients in the GI group, 99 (75.57%) females. The most frequent complaint was upper abdominal pain, loose stools accompanied by bloating and abdominal discomfort irrespective of bowel movement. In the non-GI group composed of 64 patients (39: 60.9% females), most of the patients (47: 24.10%) were referred to our clinic for investigations unrelated at first glance to digestive disease: chronic fatigue, joint pain, headache and low iron levels which failed to return to normal after iron supplementation.

Most of the patients had at least one prior admission and at least one other medical prescription. CD was diagnosed in 84 (64.12%) patients in the GI group, and 29 (45.31%) in the non-GI group.

There were 4 patients diagnosed with dermatitis herpetiformis (biopsy-proven) none having any digestive complaint (fig. 2).

Body mass index was available in 96 cases. We found that severe atrophy was predominant in patients with a BMI<18 kg/m², and Marsh I, II were common in patients with normal BMI, but there was no statistically significant correlation between Marsh type and BMI values (p = 0.470).

**The clinical utility of serology testing:** Serum IgA class anti-TTG and anti-gl were measured in 145 (74.3%) patients. Values greater than 30U/L (anti-TTG) and 12 U/L (anti-gl) were considered positive. Anti-endomysial (EmA) test results were available in a few cases thus its utility cannot be commented upon.

All patients were screened for IgA deficiency. In case of deficiency the corresponding antibodies were measured in immunoglobulin G (IgG) class.

Nine patients had selective IgA deficiency; IgG-anti-tissue transglutaminase antibody tests were performed.

Seventy-eight out of 145 patients had anti-TTG, 5 patients had only anti-gl anti-
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bodies and 52 patients both anti-gl and anti-TTG. Seropositivity was detected in 109/145 (75%) of cases.

There was a significant association between serum TTG level and clinical presentation, low levels being more common in the screen rather than symptom-detected subjects (fig. 3).

### TABLE I
Demographic data on the study participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients, no=195</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, %</td>
<td>147 (75.3%)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>33 (18-68)</td>
</tr>
<tr>
<td><strong>Main reason for disease suspicion</strong></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal symptoms¹, %</td>
<td>131 (67.17%)</td>
</tr>
<tr>
<td>Iron deficiency anemia/low iron levels %</td>
<td>47 (24.10%)</td>
</tr>
<tr>
<td>Extra-intestinal symptoms², %</td>
<td>64 (32.82)</td>
</tr>
<tr>
<td>Family history of CD, %</td>
<td>14 (7.17%)</td>
</tr>
<tr>
<td>IgA deficiency, %</td>
<td>9 (6.2%)</td>
</tr>
<tr>
<td>Autoimmune disease, %</td>
<td>7 (3.5%)</td>
</tr>
</tbody>
</table>

¹ abdominal pain, dyspepsia, bloating, flatulence, heart burn, chronic diarrhea, unintentional weight loss
² iron deficiency anemia, dermatitis herpetiformis, osteoporosis, elevated liver enzymes, chronic fatigue, joint pain, headache, infertility, ataxia, epilepsy, aphthous stomatitis.

**Fig. 2.** Flow chart representing the features of celiac disease in our cohort

**Fig. 3.** Serum transglutaminase antibody levels according to clinical presentation
Duodenal mucosal histology: Multiple biopsies were taken from the duodenum (DII, DIII) and histological samples were available in 152 (77.9%) patients.

Using the Marsh-Oberhuber classification we found: Marsh 0 in 17 patients, Marsh I-II in 27 patients, Marsh 3a in 35 patients, Marsh 3b in 23 patients, and Marsh 3c in 50 patients. Small bowel mucosal villous atrophy and crypt hyperplasia (Marsh III) were found in 75% of the TG positive subjects. All patients with dermatitis herpetiformis had severe villous atrophy and elevated antibody titers.

Associations between serological testing and mucosal damage: Serological and histological results were available in 132 (67.69%) patients with CD. Ninety-nine (75%) of these patients were serologically and histologically positive for CD. Negative serology and positive histological results were present in 23 patients (17%), and positive serologies with negative histology were found in 10 patients (7%).

Correlation between histological lesions and anti-TG titer was examined in 111 cases. There was a significant association between high levels of antibody and the severity of small bowel mucosal involvement (fig. 4).

**DISCUSSION**

In this study we reported data using a multiparametric approach to describe the dynamics of CD over a ten-year period. We analyzed the clinical, serological, histological, and in particular cases the laboratory findings, family history and associated disease of the 195 celiac patients hospitalized in our department between January 2003 and December 2013. Female predominance was obvious in our cohort (75.3% vs. 24.7%), and this prevalence was confirmed by other clinical studies available in literature (2). The mean age of 33 years was indicative of a disease which can be identified in all age groups and not only in children as previously considered.

Serology testing showed a majority of seropositive subjects, but it is important to add that not all the patients met the serology criteria thus stating the need to perform a further duodenal biopsy. In our cohort, 23 patients proved seronegative but with a positive histology. Relying solely on antibody titers to make a positive diagnosis would leave a significant percentage of
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patients deprived by a correct diagnosis. Elderly celiac patients were seronegative more often than younger celiac patients. One reason for the low antibody titers in older patients might be the sequestration of antibodies to the intestinal mucosa over time (4).

The vast majority of patients (75%) proved to have severe histological alterations (Marsh III) and the severity of mucosal damage correlated well with antibodies levels. Previous studies have suggested the presence of such correlation by showing parallel alleviation of histologic damage and serology findings (7).

Whilst current literature suggests a discriminatory role for high risk group, our data suggests that there is no single clinical feature of itself a reliable risk stratifies (8). The study had some limitations inevitably, consisting in the uncontrolled, retrospective designed, and in the fact that in some cases, the crucial histological parameters often lacked making the exact definition of CD by Marsh-Oberhuber classification impossible. A major strength in this study is the large number of patients representative of those in everyday clinical practice.

CONCLUSIONS

In our study, we found that celiac disease can be diagnosed at any age. The percentage of females was significantly higher. Histology diagnosis usually showed different stages of villous atrophy. Active screening for CD and its complications and associated diseases is increasing used. Celiac disease must be considered in the differential diagnosis of all patients with malabsorption symptoms despite older age in order to prevent disease complications.

REFERENCES