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ORIGINAL PAPERS

CLINICAL, BIOLOGICAL AND EPIDEMIOLOGICAL ASPECTS OF INFLAMMATORY BOWEL DISEASES IN NORTH-EAST ROMANIA

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CLINICAL, BIOLOGICAL AND EPIDEMIOLOGICAL ASPECTS OF INFLAMMATORY BOWEL DISEASES IN NORTH-EAST ROMANIA (Abstract): Aim: Inflammatory bowel diseases (IBD) are chronic conditions of unknown etiology with increasing incidence in South-East Europe. The epidemiological characteristics, clinical, biological and endoscopic profiles are very different worldwide, with little data existing from Moldova region. This study aims to characterize IBD in North-East Romania from the mentioned points of view. Material and methods: All patients with Crohn's disease or ulcerative colitis (UC) admitted to a tertiary hospital during a three year interval were retrospectively analyzed in terms of epidemiological characteristics. All IBD patients hospitalized during 2010 were complexly analyzed by noting the type and form of disease, the biological picture, the clinical and endoscopic scores. Results: UC represents 77% of all cases (one of the highest values of the recent studies). Age at onset is higher in the studied region, with the average over 40 years. In UC the forms of severity and extension are uniformly distributed, but in Crohn's disease there is a predominance of colonic forms and the number of complicated cases is high - over 50%. The parameters with the best correlation with endoscopic scores were the clinical Mayo score for UC, serum C-reactive protein and fibrinogen. Conclusions: There is a definite predominance of UC in North-East Romania, but Crohn's disease tends to present an increased number of complications. The age of onset of the two diseases is high. There is a good correlation between the clinical and biological scores with endoscopic activity, but without this assessment inflammation may be underestimated. Systematic exploration of the small bowel may increase detection of ileal manifestations. Keywords: INFLAMMATORY BOWEL DISEASES, ULCERATIVE COLITIS, CROHN’S DISEASE, EPIDEMIOLOGY, MONTREAL CLASSIFICATION.

Inflammatory bowel diseases (IBD) are chronic conditions of uncertain cause comprised of two distinct entities- ulcerative colitis (UC) and Crohn's disease (CD). If UC only affects the colon and rectum by continuous inflammation limited to the mucosa, CD may involve any segment of the digestive tract (most commonly the ileum and the colon), inflammation being discontinuous and extended in depth (1). With an incidence of tens to hundreds per 10⁵ people and a prevalence of a few hun-
IBDs, IBD represent an important cause of morbidity and impaired quality of life especially in young and middle-aged patients, by the chronic relapsing nature and lack of curative treatment (2). There is important variation worldwide in the incidence, prevalence, clinical and evolving features according to geographic region, ethnicity and race (3). It is estimated that the incidence in South-Eastern Europe is slightly increasing, especially for CD, compared to Northern and Western Europe, where it is stabilized (4,5).

The few published studies for Romania have shown a lower incidence compared to the neighboring regions, a higher mean age and the prevalence of mild to moderate forms of disease. However, the data are slightly contradictory and there are methodological difficulties (6, 7).

This study aims to evaluate from epidemiological, clinical, biological and endoscopic perspective all cases of inflammatory bowel disease submitted to a tertiary medical center within three years.

**MATERIAL AND METHODS**

This study represents a retrospective analysis of all cases diagnosed with inflammatory bowel disease hospitalized in the Center of Gastroenterology and Hepatology from the "St. Spiridon" University Hospital between 1st January 2008 and 31st December 2010. Epidemiological data as disease type, number of cases, age and gender of patients were recorded. Cases classified as indeterminate colitis were interpreted as UC or CD considering the dominant clinical, endoscopic and histological characteristics. A sample composed of all patients hospitalized during the year 2010 was complexly analyzed by studying data recorded in the medical observation documents and analyzing the colonoscopy registers and video recordings, noting the following parameters: type of disease and its duration, main symptoms, personal and family history (including possible extra-intestinal manifestations), classical inflammation tests values (ESR, fibrinogen, C-reactive protein - CRP), the extent and severity of UC and Crohn’s disease location and behavior according to the Montreal criteria (8).

We also calculated the Mayo Clinical score (for UC) (9) and Harvey-Bradshaw index (for Crohn’s disease) (10) and endoscopic Mayo score and respectively simple endoscopic score for Crohn’s disease (SES-CD) (11). Finally we assessed the degree of correlation of endoscopic scores with clinical scores and biological parameters of inflammation. Data analysis was made using Microsoft Excel and Minitab software.

**RESULTS**

The total number of patients (excluding multiple hospitalizations within one year) and the proportion of the two types of disease are illustrated below (fig. 1).

There is a clear predominance of UC, this represents 77% of all cases. Most affected age groups were 25-35 and 35-45 years, totaling 46.8% of all patients, the prevalence decreasing progressively with age. The mean age of patients was 45.7 ± 15 years, being lower for CD (44.09 ±14.9 years) than UC (46.02 ±15.1 years).

There were no statistically significant gender differences, with a slight predominance of CD in men (87 vs. 80) and UC in women (285 vs. 270), the total number being fairly equal (365 women and 375 men).

The number of patients diagnosed with IBD hospitalized more than one day in 2010, which was further taken into account
was 125.

In what regards the disease duration, as shown in the most hospitalized cases are newly diagnosed and those under 2 years from the onset, totaling 47.5% of all cases (fig. 2).

![Fig. 1. Number of patients by year and type of disease.](image1)

![Fig. 2. Duration of the disease at evaluation.](image2)

Calculating the age at diagnosis it can be noticed that the maximal incidence in the analyzed cohort was in the age group 35-45 years (35%), followed by age group 25-35 years (27%). The mean age at onset among people with CD was 37.7 ± 13 years and in those with UC 42.8 ± 14 years.

Family history of IBD was reported in only one case (1.19%), whereas colon cancer was found in first-degree relatives in a higher proportion than in the general population (5.95%). Most subjects are non-smokers (57%) or former smokers (20%), the proportion of active smokers being of 23%.

Ulcerative colitis is most commonly (in almost half of cases) presented as left side colitis inflammation up to the splenic flexure - 46.3%, followed by pancolitis (29.3%) and isolated rectal injury (24.4%). In Crohn's disease colonic involvement accounts for more than half of all cases, isolated ileal disease affecting just 14.3% of subjects. Almost 10% had lesions of the upper digestive tract and almost a quarter had perianal manifestations during evolution (fig. 3).

![Fig. 3. Crohn’s disease classification depending of localisation (%).](image3)
Most cases of Crohn's disease were non-stricturing and non-penetrating (42%), followed by stricturing and penetrating forms (29%); 16.1% are stricturing and 12.9% are penetrating forms.

Mayo clinical UC score shows a balanced distribution of the three forms of severity (37% score 0-3, 33% score 4-6 and 27% score over 7). The calculation of Harvey-Bradshaw index highlights the prevalence of mild and moderate disease forms as follows: 21.4% score<5, 17.8% score 5-7, 50% score 8-16 and only 10.7% score over 16.

The most common extraintestinal manifestations were axial arthritis (ankylosing spondylitis and seronegative spondylarthropathies) in 13.6% of patients, followed by cholestatic syndrome evidenced by increased alkaline phosphatase and ocular manifestations - uveitis, scleritis and episcleritis (fig. 4). Overall, 35.25% of patients had at least one extraintestinal manifestation. Aphthous stomatitis has not been evaluated.

Colonoscopic evaluation was performed in 72.8% of patients. Over half of the subjects had a UC Mayo score of 2 (52.38%) and another quarter score 3 (26.19%). The analysis of simple endoscopic score of Crohn's disease shows mild to moderate forms predominance, with less than 10% being severe endoscopic forms: 28.5% score<3, 23.8% score 4-10, 38.09% score 11-19 and 9.52% score>20.

The correlation expressed by Pearson coefficient (r) of endoscopic Mayo score and SES-CD index with clinical scores and biological parameters of inflammation and P value is presented below (tab. I).

![Fig. 4. Extraintestinal manifestations (%).](image)

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>The correlation coefficient $r$ of endoscopic Mayo score and SES-CD with various clinical and biological parameters and the corresponding $p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo endoscopic score</td>
<td>P</td>
</tr>
<tr>
<td>Clinical score</td>
<td>0,727851</td>
</tr>
<tr>
<td>WBC</td>
<td>0,522412</td>
</tr>
<tr>
<td>ESR</td>
<td>0,562575</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0,695638</td>
</tr>
<tr>
<td>CRP</td>
<td>0,711294</td>
</tr>
</tbody>
</table>
We can notice that Mayo clinical score is a good indicator of the colorectal inflammation (strong correlation) compared to HBI score of Crohn's disease where the correlation with endoscopic activity is moderate. In both diseases, the correlation of the parameters of inflammation with endoscopic scores revealed that CRP and fibrinogen were superior to white blood cells and ESR.

DISCUSSION

One first aspect that stands out in all the 3 years studied is the small proportion of patients with Crohn's disease compared to UC cases (about 23%). This can be considered a particular aspect of the NE region of Romania, the prevalence ratio of CD for the neighboring regions being at least 30% in most cases (4,12). A possible explanation may be that Crohn's disease is underdiagnosed, especially the forms located to the small bowel, given the technical and material difficulties of exploring this territory.

The age group distribution of our patients is similar to that reported for Europe, with the predominance of disease in young adults (up to 45 years). Most of the addressed cases are newly or recently diagnosed, probably because the optimal treatment for maintaining remission is reached after few years. Age of onset was higher among patients with UC, which is found in most epidemiological studies. Its average in the studied population is higher than in areas with a high incidence from northern Europe, being around 40 years (13). The second peak of incidence observed in older studies is not present in our cohort. The high age at onset may be a characteristic of the studied region.

Although there are no significant differences in prevalence according to patients' gender, we noticed a slight predominance of CD in men and UC in women, opposite to the trends from other regions (14).

Considering the limits of a retrospective study, we can conclude that extraintestinal manifestations are still in considerable proportion (about one third of the subjects) and in accordance with the literature (15). Osteoarticular manifestations are by far the most frequently encountered, and among them we mention the seronegative spondyloarthropathies and ankylosing spondylitis.

On a review of disease types, if for UC the relatively balanced distribution of the three forms with the predominance of left-side colitis is most often seen, in Crohn's disease we noticed an unusual predominance of colonic and ileo-colonic forms, the number of limited ileal forms being extremely small (14%). We believe that this may represent a feature of CD in this region, although insufficient exploration of the small bowel may contribute to the low proportion of pure ileal forms.

Even though the incidence and prevalence of CD are smaller than in neighboring regions (6), however the disease tends to be more aggressive, 48% of cases presenting an endoscopic score of moderate or severe injury, and the proportion of the stricturing and/or penetrating cases is more than a half (58%).

Another interesting aspect especially seen in UC by comparing the clinical and endoscopic scores is that although more than 70% of cases can be clinically classified as mild or moderate; in endoscopic examination 78% of subjects have Mayo endoscopic score of 2 or 3. Hence it can be concluded that UC is often undervalued when taking into account only the clinical picture, many less symptomatic patients
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presenting at least moderate inflammation of the colonic mucosa.

From the biological parameters correlated with intestinal inflammation, C-reactive protein is superior to ESR and white blood cells in the evaluation of inflammation. Serum fibrinogen had surprisingly similar correlation numbers to CRP and thus significantly better than the ESR and WBC. Therefore, this often neglected and abandoned parameter in assessing systemic inflammation remains extremely valuable, especially where CRP determination is not available.

CONCLUSIONS

The main epidemiological features of inflammatory bowel diseases in NE region of Romania are the clear predominance of UC compared to Crohn’s disease, older age at onset for both entities, higher tendency of CD to develop intestinal complications (stenosis, fistulas, perianal manifestations) and underestimation of intestinal inflammation by using only clinical and biological parameters. We propose a more careful and systematic exploration of the small bowel (videocapsule endoscopy, ileoscopy during colonoscopy, enteroscopy, CT, enterography) to diagnose Crohn’s disease in case of subtle symptoms and in those already diagnosed with colonic forms and also the evaluation whenever possible of inflammation by endoscopic examination with biopsy or at least by the new non-invasive markers (calprotectin, lactoferrin).

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REFERENCES

TREATMENT OF TB-HIV CO-INFECTION - A BIG CHALLENGE

Tuberculosis (TB) is a major public health problem worldwide. The association of TB with HIV infection induces a higher rate mortality caused by TB complications or by evolution towards AIDS. The treatment of patients TB-HIV co-infected is a big challenge. Even though the deferment in the initiation of antiretroviral treatment (ART) increased mortality, frequently the start of ART is delayed after completing TB therapy as a result of drug interactions between rifampicin and antiretroviral drugs, summation of side effects and low compliance to treatment with many drugs. By analyzing the several clinical trials, Naidoo and his collaborators showed that initiating ART earlier (within 2–4 weeks) after TB treatment initiation has induced reduction in mortality for the TB–HIV co-infected patients with advanced immunosuppression (CD4+ T-cell count <50 cells/μl). Mortality rate for the patients with baseline CD4+ T-cell counts of 50 cells/μl or higher was not influenced by the time of initiating ART in the course of TB treatment. The same analysis showed that an earlier ART initiation in immunosuppressed patients was associated with a higher risk for Immune Reconstitution Inflammatory Syndrome (IRIS). The same researchers showed that early ART initiation in the course of TB treatment for immunosuppressed patients will be based on compromise between increased survival and increased risk of IRIS (Naidoo K, Baxter C, Abdool Karim SS. When to start antiretroviral therapy during tuberculosis treatment? Curr Opin Infect Dis. 2013; 26: 35-42).