

CHARACTERISTICS OF EPIDEMIOLOGY AND DIAGNOSTICS OF PEDIATRIC INFLAMMATORY BOWEL DISEASE

Ph.D. thesis

Katalin Eszter Müller, M.D.

**Semmelweis University
Doctoral School of Clinical Medicine**



Supervisor: Gábor Veres, M.D., D.Sc.

Opponents: Katalin Müllner M.D., Ph.D..
Imre Szabó M.D. Ph.D.

Chairman of the Examination Committee:
Janina Kulka, M.D., Ph.D.

Members of the Examination Committee:
Miklós Tóth, M.D., Ph.D.
Béla Lestár, M.D., Ph.D.

Introduction

The inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract of unknown etiology. Regarding the etiology of UC and CD, publications indicate that both genetic and environmental factors are important in the pathogenesis of inflammatory bowel disease. The two types of inflammatory bowel disease are ulcerative colitis and Crohn's disease. The term "inflammatory bowel disease, type unclassified" (IBDU) is suggested for patients in whom there is evidence on clinical and endoscopic grounds for chronic inflammatory bowel disease affecting the colon, and no definitive histological or other evidence to favour either Crohn's disease or ulcerative colitis.

Recently, the incidence and prevalence of IBD have been increasing worldwide. Consequently, increasing number of patients with CD and UC account for substantial costs to the health care system and society. According to the latest report from the USA (University of Cincinnati), the mean yearly cost for paediatric CD was 10,176 USD, and for paediatric UC was 11,836 USD.

Epidemiological studies described that paediatric-onset IBD might present differently and might have a different natural history than adult-onset IBD. A family history of IBD is more often present in children. In contrast to adults, CD is twice as frequent as UC in children in most reports. Furthermore, male dominance was observed in paediatric CD, while in adult-onset CD female gender is the predominant. Isolated involvement of the terminal ileum is significantly less common in paediatric disease, while in children panenteric extent is the most typical. Finally, in adult series UC is predominantly confined to the rectum or left side of the colon, but in children the majority have pancolitis. However, epidemiological studies are heterogeneous; it is difficult to compare them due to different methodology (difference in diagnostic criteria, definition of location).

The lack of consistent data on the epidemiology, natural course of disease and therapeutic behaviour in children with IBD obviated the need for commonly agreed-on diagnostic criteria and work-up of new patients. In 2005, the ESPGHAN (European Society of Paediatric Gastroenterology, Hepatology and Nutrition) inflammatory bowel disease working group defined consensus-based criteria for the diagnosis of IBD in children (Porto Criteria). The published reports have raised several questions if pediatric-onset IBD is a distinct entity, whether age of onset dictates any difference in disease phenotype or outcome. Recently, a number of multicentre studies have been presented to answer these questions.

For the above mentioned reasons, the Hungarian Association of Paediatric Gastroenterology founded the Hungarian Paediatric IBD Registry (HUPIR) in 2007. Cooperation of all the 27 paediatric gastroenterology institutes where paediatric IBD patients are seen, has ensured the coverage of the whole country. The primary aim of this registry was to determine the incidence of paediatric IBD in Hungary, and the clinical characteristics of paediatric IBD, furthermore to evaluate the diagnostic practice.

Aims:

My aim was to determine the incidence of pediatric IBD between 2007-2011 in Hungary based on the database of HUPIR. Furthermore, the demographic and clinical characteristics of pediatric IBD were evaluated in Hungary. Finally, I have analysed the first data of the one-year follow-up. The most important questions were:

1. **Incidence of pediatric inflammatory bowel disease based on HUPIR (2007-2011)**
2. **Clinical characteristics of patients recorded in HUPIR**
 - 2.1. Phenotype of CD and UC patients according to **Paris Classification**
 - 2.2. Frequency of **extraintestinal manifestations**, and associations with clinical characteristics of pediatric inflammatory bowel disease
 - 2.3. **Frequency of granulomas** and associations with clinical characteristics of pediatric Crohn's disease
 - 2.4. **Disease activity indices** at diagnosis and its associations with clinical characteristics of IBD
 - 2.5. **Laboratory parameters** at diagnosis and their relationship with clinical characteristics of IBD
3. **Diagnostic work-up** of pediatric IBD patients in general practice and **adherence to Porto Criteria** in the first five years of HUPIR

4. **Diagnostic yield of esophagogastroduodenoscopy** in pediatric inflammatory bowel disease
5. First results of **one-year follow-up** of patients registered in HUPIR
 - 5.1. **Disease activity indices at one-year follow-up**
 - 5.2. **Medical therapy at diagnosis and at one-year follow-up**
 - 5.3. **First results** of one-year follow-up of patients registered in HUPIR : associations between initial activity indices, laboratory parameters and the therapy at one-year follow-up

Methods

The Hungarian Pediatric Gastroenterology Society initiated a prospective registry of pediatric inflammatory bowel disease (HUPIR, Hungarian Pediatric IBD Registry), that was launched on the 1st of January, 2007. Cooperation of all the 27 pediatric gastroenterology institutes where pediatric IBD patients are seen, has ensured the coverage of the whole country. The participating institutes include all the 4 academic (university) centres in Hungary, 17 tertiary hospitals, where pediatric gastroenterology is present, and 4 secondary hospitals with pediatric gastroenterologists, as well as 2 pediatric gastroenterology outpatient offices. Private pediatric gastroenterology offices with endoscopy are not available in Hungary. All the participants send their data voluntary without any compensation. The author of this thesis has been the coordinator of the registry from the beginning.

The diagnosis of IBD was established by the local pediatric gastroenterologist based on clinical signs, endoscopic, histological, laboratory and MRI/CT results. Exclusion criteria were: age at diagnosis older than 18 years, missing information on ileocolonoscopy and ileocolonic histology, and a diagnostic workup without endoscopic, histologic, and radiologic abnormalities.

Questionnaires are filled out by gastroenterologists who made the IBD diagnosis. Newly diagnosed IBD patients younger than 18 years are reported. Age, gender, weight, height, presenting symptoms, extraintestinal manifestations (EIM), familiarity (first-degree) and disease activity indices were recorded. Furthermore, characteristics of diagnostic procedures including endoscopy, radiology, histology, laboratory parameters. Surgical interventions, and initial therapy were documented. Physicians have to report the applied therapy, actual disease activity index, anthropometrical data as well as surgical interventions at one-year follow-up.

The questionnaires are collected via email or by post and original data are validated by Gabor Veres, a pediatric IBD specialist.

The age- and gender-specific demographical data for calculating incidence were obtained from the Hungarian Central Statistical Office. Location and phenotype of disease were based on the Paris classification criteria. Disease activity at baseline is determined using validated multi-item disease activity indices, PUCAI (Pediatric Ulcerative Colitis Activity Index) and PCDAI (pediatric Crohn's Disease Activity Index).

The study was approved by the National Ethical Committee. Data analysis was performed with Microsoft Excel and SPSS software. A $p < 0.05$ was considered as significant.

Results

1. Incidence of pediatric inflammatory bowel disease based on HUPIR (2007-2011)

A total of 713 children with IBD were diagnosed between January 1, 2007 and December 31, 2011 in Hungary. Fourhundred-fortysix CD cases, 219 UC patients were registered. Inflammatory bowel disease type unclassified (IBD-U) was diagnosed in 48 cases.

The mean incidence of IBD was $7.8/10^5$ between 2007-2011. The standardized incidence rate showed an increasing tendency (from $7/10^5$ to $8.6/10^5$). Incidence of CD was twice as high as incidence of UC ($4.8/10^5$ vs. $2.3/10^5$). A male predominance was observed in patients with CD older than 10 years, in contrast we found a slight female predominance in UC.

2. Clinical characteristics of patients recorded in HUPIR

2.1. Phenotype of CD and UC patients based on Paris Classification

Twohundred-fortyseven children with CD were classified. Most CD patients (n=197, 74.3%) belonged to the age-group A1b (between 10-17 years). Thirteen percent of the patients (33/247) showed L1 (involvement of terminal ileum and/or cecum) location. Isolated colonic disease (L2) was seen in 27.5% (n=68) of children with CD, and ileocolonic disease (L3) occurred in 58.7% (n=145) of CD patients.

Upper GI abnormality was found in 74 (29.9%) of all children with CD, and there was only one patient of 247 (0.4%) with isolated upper GI disease. Esophagogastroduodenal involvement (L4a) was present in 30.4% (n=56) of pediatric CD, while L4b (jejunal/proximal ileal) disease occurred in 10.1% (n=25) of children.

Most CD patients had inflammatory disease at diagnosis (B1+B1p 84.4%), while 12.1% CD patients had stricturing disease (B2), 2.3% had fistulizing disease (B3), and 1.2% belonged to B2/B3 phenotype. Frequency of perianal disease (abscess, fistula) was 14.5% (37/247).

Onehundred-twentyone cases with UC were classified according to Paris Classification. Fifty-seven percent of UC patients (69/121) had pancolitis, and only 5% (6/121) were diagnosed with ulcerative proctitis. Severe disease (S1: PUCAI higher than 65) occurred in 18.6% children (13/121) at diagnosis.

2.2. Frequency of extraintestinal manifestations, and associations with clinical characteristics of pediatric inflammatory bowel disease

EIMs (skin, hepatic, eye and joint manifestations) were present in 13.6% of IBD patients (97/713) at the time of the diagnosis. The frequency of EIM was 15.3% in CD (68/446), 11.4% in UC (25/219), and 8.3% IBD-U (4/48). Occurrence of EIM was not significantly different in UC and CD ($p=0.177$). The most common EIM in CD was joint involvement (37.5%, 36/96), meanwhile hepatic involvement was the most frequent in UC (37.5%, 12/32). Multiple EIM was observed in 1.8% of patients with EIM ($n=713$). Relationship between location and EIM were analysed. Terminal ileal involvement was frequent in CD patients with EIM than in CD patients without EIM (17.5% vs. 29.3%, $p=0.036$). EIMs in CD were associated with stricturing/penetrating disease ($p=0.009$). There were no associations between disease extent and EIMs in UC.

2.3. Frequency of granulomas, and associations with clinical characteristics of pediatric Crohn's disease

Three hundred and fifty-three children with Crohn's disease were registered between January 1st, 2007 and December 31st, 2010. The frequency of granuloma was 31.4% (111/353) at diagnosis. Multiple granulomas were described in half of the cases (52, 14.7%).

Granulomas were found in 81 patients (22.9%) in the lower gastrointestinal tract, and in 14 cases (4%) in the upper gastrointestinal tract. Presence of isolated granuloma in the upper gastrointestinal tract was 2.5%, and in the terminal ileum 4.8%.

In patients, who had biopsies from all 10 gastrointestinal segments, frequency of granuloma was 40% ($n=43$), while in the rest

of the cases (n=246), granuloma was described only in 27% (n=66) (p=0.048).

There was no difference in demographic and clinical characteristics between patients with granuloma and without granuloma. Need for immunomodulators, biological therapy and surgical intervention was similar in the two groups in the first year of diagnosis.

2.4. Disease activity indices at diagnosis and their associations with clinical characteristics of IBD

Disease activity indices and laboratory parameters were analyzed based on patients registered between January 1, 2008 and December 31, 2010. Initially, 48% (124/256) of CD patients had moderate to severe disease (PCDAI>30), and 67 of 120 UC patients had moderate to severe disease (PUCAI>35) at diagnosis

Terminal ileal involvement (L1 and L3) correlated with higher PCDAI (p=0.026). Furthermore, PUCAI was higher in more extent disease, though this tendency was not significant (p=0.086).

2.5. Laboratory parameters at diagnosis and their relationship with clinical characteristics of IBD

CRP, haematocrit, platelets and iron level were documented in 411 children (97.6%). Levels of CRP, platelets, were significantly higher and iron was lower in CD than in UC. However, haematocrit were comparable in CD and in UC.

CRP in girls was significantly lower than in boys (p=0.015) in CD. The difference in CRP between genders was significant only in children older than 10 years (A1b) (47.5 vs. 28.3 mg/L, p=0.004).

Involvement of TI was associated more often with elevated CRP (p=0.021). Meanwhile, comparing the other laboratory parameters of patients with involvement of terminal ileum and of Crohn colitis, significant difference was not revealed. Meanwhile, laboratory parameters of UC patients and Crohn colitis patients were not significantly different, even CRP levels were comparable.

Elevated CRP and thrombocyte levels were significantly more frequent in CD patients with upper gastrointestinal involvement ($p=0.030$ and $p<0.001$). Elevated CRP and low iron concentrations were associated with stricturing and fistulizing phenotype (B2, B3 or B2B3) ($p=0.01$, $p=0.006$).

In ulcerative colitis elevated CRP and decreased iron levels were related to disease extension ($p=0.002$, $p=0.004$).

3. Diagnostic work-up of pediatric IBD patients in general practice and adherence to Porto Criteria in the first five years of HUPIR

Diagnostic work-up was evaluated in patients registered between 2007 to 2011. Porto criteria were fulfilled in 28.4% of the children (200/713) with IBD. The recommended tests were more frequently performed in CD than in UC (38.3% vs. 5%, $p<0.0001$).

The diagnostic work-up in general practice changed significantly during the first five years of the HUPIR. The frequency of esophagogastroduodenoscopy has risen from 51% to 74% ($p=0.009$). The rate of ileocolonoscopy increased from 51% to 70% of children with CD ($p=0.002$). Similar tendency in the rate of small bowel imaging was not revealed. Small bowel imaging was performed in the third of newly diagnosed IBD patients (30.3%). However, some development was also observed in this field since proportion of MRI has elevated (from 7.4% to 23.9%) at the expense of CT imaging.

4. Diagnostic yield of esophagogastroduodenoscopy in pediatric inflammatory bowel disease

Together with Marta Kovacs, M.D, we evaluated the role of EGD in the diagnostic work-up of pediatric IBD. based on data of 420 children registered in the Hungarian Pediatric IBD Registry (HUPIR) from 1st of January 2007 to 31th of December 2009.

EGD was performed in 237 patients (56%). Macroscopic lesions on EGD were described in 64% of patients with CD and 40%

of children with UC. Granuloma in the upper gastrointestinal tract was found in 12 patients (12/176, 7%), in 8 cases of these granulomas were solely there (5%).

Macroscopic and microscopic lesions were not specific in UC, and did not provide diagnostic help. Consequently, these lesions should be evaluated with caution.

Regarding characteristic endoscopic lesions for CD (erosion, ulcer, aphthous lesions, and cobblestoning and granuloma) EGD helped to establish the diagnosis in 55 children with CD (55/176, 31%). In the subgroup of patients with colitis (L2) without colonic granuloma, EGD helped to establish the final diagnosis in 16 (9%) CD patients. On the basis of the above criteria the diagnostic yield of EGD was 9% (16/176) for CD.

5. First results of one-year follow-up of patients registered in HUPIR

At the first year follow-up 103 UC patients (83%) and 240 CD (90.2%) patients had available data regarding disease activity, therapy and surgery.

5.1. Disease activity indices at one-year follow-up

The median PCDAI decreased from 30 to 5 by the end of the first year ($p < 0.001$). Median PUCAI changed similarly from 35 to 5 by the end of the first year ($p < 0.001$). The proportion of CD patients with moderate to severe disease at diagnosis (48%) decreased after 1 year of follow-up to 2.1% (5/240). Median PUCAI changed similarly from 35 to 5 by the end of the first year ($p < 0.001$). Rate of UC patients with moderate to severe disease activity declined from 55% to 7.8% (8/102).

5.2. Medical therapy at diagnosis and at one-year follow-up

Most CD and UC patients received 5-ASA at diagnosis (UC: 92%, CD: 85%). Corticosteroids as initial therapy were used in 75% (180/240) of CD patients. Thirty-one percent (75/240) of CD children were treated with azathioprine. In UC, corticosteroid was administered in 65% (67/103) at diagnosis. Initial immunomodulator use was 3.8% (4/103) in UC. Exclusive enteral nutrition in CD was tried only in three institutes (10/240).

Infliximab was administered in 35 of 240 CD patients (14.5%) and azathioprine was applied in 51.7% of cases (123/240) one year after diagnosis. Cumulative incidence of intestinal resection (small bowel resection or/with partial colectomy) was 4.2% (10/240) at one year.

In UC, 21% (n=22) of patients were treated with azathioprine. Surgical intervention was not indicated in any of the 103 UC patients.

5.3. First results of one-year follow-up of patients registered in HUPIR : associations between initial activity indices, laboratory parameters and the therapy at one-year follow-up

Initially elevated PCDAI was related to the prescribed azathioprine ($p=0.015$) and infliximab ($p<0.005$) at one year. Elevated CRP at diagnosis also correlated with the need for azathioprine ($p<0.001$) and biologicals ($p=0.038$).

In UC, initial PUCAI was not related to the following therapy. In contrast, elevated CRP level was associated with the prescription of azathioprine (CRP: $p=0.01$).

Conclusions:

1. The mean incidence of pediatric IBD was 7.8/105 based on data of HUPIR between 2007-2011 in Hungary. The standardized incidence rate showed an increasing tendency (from 7/105 to 8.6/105). The incidence rate of pediatric IBD in Hungary is comparable with incidence rates reported other areas. The increasing tendency of incidence calls the attention to the burden of disease in Hungary. Elevating number of children with IBD becoming adult account for substantial health care costs.
2. Clinical and demographic characteristics of Hungarian children with IBD are comparable with results of other studies:
 - Frequency of CD is twice as high as frequency of UC (4.9/105 vs. 2.32/105)
 - In CD dominance of male gender, in UC female preponderance was observed
 - Occurrence of extraintestinal manifestations was 13.6% at diagnosis
 - Majority of patients with CD had ileocolonic disease, in UC most children have pancolitis
 - Strictureing/penetrating phenotype in CD at diagnosis was described in 15.6%
 - CD was associated with a stronger response of laboratory markers .
3. This is the first nationwide pediatric incident cohort study that reports activity indices for IBD (PCDAI, PUCAI) at diagnosis and one-year later. Our study demonstrated that half of the newly diagnosed IBD patients had moderate to severe disease activity at diagnosis. The first result of the one-year follow-up is that most children have reached remission by the end of the first year of disease course.

4. Regarding the pathomechanism of IBD interesting findings were as follows:
 - Terminal ileal involvement (L1 és L3) correlated with higher CRP and elevated PCDAI. Meanwhile the CRP level was comparable in Crohn-colitis and in UC. These show the disease modifying role of terminal ileum.
 - CRP in girls older than 10 years was significantly lower than in boys in CD. The difference in CRP between genders may refer to the relationship between sex hormones and inflammatory process.
5. One of the most important results of the HUPIR is that the diagnostic work-up practice has changed in Hungary. During the first five years of HUPIR the frequency of ileal intubation and EGD has reached the mean rate of international IBD centres. At the same time the Porto Criteria were fulfilled only in 28.4% of patients, that shows our further aims: to promote the small bowel imaging in pediatric IBD patients.
6. EGD helped to establish the diagnosis in 31% of children with CD. EGD was essential to establish the final diagnosis in 9% of CD patients. As a result, the diagnostic yield of EGD was 9% for CD based on data of HUPIR. It is important, that upper gastrointestinal involvement is associated with poor prognosis. Since EGD is a low risk procedure, EGD is recommended in children to establish the most accurate diagnosis and to provide the most sufficient therapy.
7. Our results underlie the importance of multiple biopsies from all bowel segments. In patients, who had biopsies from all 10 gastrointestinal segments, frequency of granuloma was 40%, while in the rest of the cases granuloma was found only in 27%.
8. Initial use of 5-ASA and corticosteroids for induction in Hungary was comparable to other studies. However, exclusive enteral nutrition as a first-line therapy in induction is not accepted in our country.
9. According to the first results of the one-year follow-up:

- Initially elevated PCDAI was related to the prescribed azathioprine at one year, however, in UC initial PUCAI was not related to the following therapy. The difference is probably due to the difference of the method of the two disease activity indices. Based on our finding initially elevated PCDAI may predict the need for early immunomodulation.
- In CD, elevated CRP at diagnosis also correlated with the need for azathioprine and biologicals. Similarly, elevated CRP level was associated with the prescription of azathioprine at one year in UC. Need for immunomodulators and biologicals refer more severe disease course. Consequently, elevated CRP may be a reason for strict follow-up of patients and earlier aggressive therapy may be indicated to prevent complications.

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