„Changing epidemiological trends of Crohn's - disease, result fromVeszprem province, population - based IBD database"

PhD Thesis

Barbara Dorottya Lovasz, MD

Semmelweis University

Doctoral School of Clinical Medicine

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Background

Inflammatory bowel disease (IBD) is multifactorial: both genetic and environmental risk factors contribute to its pathogenesis leading an uncontrolled inflammatory response against normal, commensal gut microbiome. Genome wide association studies revealed more than 200 gene polimorphism playing role int he development of IBD.

In recent decades, there has been a significant increase in the incidence of both CD and UC worldwide, with increased incidence reported from developing countries. Originally, IBD was more common in developed, industrialized countries, implicating urbanization as a potential risk factor. A parallel evolution is a trend for the previously reported predominance of UC to diminish, as CD becomes more prevalent. The geographical incidence of IBD also has varied considerably the highest incidence rates were traditionally reported in Northern and Western Europe as well as in North America, whereas lower rates were recorded in Eastern Europe, South America and Asia.

Incidence of pediatric onset CD cases is increasing also, moreover first symptoms of IBD often appear in youths with lifelong standing relapsing course, involving the quality of life and work productivity of the patients.

According to the available literature, pediatric onset CD runs a more aggressive course, including more extensive disease location, more upper GI involvement, growth failure, more active disease, and need for more aggressive medical therapy, in predominantly referral center studies.

IBD associated chronic transmural intestinal inflammation may enhance cell proliferation, ultimately leading to uncontrolled proliferation and carcinogenesis.

Only limited data are available on the evolution of disease phenotype in patients with a pediatric and adult-onset CD from Eastern Europe in a single population-based cohort over a long-term follow-up.

Aims

Our aim was to analyze incidence and clinical characteristics of IBD using data from a population-based Veszprem province database, which includes incident patients diagnosed from January 1, 1977.

Detailed aims of the present PhD thesis:

1. Characteristics and incidence of pediatric onset Crohn's disease in the Veszprem province IBD population- based database
2. Evolution of disease phenotype in pediatric and adult onset Crohn's disease in
3. Development of malignancies (colorectal cancer and lymphoma) in patients with Crohn's disease

Methods

Data were collected from seven general hospitals and gastroenterology outpatient units (internal medicine, surgery, paediatric
and outpatient departments) from the Veszprem province. Data collection was prospective since 1985; prior to that, only in Veszprem were data collected prospectively. In other sites throughout the province, data for this period (1977-1985) were collected retrospectively in 1985. Both in- and outpatients permanently residing in the area were included in the study. Diagnoses (based on hospitalization records, outpatient visits, endoscopic, radiological, and histological evidence) generated in each hospital and outpatient unit andwere reviewed thoroughly by at least 2 expert gastroenterologists and a paediatric gastroenterologist in Veszprem, using the Lennard–Jones or Porto criteria, as appropriate. Disease phenotype was determined according to the Montreal Classification, which includes age at onset, location and behaviour, with perianal and upper GI disease as additional modifiers. Clinical characteristic and phenotype were investigated by reviewing medical records during follow-up and by the completion of a questionnaire.

Results

1. Characteristics of pediatric onset IBD in Veszprem province

One hundred and eighty-seven patients (10.5% of 1565 incident IBD patients) were diagnosed with a paediatric-onset IBD in Veszprem province in the period (10.5%, ulcerative colitis: 88, Crohn's disease: 95, indeterminate colitis: 4). Incidence of both CD and UC increased in the study period időszakban (from 0 and 0.7 in 1977-1981 to 7.2 and 5.2 per 100,000 person-years. Ileocolonic location (45%), inflammatory disease behaviour phenotype (61%) were frequent in the paediatriconset CD population, with higher rates of azathioprine treatment (66%) and surgery (33% after 5-years disease duration), however upper GI involvement was relatively rare in this population based study.

In UC, about one-third of paediatric-onset patients were diagnosed with extensive disease (34%) with recurrent acute fulminant severe episodes and higher rates of systemic steroid treatment (52,3%). Proximal extension in patients with proctitis or left-sided colitis was 26% and 40.6% in paediatric-onset patients with UC after 5 and 10 years. Rate of colecytomy was low (6.9%).

The incidence of paediatric inflammatory bowel diseases has rapidly increased in the last three decades in Western Hungary. Ileocolonic disease and a need for azathioprine were characteristic in paediatric Crohn's disease, while paediatric onset ulcerative colitis was characterised by extensive disease and disease extension, while the need for colectomy was low.

2. Evolution of disease phenotype in adult and pediatric onset Crohn's disease

There was no significant difference in the distribution of disease behavior between pediatric (B1: 62%, B2: 15%, and B3: 23%) and adult onset CD patients (B1: 56%, B2: 21%, and B3: 23%) at diagnosis (P = NS). In addition, the distribution of disease behavior after 1, 3, 5, 7, 10 and 15 years and the probability of developing penetrating or complicated (stenosing/penetrating) disease behavior during follow-up did not significantly differ in patients with pediatric and adult onset disease by χ 2 and Kaplan-Meier analysis (PLogRank = NS, PBreslow = NS)

Similarly, the probability and time to change in disease behavior from B1 to B2/B3 disease was not significantly different between pediatric- and adult-onset CD in a Kaplan-Meier analysis. The probability of complicated disease behavior for patients who initially exhibited inflammatory disease behavior was 7.6%, 27.5%, and 42.0% in the pediatric and 12.1%, 26.4%, and 37.5% in the adult-onset patients after 1, 5, and 10 years of follow-up (PLogRank = NS, PBreslow = NS).

Predictors of complicated disease behavior even at diagnosis, were calendar year of diagnosis (p=0,04), ileal involvement (p<0,001) , perianal dissease(p<0,001) , smoking (p=0,038, need for steroid treatment (p<0,001)

.Change in disease location was associated with smoking habits, but not with the age at onset, and observed in 8.9% of patinets,

Evolution of disease behavior was not differ in pediatric and adult onset Crohn's disease in this population based cohort. On the other hand, development of complications was related to disease location, presence of perianal disease and smoking habits.

3. Crohn's disease and development of malignancies

Data from 1420 incident patients were analyzed (UC: 914, age at diagnosis: 36.5 years; CD: 506, age at diagnosis: 28.5.5 years). Both in- and outpatient records were collected and comprehensively reviewed. The rate of lymphoma was calculated as patient-years of exposure per medication class, of medications utilized in IBD.

Of the 1420 patients, we identified three patients who developed lymphoma (one CLL, two low-grade B-cell NHL including one rectal case), during 19,293 patient-years of follow-up (median follow-up: 13 years). All three patients were male and none of them had received azathioprine or biologicals. The absolute incidence rate of lymphoma was 1.55 per 10,000 patient-years, with 3 cases observed vs. 2.18 expected, with a standardized incidence ratio (SIR) of 1.37 (95% confidence interval [CI]: 0.44–4.26).

In conclusion, the overall risk of lymphoma in IBD was not increased in this population-based incident cohort, with only three cases seen over a 30-year period. Similarly, we did not find an association with thiopurine exposure. However, due to the relatively short follow-up under AZA exposure, a definite conclusion on the risk of lymphoma in patients under AZA or 6-MP

therapy could be reached. In addition, we were unable to confirm an association with either immunomodulator or biological exposure, although exposure to these drugs (AZA exposure: 3649 patient-years; biological exposure: 40 patient-years) was insufficient to exclude a possible association.

Regarding to colorectal cancer (CRC), data from 640 incidental CD patients were analyzed (M/F ratio: 321/319, age-at-diagnosis: 28 years (IQR: 22-38)). Both hospital and outpatient records were collected and comprehensively reviewed. CRC was diagnosed in six CD patients during a follow-up of 7759 person-years. Sixty-two patients presented with colonic/ileocolonic disease and a stenotic lesion in the colon with a follow-up of 702 personyears (median:10.5, IQR:5-16years). Colorectal cancer developed in 6.5% (equaling 0.57/100person-years), the SIR (6.53, 95%CI:2.45-17.4) was increased with four patients observed versus 0.61 expected.

In a Kaplan- Meier analysis, the probability of developing CRC was 5.5% and 7.5% after 5- and 10 years, respectively, versus 0.4% in patients with other phenotypes (HR:18.8, $p<0.001$). A sensitivity analysis included patients with stenosing colonic lesion at diagnosis or during follow-up (n=91, follow-up:1180 person-years,median:12, IQR: 6-17years). The probability of developing CRC was 3.6% and 4.9% after 5- and 10 years, respectively

Thee risk of CRC in CD patients presenting with or developing a stenotic lesion in the colon is high even after a short disease duration, suggesting the need for careful surveillance. Any other phenotype was not associated with higher CRC.

Conclusions

Based on our studies, in the Veszprém centralised population-based IBD database, the incidence and prevalence Crohn's disease is high, with a larger proportion of newly diagnosed cases in recent years.

In concordance with the global trends IBD has become more common, with a specially rapid increase in the pediatric cases.

Incidence rates of IBD in Veszprém County are as high as the Western European countries according to the EpiCom database. Increasing incidence in Eastern European countries is not

only based ont he higher awareness of the disease and better diagnostic tools, but a real increase with the widespread of westernized lifestyle.

Pediatric onset IBD has an agressive behavior, extensive location and higher need for early immunosuppressant treatment.

Crohn's disease is a progressive disease with development of complications (stricturing or penetrating diesase from the initially inflammatory phenotype) during follow-up.

In pediatric CD, ileocolonic location and higher need for azathioprin treatment were characteristic, but evolution of disease behavior and surgical rates were not different compared to adult onset cases.

Despite the adequate treatment strategy, chronic intestinal inflammation could affect the immune system and play role in carcinogenesis. In Crohn's disease the connection with the development of colorectal cancer is still unclear. In our study, the elevated risk is observed only in one, special phenotype, the stricturing colon localisation. Our results suggest the importance of CRC surveillance colonoscopy from the diagnosis in this patient subgroup.

The incidence of lymphoma was not increased in this population-based study from Eastern Europe; however there was a tendency toward increased incidence in males. In addition, we were unable to confirm an association with either immunomodulator or biological exposure.

These lifelong standing relapsing disease with complications affect the quality of life and work productivity of the patients. The factors result an important health care burden and needs multidisciplinary approach in both diagnosis and treatment of IBD.

Major novel findings of present PhD thesis:

1. The incidence of paediatric-onset CD and UC has rapidly increased in western Hungary between 1977 and 2011. Ileocolonic disease, male dominancy and need for azathioprine were characteristic in paediatric CD patients with a relatively high rate of surgery, while upper GI involvement were relatively low in our study.

2. the long-term evolution of disease behavior and initial characterisation of pediatric- and adult-onset CD patients did not differ in this population-based incident cohort.

3. Ileal location, smoking, need for steroids and early azathiorpin treatment were associated with presence of, or progression to, complicated disease behavior at diagnosis and during follow-up.

4. There was a change in the evolution of the disease behavior according to the calendar year of diagnosis.

5. The overall risk of lymphoma in IBD was not increased in this population-based incident cohort, however male predominancy was tendentially observed. Similarly, we did not find an association with thiopurine exposure.

6. The risk of CRC in CD patients presenting with or developing a stenotic lesion in the colon was significantly higher compared to the background population and to patients with any other phenotype. Moreover, the risk elevation occurred early during the disease course after a relatively short disease duration while the CRC risk in patients with any other disease phenotype was minute. Therefore, our results from the present study suggest that it may be sufficient to target CRC surveillance only to this subgroup of CD patients.

Publication's list

Directly related to the thesis

1. Lovasz BD , Lakatos L , Horvath A , Pandur T , Erdelyi Z , Balogh M , Szipocs I , Vegh Z , Veres G , Müller KE , Golovics PA , Kiss LS , Mandel MD , Lakatos PL Incidence Rates and Disease Course of Pediatric IBD in Western Hungary Between 1977 and 2011 DIGESTIVE AND LIVER DISEASE 46:(5) pp. 405-411. (2014) *IF: 3,162*
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Collaborations: Ildikó Kis, Éva Pollák, Ildikó Rosta, Károly Schultz, Ferenc Harangi,

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