Kocatepe Tıp Dergisi
Kocatepe Medical Journal
22:14-20 / Ocak / 2021

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

İNFLAMATUVAR BARSAK HASTALIKLARININ İZLEM VE TEDAVİSİ: RETROSPEKTİF BİR ÇALIŞMA

FOLLOW-UP AND TREATMENT OF INFLAMMATORY BOWEL DISEASE: A RETROSPECTIVE STUDY

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ÖZ

AMAÇ: 1990–2009 yılları arasında İnflamatuvar barsak hastalığı (İBH) tanısı alan hastaların sosyo-demografik, klinik özellikleri ile teşhis ve tedavilerinin retrospektif olarak incelenmesi amaçlandı.

GEREÇ VE YÖNTEM: 1990–2009 yılları arasında Tıp Fakültesi Gastroenteroloji Kliniğinde İBH tanısı alan 237 hastanın dosya kayıtları incelenerek yapılmıştır. Hastaların yaş, cinsiyet, sigara kullanımı, endoskopi ve histopatoloji bulguları, hastalarda gelişen lokal ve sistemik komplikasyonlar, uygulanan tedavi tipleri ve cerrahi tedavi nedenleri incelenmiş ve karşılaştırılmıştır.

BULGULAR: 1990 ile 2009 yılları arasında 144 Ülseratif Kolit, 73 Crohn Hastalığı ve 20 İndetermine Kolit hastası takip edildi. Ülseratif Kolit'li hastaların teşhis anındaki tanı yaşı ortalaması 37 yıl idi. Hastaların %28,7'sinde sol kolon tutulumu, %25,2'inde pankolit ve %21 proktit tablosu mevcuttu ($p<0.01$). Sistemik komplikasyon olarak bir hastada eritema nodosum, üç hastada sakroileit, üç hastada primer sklerozan kolanjit, bir hastada da malign dönüşüm görüldü. Crohn hastalığı tespit edilen hastaların yaş ortalaması 35 yıl idi. Hastaların %34'ünde kolon, %64,2'sinde ince barsak tutulumu saptandı. Sistemik komplikasyon olarak dört hastada üveit, beş hastada sakroileit görüldü. 222 hasta 5-aminosalisilat (5-ASA) bilesiği tedavisi alıyordu. Immünsupresif tedavi alan 6 hasta saptandı. 159 hasta monotedavi (5-ASA), 19 hasta kombine tedavi alıyordu.

SONUÇ: Hastalığın klinik seyrinin ve klinik tablosunun belirlenmesi, uygulanacak tıbbi ve cerrahi tedavileri ve farklı subgrup hastaların takip stratejilerini saptamak için önemlidir.

ANAHTAR KELİMELER: Inflamatuvar Barsak Hastalıkları, Ülseratif Kolit, Crohn Hastalığı

ABSTRACT

OBJECTIVE: The aim of this retrospective study was to investigate the socio-demographic and clinical characteristics as well as the diagnosis and treatment of patients with Inflammatory Bowel Disease between 1990 and 2009.

MATERIAL AND METHODS: Between 1990 and 2009, the records of 237 patients diagnosed with Inflammatory Bowel Disease in the Gastroenterology Clinic of Faculty of Medicine were examined. The age, sex, smoking history, endoscopy and histopathology findings of the patients, local and systemic complications developed in the patients, types of treatment applied and reasons for surgical treatment were examined.

RESULTS: Between 1990 and 2009, 144 Ulcerative Colit, 73 Crohn Disease and 20 Indeterminate Colit patients were followed. The mean age of diagnosis, at the time of diagnosis of Ulcerative Colit patients was 37 years. 28.7% patients had left colon involvement, 25.2% patients had pancolitis, and 21% patients had proctitis ($p<0.01$). Erythema nodosum in one patient, sacroiliitis in 3 patients, primary sclerosing cholangitis in 3 patients, and malign transformation in one patient were determined as systemic complications. The mean age was 35 years in patients with Crohn Disease. Involvement of colon and small intestine was determined in %34 and %64,2 patients, respectively. Uveitis in 4 patients, sacroiliitis in 5 patients were determined as systemic complications. 222 patients were treated with 5-ASA. Immunosuppressive treatment was given to 6 patients. 159 patients were given mono treatment (5-ASA) while 19 patients were given combine treatment.

CONCLUSIONS: Understanding of the prognosis and clinical course are important for determining medical and surgical treatment and follow up strategies for different subgroups of the patient.

KEYWORDS: Inflammatory bowel disease, Ulcerative Colitis, Crohn's Disease

Geliş Tarihi / Received: 31.07.2019
Kabul Tarihi / Accepted: 14.02.2020
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INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases that manifest involvement in various regions and layers of the gastrointestinal tract and are accompanied with remission and inflammations. Ulcerative Colitis (UC), Crohn's Disease (CD) and indeterminate colitis, which are between the first two, are among inflammatory bowel diseases. Causes like genetic and environmental factors and the immune response of the host organism are responsible for the etiology of inflammatory bowel diseases.

Disease activity of IBD is determined based on clinical, endoscopic, histopathological and laboratory findings. Anti-Saccharomyces cerevisiae (ASCA) is positive in 40-70% of Crohn's Disease, 5-15% of Ulcerative colitis, and Peri-Anti neutrophile cytoplasmic antibody (P-ANCA) is positive 40-80% of Ulcerative colitis and 2-20% of Crohn's Disease. These two serologic markers are used together for the differential diagnosis of UC and CD in IBD patients (1).

Inflammatory bowel diseases can be primarily characterized by bowel involvement as well as accompanied by symptoms in other organ systems. There are extraintestinal findings in 21-36% of IBD cases (2).

The purposes of IBD treatment are to provide symptomatic recovery, to reduce inflammation, to restore the nutrition of the patient, and to ensure remission and continuance. Anatomic localization of the disease, disease activity and disease duration, tolerability of the patient, response of the disease to previous treatments must be taken into consideration in the planning process of IBD treatment.

The aim of this study is to evaluate the epidemiological characteristics, possible etiological factors; clinical, laboratory, endoscopic characteristics during diagnosis, activation, and remission periods; serological markers, extraintestinal findings and complications that are important for differential diagnosis of UC and CD, and treatment types with a retrospective investigation on patients who are followed-up in our clinic with inflammatory bowel disease diagnosis.

MATERIAL AND METHODS

Medical files of 237 cases, who were followed-up for inflammatory bowel disease diagnosis in Faculty of Medicine Gastroenterology clinic between 1990 and 2009, were retrospectively evaluated.

Patients followed-up with inflammatory bowel disease diagnosis were separated into three groups as Ulcerative Colitis, Crohn's Disease and Indeterminate Colitis. Epidemiological factors of age, sex and etiological factors were investigated. The number of new cases in 5-years period between 1990 and 2009, the admission complaint of the patient, histological diagnosis of the disease and intestinal involvement locations were determined. Colonoscopic activity at the time of diagnosis was specified as acute, subacute or chronic depending on the macroscopic appearance in colonoscopy. In terms of colonoscopy, acute Ulcerative Colitis was defined with typically red, fragile and granular mucosa bleeding upon palpation; chronic Ulcerative Colitis was defined with mucosa having erythema, vascular pattern loss and friability, and subacute Ulcerative Colitis was defined with milder endoscopic findings than acute ulcerative colitis. For Crohn's Disease, in terms of colonoscopy, the acute phase was defined with skipping areas where normal mucosa is observed sporadically, presence of aphthous ulcers or larger ulcers called serpiginous ulcers, which are formed by the combination of aphthous ulcers, presence of large and linear deep ulcers, fissures between deep linear ulcers, submucosal edema and cobblestone appearance of the mucosa caused by the damages; and the chronic phase was defined with the presence of fibrous tissue and stricture. Clinical disease activity was determined for UC patients based in Truelove-Witts criteria according to the clinical and biochemical data at the time of diagnosis.

Patients were categorized into three groups: severe, moderate, and mild (3). Crohn's Disease patients were scored based on the eight criteria of CDAI (Crohn's Disease Activity Index) (4).

Extraintestinal findings, presence of ANCA and ASCA in patients were investigated. It was aimed to investigate the treatments received by

the patients, their surgery frequencies, and reasons.

SPSS 13.0 software was used for statistical analysis. Data was represented as mean ± standard deviation. P<0.05 was considered as statistically significant. The difference between groups was evaluated with Pearson's Chi-square Test, Kruskal-Wallis Chi-square Test, T-Test and Mann-Whitney U Test, Two Proportion Z Test.

ETHICS COMMITTEE

Ethics committee approval of the Eskişehir Clinical Trials Ethics Committee was obtained with 30.06.2009 dated and PR-09-06-30-12 numbered resolution.

RESULTS

For 237 patients diagnosed with IBD between 1990 and 2009, 60.8% of them (n=144) had Ulcerative Colitis, 30.8% of them (n=73) had Crohn's Disease and 8.4% of them (n=20) had Indeterminate Colitis. For patients diagnosed with Crohn's Disease, 56.2% was male and 43.8% was female and the mean age for the diagnosis was 35 years; 51.4% of the patients with Ulcerative Colitis were male and 48.6% was female and the mean age for the diagnosis was 37 years; 45% of the patients with Indeterminate Colitis were male and 55% was female and the mean age for the diagnosis was 41 years (p>0.05).

The number of new cases for the 5-year period was found to be increased (p>0.05) **(Figure 1)**.

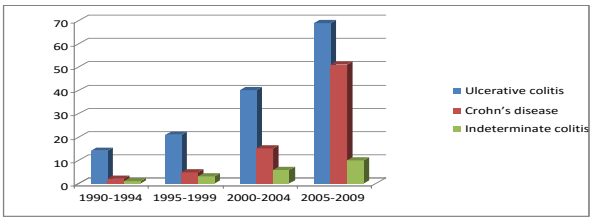

Figure 1: Number of new cases in IBD patients for 5-year periods

There was no significant difference in terms of diagnosis age and diseases related to smoking patients (p>0.05). In terms of chronic diseases, Diabetes Mellitus (7.6%) and cardiac diseases were frequent in UC patients and Behcet's Disease (6.8%) was more frequent in CD patients.

Among patients who had admitted to the clinic with bloody diarrhea, 135 (93.7%) of them had Ulcerative Colitis, 10 (13.7%) had Crohn's Disease and 17 (85%) had Indeterminate Colitis. Among patients who had admitted to the clinic only with diarrhea, 4 (2.8%) of them had UC, 39 (53.5%) had Crohn's Disease and 3 (15%) had Indeterminate Colitis. Five of the patients (3.5%) who had admitted with abdominal pain and weight loss gain had Ulcerative Colitis, twenty-four of them (32.8%) had Crohn's Disease (p<0.01). Admission complaints of IBD patients based on intestinal involvement locations were determined to be bloody diarrhea in cases of colon involvement, and only diarrhea and/or abdominal pain and weight loss in cases of ileocecal region and terminal ileum involvement (p<0.01).

In endoscopic findings during the diagnosis of IBD patients, CD and IC had granular mucosa appearance (26.9% and 26.3%) (p>0.05), and vascular pattern was decreased in UC and IC (63.4% and 73.7%) and normal in CD (59.7%) (p<0.01). Although fragility was not frequent in CD (75.4%), frequency of bleeding upon palpation was higher in UC and IC (81.3% and 70%, respectively) (p<0.01), mucosal damage in CD was either mild or severe, and severe mucosal damage was more frequent in UC and IC patients, 74.5% and 75%, respectively. Ulcer was more frequent in UC and IC patients, 68.8% and 75%, than CD patients (p<0.01), and presence of narrowness was more frequent in CD (p>0.05). In comparison to other groups, UC patients were determined to have statistically significant different acute phase and/or activation in colonoscopy at the time of diagnosis (p<0.01) **(Table 1.1)**.

Table 1.1: Colonoscopic activity at diagnosis

	N	%	N	%	N	%	N
Acut	121	85,2	39	54,3	16	80	176
Subacut/Chronic	23	14,8	34	45,7	4	20	61
Total	144	60,8	73	30,8	20	8,4	237

χ^2=24,113 Sd=2 p<0.001

The Clinical Disease activity of UC patients at the time of diagnosis were mild in 15.3%, moderate in 51.4% and severe in 33.3%; all CD pa-

tients were determined to have active disease (p<0.01). P-ANCA was measured for 51 of all IBD patients and ASCA was measured for 50 patients. P-ANCA was positive most frequently in UC and IC patients, 70% and 30%, and it was negative in CD. ASCA positive measurements were most frequent in CD patients (66.7%) (p<0.01). Colon involvement was observed frequently in P-ANCA positive patients, whereas ASCA positive patients had higher colon involvement and ileocecal region and/or terminal ileum involvement in addition to colon.

There were 53 IBD patients who had extraintestinal findings. Extraintestinal findings were found in 18.9% of UC patients, 30.1% of CD patients and 20% of IC patients (p>0.05) **(Table 1.2)**.

Table 1.2 : Distribution of extraintetinal findings.

	Ulcerative colitis N=27	Crohn disease N=22	İndetermine colitis N=4	Total N=53
Periferal arthropathy(PA)	13	8	1	22
Anterior Üveitis	0	3	1	4
Aphtous stomatitis (AS)	2	2	0	4
primary sclerosing cholangitis(PSK)	2	2	0	4
Episcleritis, HLAB27(-) Sacroileitis	0	2	0	2
PA,AS	4	2	0	6
Episcleritis, HLAB27(-) Sacroileitis,PSK	1	0	0	1
PA, AS HLAB27(-) Sacroileitis	2	1	1	4
PA,Erythema Nodosum	1	0	0	1
PA, HLAB27(+) Sacroileitis	0	1	0	1
Anterior Üveitis, HLAB27(+) Sacroileitis	0	1	0	1
Gallstone	2	1	0	3

Twenty-eight of IBD patients had developed complications. The most common complications during all follow-up periods were fistula and abscess **(Table 1.3)**.

Table 1.3 : Complications in patients according to follow-up periods

	Perforation n %	Shortness n %	Fistüla,Abscess n %	Malignancy n %	ToxicMegacolon n %
0-5years n=16	1 6,25	4 25	10 62,5	0 0,0	1 6,25
>5years n=12	1 8,3	0 0,0	9 75	1 8,3	1 8,3
Total n=28	2	4	19	1	2

5-ASA oral and 5-ASA enema treatment were the most frequent modes of therapy during the follow-up periods and the number of patients receiving 5-ASA oral treatment was statistically significantly higher than the number of patients receiving other treatments (p<0.01). Immunosuppressive treatment was given to 6 patients (4 UC ,2 CD). 159 patients with mono treatment (5-ASA), 19 patients (16 patients Azathioprine + 5-ASA, 3 patients İnfliximab + 5-ASA) were given combine treatment.

During the follow-up period, 16 out of 186 patients were determined to have received surgery. Mechanical ileus, massive bleeding and toxic megacolon were the reasons of surgery.

DISCUSSION

In recent years, the incidence of Inflammatory Bowel Disease has increased due to increased diagnostic possibilities. The increase was consistent with the literature findings and UC patients (n=144) were more than CD patients (n=73) (5).

Identification of risk factors of IBD will shed light to new advancements in prevention of disease activation and treatment. In our study, we evaluated smoking among these risk factors in our patients. The risk of ulcerative colitis development is higher in smokers than non-smokers. Quitting smoking provokes ulcerative colitis development. On the other hand, incidence of smoking is higher in Crohn's Disease than in general population. Smoking addicts exhibit a more severe course, higher immunosuppressive treatment need and faster post-surgical recurrence for Crohn's Disease (6). In our study, disease onset age for smoking UC patients was higher.

IBD symptoms can vary depending on the involvement location in the gastrointestinal system.

While patients admitted with bloody diarrhea complaint had dominant colon involvement, patients with terminal ileum and cecal involvement had abdominal pain, diarrhea and weight loss complaints. IBD must be considered for the differential diagnosis of patients with bloody diarrhea.

Lower gastrointestinal endoscopy in IBD is of crucial importance in terms of disease activity, condition of inflammatory lesions, whether bleeding or strictures developed, and to determine dysplasia or malign changes. In our study, statistically significant differences were determined in endoscopic findings of UC and CD patients at the time of diagnosis ($p<0.001$); however, endoscopic findings of UC and IC patients were similar (3,4).

Serological markers are reported in various rates around the world depending on ethnic and environmental factors. In a study conducted by Kılıç et al. (7) on Turkish population showed 65% p-ANCA prevalence for Ulcerative colitis. ASCA prevalence in CD patients was determined to be 63.9%. As this value is higher than the previous reports, they considered that this situation might be a result of geographical difference. In our study, similar to the literature, positive p-ANCA was determined in 70% of UC patients ($p<0.01$) and positive ASCA was determined in 66.7% of CD patients. While colon involvement was higher in p-ANCA positive and negative patients, we determined that colon and small intestine involvement in ASCA positive patients was more frequent. In addition to using these tests for diagnosis and differential diagnosis, we believe that they can also be used for screening test purposes for patients with gastrointestinal symptoms.

Extraintestinal findings occur in 21-36% of IBD patients (2). In our study, extraintestinal findings were found in 18.9% of UC patients, 30.1% of CD patients and 20% of IC patients (Table 1.2).

In the literature, peripheral arthropathy was reported to be more frequent in CD; in our study, we found that peripheral arthropathy was higher in CD, however, there was no significant difference between UC ($p>0.05$). Consistent with the literature, we found skin symptoms together with peripheral arthropathy (erythema nodosum and aphtosis stomatitis). Similar with the literature, we found sacroiliitis in 2.5% of IBD patients and 83.3% of them were CD patients.

While HLA-B27 negative Sacroiliitis patients had episcleritis association, HLA-B27 positive patients had anterior uveitis association. As per our interpretation, in IBD, especially when CD patients diagnosed with sacroiliitis, they should also be examined in terms of eye findings.

Maintenance of remission and controlling the active disease in IBD are very important for the management of potential intestinal complications. Effective management of complications will enable the patients to have quality life in terms of health and decrease morbidity and mortality. Strictures are a common complication of CD. In our study, we observed strictures in 5.4% of CD and in none of the intestinal obstruction UC patients. Fistula and abscess were found in 4.4% of UC patients and 22.8% of CD patients.

In our study, malignity was found in 1 UC patient (0.8%) who had been under follow-up for over 5 years. We believe that colorectal cancer frequency can be reduced through regular endoscopy and biopsy, determination of dysplasia and early surgical treatment of cases that are not responsive to medical treatment.

The purpose of IBD treatment is to provide symptomatic recovery, to reduce inflammation, to restore the nutrition of the patient, and to ensure remission and continuance. Today, many new and alternative treatment models are being studied for IBD, however, glucocorticoids and amino salicylates are the most important elements of medical treatment practice and they are used both for establishing and maintaining remission (8). In a study conducted by Jiang et al (9) in 2006, they found 88% 5-ASA/Sulfasalazine, 43% steroid and 3% surgical treatment in UC patients and 73% 5-ASA/Sulfasalazine, 35% steroid and 27% surgical treatment use in CD. In our study, 94-70% of the patients received 5-ASA oral treatment. During the follow-up 36.7%-51.4% of UC patients with left colon involvement and/or rectosigmoid involvement used 5-ASA supp., and Corticosteroid treatment varied between 22.2% and 24.2% among all groups.

Studies on new treatments are ongoing because of lack of complete success of conventional treatments used in IBD and due to the resistance of some patients against treatment or frequ-

ent recurrence. The goal of treatment is to control symptoms, prevent progression and prevent bowel damage (clinical and endoscopic remission). Today, IBD is considered to be a progressive disease that causes intestinal damage and disability. Therefore, it is imperative to start the individualized treatment quickly in the early stages to prevent irreversible complications, reduce hospitalization and surgery rates and achieve better results (12).

In cases where remission maintenance cannot be established with 5-ASA, immunosuppressive agents or anti-TNF agents are used to establish remission for patients' refractory against steroid or when complications occur [10]. In recent years, there are an increased number of studies on biological treatment options, especially for Crohn's Disease, based on the role of immune system in etiopathogenesis of IBD. During the course of the disease, it has been shown to be superior to conventional treatment in terms of early immunosuppressants and / or biological therapy, better mucosal healing in patients diagnosed with IBD, induction of steroid-free remission and hospitalization (13-15).

In Crohn's Disease patients, successful results have been obtained by using TNF-α blocker (Talidomid) and TNF-α monoclonal antibodies (Infliximab) (10). In our study, patients receiving Infliximab and 5-ASA were found in the group of patients who had been followed up for more than 5 years. When the optimal medical treatment of IBD is considered, individualization of the treatment according to the specific needs of each patient is the most crucial part. Although chronic, new advancements in medicine and mutual efforts of doctors and patients will render IBD more tolerable.

While the primary treatment of inflammatory bowel diseases is medical, surgery can be the primary choice for certain patients. Ulcerative colitis is differentiated from Crohn's Disease especially with its possibility to be completely cured with surgical treatment. It would be more accurate to consider surgery at an earlier stage especially for younger patients due to the frequent hospitalization during the expected lifetime, low quality of life expectation and malignity risks. As UC has only rectum and colon involvement, proctocolectomy can be curative.

Indications of colectomy in UC are medically uncontrolled conditions such as malignity (or dysplasia), massive hemorrhage, perforation, toxic megacolon and fulminant colitis. Anti-TNF antibodies and immunosuppressive options should be used in Crohn's Disease and surgical treatment should be reserved for complicated cases where such medication is ineffective or cannot be used. Surgical treatment in CD is not curative. Indications of surgical treatment in CD are intestinal obstruction, internal fistula or abscess, perianal disease, toxic megacolon, severe disease unresponsive to medical treatment, malignity (or dysplasia) and growth retardation (11). In our study, we observed an increased operation frequency as follow-up period extended (15.5% in patients followed-up for more than 5 years). Small intestine resection due to intestinal obstruction was the most frequent reason for surgery; other reasons were unresponsiveness to medical treatment, massive bleeding, toxic megacolon and total or hemicolectomy due to malignity.

ACKNOWLEDGEMENT

I would like to thank my dear advisor, Professor Doctor Tülay SARIÇAM, who passed away.

CONCLUSIONS

In conclusion, IBD is a chronic disease with different clinical manifestation. Understanding the prognosis and clinical course of the disease are necessary for determining medical and surgical treatment and follow up strategies for different subgroups of patients.

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