ORIGINAL RESEARCH

Clostridium difficile infection in inflammatory bowel disease

İltihabi barsak hastalığında Clostridium difficile infeksiyonu

Necla OSMANOĞLU[1], Tijen ÖZACAR[2], Galip ERSÖZ[1]

Departments of [1]Gastroenterology, and [2]Microbiology, Ege University School of Medicine, İzmir

Background and Aims: *A recent rise in Clostridium difficile-associated diarrhea has been observed. A higher incidence of Clostridium difficile-associated diarrhea has also been suggested in patients with inflammatory bowel disease and may be a challenging factor in the differential diagnosis of flares. Prior antibiotic use, older age, prolonged hospital stay, poor immunity, chemotherapy, and acid suppression are the risk factors.* **Materials and Methods:** *Between June 2009 and October 2010, 42 patients were admitted with active bloody diarrhea and diarrhea in Ege University, Clinic of Gastroenterology, Inflammatory Bowel Disease Polyclinic. We investigated Clostridium difficile toxin A+B in stool samples (Clostridium difficile toxin A+B, VIDAS, bioMérieux, France) during inflammatory bowel disease flare, and clinical, laboratory and endoscopic findings of the admitted patients were recorded. We queried the patients regarding their use of antibiotic, corticosteroid and azathioprine.* ***Results:*** *Among the inflammatory bowel disease patients, 41 had ulcerative colitis and 1 had Crohn's colitis. Five of the 42 patients were taking corticosteroid and 3 of the 42 were taking azathioprine; none of them was on antibiotic. In 41 patients with inflammatory bowel disease, Clostridium difficile toxin A+B were negative in stool; in one patient, the value was borderline.* **Conclusions:** *Recently, Clostridium difficile infection has been suggested frequently in patients with inflammatory bowel disease in the North American and European literature. However, we were unable to demonstrate this infection in our inflammatory bowel disease patients with flare.*

Keywords: Clostridium difficile, toxin A and B, inflammatory bowel disease

Giriş ve Amaç: *Son zamanlarda Clostridium difficile bağlı diyarelerde artış gözlenmiştir. Yine Clostridium difficile bağlı diyare iltihabi barsak hastalarında artmış bir insidense sahiptir ve aktivasyonla ayırıcı tanıda karışıklığa yol açabilir. Önceden antibiyotik kullanımı, ileri yaş, uzamış hastanede kalış, bağışıklığın zayıflığı kemoterapi ve asid supresyonu risk faktörleridir.* ***Gereç ve Yöntem:*** *Haziran 2009 ve Ekim 2010 arasında Ege Üniversitesi Gastroenteroloji Kliniği İnflamatuvar Barsak Hastalıkları polikliniğine başvuran, aktif kanlı diyaresi ve diyaresi olan 42 hastada dışkıda Clostridium difficile Toksin A+B (Vidas Bio – Merieux France) arandı. İnflamatuvar barsak hastalığı aktivasyonu klinik, laboratuvar ve endoskopik bulgularla tayin edildi. Hastalara antibiyotik kortikosteroid ve azothioprin kullanımı soruldu.* ***Bulgular:*** *Kırkiki inflamatuvar barsak hastasının 41'i Colitis ülseroza ve biri Crohn kolitiydi. Kırkiki hastanın 5'i kortikostreoid, 3'ü azothioprin alıyordu, hiç biri antibiyotik almıyordu. İnflamatuvar barsak hastalığı olanların 41'inde Clostridium difficile toxin A+B gaitada negatifti ve bir hastada sınır değerdeydi.* ***Sonuçlar:*** *Clostridium difficile infeksiyonu Kuzey Amerika ve Avrupa literatüründe inflamatuvar barsak hastalığı'nda sıklıkla ileri sürülmektedir. Fakat biz bu infeksiyonu aktivasyon esnasında inflamatuvar barsak hastalarımızda bulamadık.*

Anahtar kelimeler: Clostridium difficile, toksin A+B, inflamatuv ar barsak hastalığı

INTRODUCTION

Clostridium difficile (C. difficile) is an aerobic, rod-shaped, gram-positive bacterium, which exists in two forms: a toxin-producing vegetative form and a dormant spore form. The toxin produced by the bacteria may cause colitis (1). There are two types of toxins: a more potent toxin A (entero toxin) and a less severe toxin B (cytotoxin) (1).

The typical clinical presentation of *C. difficile*-associated diarrhea (CDAD) was described over 30 years ago, and may vary from mild diarrhea to toxic megacolon with severe sepsis and multiorgan failure. CDAD is associated with a substantial mortality varying between 4.5-22% depending on the studies (3). A recent report demonstrated that more than 2% of all in-hospital deaths were linked to *C. difficile* infection (CDI). Prior antibiotic use is the most important risk factor (1,3,5). Other risk factors that have been reported include older age, prolonged hospital stay, poor immunity, chemotherapy, and acid suppression (1-3). Endoscopic documentation of pseudomembranes is almost pathognomic, but is seen in only one-third of the patients.

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory conditions that frequently require

Address for correspondence: Necla OSMANOĞLU
Departments of Gastroenterology, Ege University School of Medicine, Bornova, İzmir, 35100, Turkey • Phone: +90 232 390 34 77
Fax: +90 232 342 77 64 • E-mail: necla.osmanoglu@ege.edu.tr

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long-term medical therapy, periodic hospitalisations and even surgery (5). Chronic use of antibiotics, corticosteroids, and immunomodulators has been shown to increase the risk of CD in IBD patients (5-7).

Approximately 5-19% of patients admitted for relapsing IBD were tested for C. difficile toxins (4,5). Patients with UC appear to be at a higher risk for CDI (2,3) than those with CD, and patients with UC and CDI had a higher mortality and a higher risk for colectomy.

Indeed, CDI was identified most commonly in older patients (especially those over 70). Furthermore, most IBD patients are young and do not carry risk factors. For this reason, we aimed to investigate CDI in IBD.

MATERIALS AND METHODS

Between June 2009 and October 2010, 42 patients admitted with active bloody diarrhea and diarrhea in Ege University, Clinic of Gastroenterology, IBD Polyclinic. We investigated *C. difficile* toxin A+B in stool samples (*C. difficile* toxin A+B, VIDAS, bioMéreieux, France) during IBD flare, and the clinical, laboratory and endoscopic findings of the admitted patients were recorded. Patients were queried regarding the use of antibiotic, corticosteroid and azathioprine. None of them was on antibiotics.

RESULTS

Overall, 42 patients (17 female, 25 male) were included in the study. The demographic features of the patients and disease characteristics are shown in Table 1. In 41 patients with IBD, *C. difficile* toxin A+B were negative in the stool; values were borderline in 1 patient.

Among the IBD patients, 41 had UC and 1 had CD. Five of 42 patients were taking corticosteroid and 3 of 42 patients were taking azathioprine; none of them was on antibiotic.

DISCUSSION

A global increase in CDAD has been documented over the last decade, and has drawn the attention of clinicians, given the excess in morbidity and mortality associated with the condition.

The diagnosis of CDAD may be particularly obscured in patients with IBD, since the clinical presentation often mimics flare, and stool cultures are not always performed in patients presenting with flare. Studies reported from North America have described a two-fold increase in *C. difficile* incidence in recent decades.

Tablo 1. Demographic features of patients and disease characteristics

Median age (year)	40
Gender (Female/Male)	17/25
IBD type (Crohn/UC)	1/41
Colonic IBD involvement	42
Corticosteroid use	5
Immunomodulator use	3

Traditional risk factors including advanced age (>65 years) and use of broad-spectrum antibiotics must now include use of fluoroquinolone as a major risk factor. Immunomodulator use and presence of IBD colitis are also shown as significant risk factors for development of CDI. In *C. difficile*-infected IBD patients, it is essential that clinicians identify and address this infectious complication. Empiric treatment without appropriate antibiotics may precipitate deterioration.

The majority of IBD patients appear to contract *C. difficile* as an outpatient, and prior history of colitis appears to be the most significant risk factor for acquiring this infection. A recent study also demonstrated more frequent infection in IBD patients in complete remission with recent hospitalization or antibiotic exposure (8.2% versus 1% in healthy volunteers) (5). Studies have shown that there is increased risk of CDI with use of antibiotic disrupting the bacterial flora, intensive care, or prolonged hospital stay, and more recently, IBD (5). Multiple studies from tertiary care institutions as well as large nationwide inpatient databases have demonstrated an increase in the incidence and severity of CDI in patients with IBD when compared with the general population (5). In a study of risk factors for CDI in IBD patients, maintenance immunomodulator use and colonic involvement were independently associated with risk factors of CDI (5).

In a retrospective cohort study, it was shown that the use of maintenance immunomodulator therapy in IBD patients was significantly associated with CDI (8). In the present study, we determined the incidence of *C. difficile* toxin A+B as 0% in active IBD patients. The possible reasons for this are that we studied IBD patients with no history of hospitalization and no antibiotic use, and further, five were taking corticosteroid and three were taking immunomodulator therapy.

In conclusion, recently, CDI has been suggested frequently in patients with IBD in North American and European literature; however, we did not find this infection in our IBD patients with flare.

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