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ARTÍCULO ORIGINAL

Infección por *Clostridiodes difficile* en un centro de referencia neurológico de la Ciudad de México

Tadeo-Escobar Isabel, Ángeles-Morales Verónica, Soto-Hernández José Luis, Cárdenas Hernández Graciela Agar

Neuroinfectology Department. Instituto Nacional de Neurología y Neurocirugía

Correspondencia: Graciela Agar Cárdenas Hernández MD, PhD. Insurgentes Sur 3877, Col. La fama, Tlalpan 14269, Mexico City

Email: gcardenas@innn.edu.mx

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Resumen

Antecedentes: *Clostridioides difficile* es un patógeno reemergente que causa diarrea nosocomial a nivel mundial, particularmente en países industrializados.
Objetivo: Presentar una serie de casos clínicos de infección por *Clostridioides difficile* en un centro de referencia neurológico.
Método: estudio retrospectivo y observacional de casos de infección por C. *difficile* (ICD) en el Instituto Nacional de Neurología de enero de 2016 a diciembre de 2018.
Resultados: se incluyeron 16 pacientes con CDI durante el periodo de estudio. Todos ellos tuvieron el antecedente de terapia antimicrobiana de amplio espectro en las 6 semanas previas al inicio de los síntomas. Más de la mitad de la población afectada correspondió a mujeres. El principal diagnóstico de admisión fue enfermedad cerebrovascular, seguido de enfermedades infecciosas. Otros factores de riesgo (adicionales al uso de antimicrobianos) fueron inhibidores de bomba de protones, corticosteroides y obesidad.
Conclusiones: los pacientes con afección neurológica son proclives al desarrollo de diarrea nosocomial debido a un conjunto de factores de riesgo, incluyendo uso concomitante de corticosteroides, inhibidores de bomba de protones, obesidad/diabetes (previos al uso de antibióticos de amplio espectro). Se requieren programas de gerencia de antibióticos para asegurar un uso racional de éstos y con ello disminuir el riesgo de diarrea nosocomial en esta población.

Palabras claves: *Clostridiodes difficile*; colitis; epidemiología.

ORIGINAL ARTICLE

Clostridioides difficile infection in a Mexico City neurological referral center

Abstract

Background. *Clostridioides difficile* is an important re-emerging pathogen and the primary cause of nosocomial diarrhea worldwide, particularly in high-income countries.
Aim of study. To present a case series of *Clostridioides difficile* infection in a neurological referral center.
Methods. Observational, retrospective study to present cases of C. *difficile* infection (CDI) in a neurological referral center in Mexico City from January 2016 to December 2018.
Results. Sixteen inpatients developed CDI during the period of study. All infected patients received wide-spectrum antimicrobial therapy within six weeks before symptom onset. More than one-half of affected patients were females. Cerebrovascular disease was the main diagnosis on admission, followed by infectious diseases. Other risk factors included the administration of proton pump inhibitors, corticosteroids, and obesity.
Conclusions. Neurological patients are prone to develop CDI because of a conjunction of several risk factors, indeed the concomitant use of corticosteroids, proton pump inhibitors and obesity / diabetes (before the use of extended-spectrum antibiotics). Antibiotic stewardship programs must be enforced to ensure the rational use of antibiotics in order to decrease the risk of CDI.

Keywords: *Clostridiodes difficile*; colitis; epidemiology

Introduction

Clostridioides difficile, is a re-emerging pathogen that mainly causes nosocomial diarrhea in Europe and North America[1-3], is associated to a high economic burden[4]. Several risk factors are linked to the colonization of the gastrointestinal tract and subsequent development of C. difficile infection (CDI) in a patient. The main triad consists of disruptive factors, host factors, and an increased exposure to C. difficile spores. Disruptive factors include wide-spectrum antimicrobial therapy[5], surgery, feeding tubes, and other medications (proton pump inhibitors). Host factors like aging, sex, and comorbidities (cancer, obesity, and others[6-8], are known to be associated to CDI.
Classic clinical manifestations of CDI include fever, watery diarrhea, and leukocytosis; severe cases may progress to life-threatening pseudomembranous enterocolitis and toxic megacolon. A relapsing infection occurs in approximately 20% of cases after initial CDI, and the frequency increases with subsequent recurrences[9]. Despite the increasing incidence of CDI worldwide, the number of reports of this condition in Mexico is limited[10-13]. In this context, herein we describe a case series of CDI in a neurological referral center in Mexico.

Methods and patients

The Instituto Nacional de Neurología y Neurocirugía is the main neurological referral center in Mexico; it counts 126 census beds and has three major hospitalization areas: Neurology, Neurosurgery, and Psychiatry, as well as intensive care units and a post-surgical recovery unit. This work, a retrospective study of CDI, covered from January 2016 to December 2018, its start coinciding with the systematic introduction of C. *difficile* toxin A/B enzyme immunoassay (EI). This study was conducted in accordance to the principles of the Declaration of Helsinki and its revisions. All patients included signed an informed consent letter to participate.

Clinical suspicion of CDI was considered in those patients who received antimicrobial therapy 4-6 weeks before symptom onset. Patients who developed diarrhea (>3 unformed stools in 24 h) during hospital stay or within three days after hospital discharge were included. CDI diagnosis was based on a combination of clinical symptoms, laboratory tests (blood leukocytosis, positive ImmunoCard toxin A/B EI *Meridian Bioscience Inc., Cincinnati*, OH; test sensitivity was 66-96.2% and specificity was 93.5-100%), and/or radiological evidence of enterocolitis/colitis. Demographic data (age, sex, comorbidities), risk factors (exposure to wide-spectrum antibiotics, proton pump inhibitors, nasogastric intubation, corticosteroids, etc.), laboratory parameters (leukocyte count, hemoglobin, platelets, albumin, creatinine, and C reactive protein levels), clinical symptoms (fever, diarrhea, abdominal pain, vomiting, hemodynamic instability), and abdominal radiography/tomography findings of all patients included were retrieved from medical records and coded in *MS Excel* (*Microsoft Co., Vermont, WA*).

Patients with diarrhea due to other causes (osmotic, drug-induced, or metabolic) were excluded. CDI was categorized either as mild, moderate, severe, or complicated in accordance to the guidelines by the American College of Gastroenterology (ACG)[14].

To control C. *difficile* dissemination, all suspected and symptomatic cases were isolated, and extensive precautions were taken to prevent contact with fomites. All healthcare workers observed strict hand hygiene and barrier precautions; additionally, terminal cleaning protocols were enforced on environmental surfaces, using sodium hypochlorite (5000 ppm) as a sporicidal agent.

Statistical analysis

All data were recorded in *MS Excel* and analyzed with *SPSS v.21 (IBM Inc., Somers, NY)*. Qualitative variables were expressed as a percentage and compared using the chi-squared test with Yates correction. Differences between continuous variables were evaluated with the Student's t-test. Differences were considered as significant for $P < 0.05$.

Results

General characteristics

In the period of study, 1479 patients were admitted to our institution; 77 patients developed diarrhea during hospitalization, but only 16 (20.7%) had a confirmed CDI diagnosis. The mean age of these patients (9 female and 7 male) was 47.5 ± 17 years. Only three patients were elderly (≥ 65 years-old). Admission diagnosis was cerebrovascular disease in seven (subarachnoidal hemorrhage in five, ischemic stroke in one, and hypertensive parenchymal hemorrhage in one), infectious disease in seven (ESBL urosepsis, AIDS/tuberculosis coinfection, AIDS/cryptococcal meningitis, spondylitis, chronic meningitis, pneumonia, and brain abscess), Creutzfeldt-Jakob disease and anoxic encephalopathy one patient in each one. The mean hospital-stay length at the onset of diarrhea was 29.3 ± 23.7 days (6-80), and the mean global hospital stay was 63.81 ± 58.1 days.

The mean Charlson comorbidity index was 4.06 ± 2.9. With respect to CDI risk factors, the use of proton pump inhibitors was observed in 100% of patients (16), corticosteroid administration in 43.8% (7), early use of extended-spectrum antibiotics in 100% (16), and obesity in 43.8% (7). The general characteristics of the patients included are summarized in *table 1*.

Clinical-radiological presentation

The main clinical signs observed were increased peristalsis in 81.25% of patients (13), abdominal distention in 62.5 % (10), and fever in 62.5% (10), while the main symptom reported was abdominal pain in 68.75% (11). Diarrhea, with more than three stool evacuations per day, was observed in all patients.

Table 1. General characteristics of population

Age	Genre	Risk factors	Diagnosis at the admission	Severity of ICD	Treatment	Outcome
56	Male	Proton-pump inhibitors Corticosteroids obesity	Esthesioneuroblastoma Nosocomial pneumonia	Pancolitis	Vacomicyn Metronidazole Fecal microbiota transplant	No clinical improvement. Voluntary discharge
29	Male	Proton-pump inhibitors corticosteroids	Coccidiodal meningitis, BLEE urosepsis	Diarrhea	Vacomicyn Metronidazole	Improvement
46	Male	Proton-pump inhibitors corticosteroids HIV/AIDS	Tuberculous meningitis AIDS	Enterocolitis	Vacomicyn Metronidazole Fecal microbiota transplant	Improvement
27	Male	Proton-pump inhibitors corticosteroids	Brain abscess	Diarrhea	Metronidazole	Improvement
34	Male	HIV/AIDS, malnourishment, Proton-pump inhibitor	Cryptococcal meningitis	Diarrhea	Vancomycin	Improvement
35	Male	Proton-pump inhibitors	Ischemic stroke in middle cerebral artery	Diarrhea	Vacomicyn	Improvement
20	Male	Proton-pump inhibitors	Anoxic encephalopathy	Enterocolitis	Vacomicyn Metronidazole	Improvement
55	Male	Proton-pump inhibitors, corticosterois	Chronic meningitis, otomastoiditis	Diarrhea	Vacomicyn Metronidazole	Improvement
59	Female	Proton-pump inhibitors Corticosteroids Obesity	Subarachnoidal hemorrhage, vasculitis	Enterocolitis	Vacomicyn Metronidazole	No clinical improvement. Voluntary discharge
66	Female	Proton-pump inhibitors Diabetes mellitus	Subarachnoidal hemorrhage, Alzheimer disease	Enterocolitis	Vacomicyn Metronidazole Fecal microbiota transplant	Improvement
60	Female	Proton-pump inhibitors Diabetes mellitus	Parenchymal hemorrhage	Enterocolitis	Vacomicyn Metronidazole	Improvement
51	Female	Proton-pump inhibitors	Subarachnoidal hemorrhage, vasculitis	Diarrhea	Vacomicyn Metronidazole	Death
35	Female	Proton-pump inhibitors Corticosteroids Obesity	Spondilytis, infectious myelopathy	Recurrent enterocolitis	Vacomicyn Metronidazole	Improvement
41	Female	Proton-pump inhibitors	Subarachnoidal hemorrhage, vasculitis	Diarrhea	Vacomicyn Metronidazole	Improvement
62	Female	Proton-pump inhibitors	Creutzfeldt-Jakob disease	Recurrent enterocolitis	Vacomicyn Metronidazole Fecal microbiota transplant	Improvement
84	Female	Proton-pump inhibitors	Subarachnoidal hemorrhage, vasculitis	Pancolitis	Vacomicyn Metronidazole Fecal microbiota transplant	Improvement

CDI was mild in 43.75% of cases (7) and severe in 56.25% (9). Three patients with a severe presentation developed relapsing CDI (RCDI). The mean leukocytosis level on admission was 9.45 ± 5.02, and it was 14.43 ± 7.7 at the onset of diarrhea. Abdominal X-ray was abnormal in 43.75% of patients (7). CDI-linked antibiotics were cephalosporins in 10 cases and carbapenems in 4; all other patients were administered with a combination of both groups and quinolones.

Treatment and clinical outcome

Oral monotherapy consisting of metronidazole 500 mg/8 h or vancomycin 125 mg/6 h was administered to two patients each, while those with severe CDI (9) received a combination of vancomycin and metronidazole; this combination was boosted either with rifaximin (one patient) or tigecycline (two patients).

Fecal microbiota transplantation (FMT) was required in five patients with severe CDI (only one failed to show any improvement). With respect to the clinical outcome, one patient suffering from severe CDI died, three were voluntarily discharged, and the rest (75%) ameliorated.

Significant differences were found among CDI patients when sex was considered: hospitalization time since the onset of diarrhea was longer in males (P = 0.05), while body mass index (BMI) was higher in females (P = 0.04) (*table 2*). With respect to CDI severity, older patients had a more severe presentation than younger ones (P = 0.04) (*table 3*). Patients showing hypoalbuminemia had higher BMI values (33.63 ± 6.9 vs. 23.33 ± 5.3, P = 0.01) and higher leukocytosis levels at the onset of diarrhea (18 ± 6.2 vs. 6 ± 2.7, P = 0.001) than patients with normo-albuminemia. Obese patients showed higher leukocytosis levels at the onset of diarrhea (P = 0.02). Significant bivariate correlations were also found between BMI and age (r= 0.503, P= 0.047), BMI and leukocytosis at the onset of diarrhea (r= 0.734, P= 0.004), and BMI and albuminemia (r= −0.692, P= 0.006).

Table 2. Comparison between sexes

	Female	Male	P
Time of hospitalization at the beginning of diarrhea	19.55 ± 23.2	41.7 ± 19.1	0.05
Time with diarrhea	20.44 ± 14.2	11.1 ± 8.9	0.1
Age	54.1 ± 17	39 ± 13.7	0.07
Body mass index	19.55 ± 23.2	19.55 ± 23.2	**0.04**
Leucocytes on admission	11.21 ± 5.36	7.1 ± 3.75	0.1
Leucocytes at diarrhea episode	17.2 ± 6.7	9.9 ± 7.6	0.09

Table 3. Comparison according to severity of CDI

	Mild	Severe	P
Time of hospitalization at the beginning of diarrhea	30.2 ± 22.3	28.4 ± 26.1	0.8
Time with diarrhea	10.5 ± 9.1	20.7 ± 13.8	0.1
Age	38.8 ± 10.7	54.2 ± 18.5	0.04
Body mass index	24.8 ± 3.5	31.5 ± 8.8	0.06
Leucocytes on admission	9.4 ± 4.7	9.45 ± 5.5	0.8
Leucocytes at diarrhea episode	10.9 ± 7.67	16.6 ± 7.40	0.1

Discussion

The global increase in CDI incidence, attributed to the emergence of hypervirulent strains (027 and 078)[15,16], has been associated with significant mortality, morbidity, and health-care costs. The neurological patients in our healthcare center usually show distinct clinical characteristics: compromised alertness, long-term hospital stay, and several disruptive factors like the extensive use of corticosteroids and proton pump inhibitors,

as well as the requirement of nasogastric tube to maintain caloric intake; particularly, this device makes patients prone to a poorer outcome in CDI[17,18].

While CDI incidence in our center was low, severe forms of the disease were observed in more than one-half of the patients included. In addition, one patient died of severe CDI and three patients were voluntarily discharged without a clear clinical improvement. Older age (65 years or older), female sex, and the use of proton pump inhibitors and corticosteroids were the most frequent risk factors. These results are similar to those reported in larger studies at the United States[19] and China[20] but are in contrast with a Latin American study in which male patients were more frequently affected and most patients were taking proton-pump inhibitors before wide-spectrum antibiotics[21]. A recent study including 487 Mexican patients reported a slight predominance of male patients, a mean age of 47 years, abdominal pain in 52% of cases and fever in 45%. The mean duration of treatment was 9.7 days. Additionally, a therapeutic failure rate of 19% and a mortality rate of 18% were observed[12]. The mean age of that population and the frequency of the main clinical signs and symptoms are not consistent with our own results.

Nearly one-half of the patients included in our study (43.75%) had a base diagnosis of cerebrovascular disease. In this regard, a study by *Dasenbock, et al*.[22] on 18 007 patients who underwent neurosurgery for cerebral aneurysm repair after subarachnoid hemorrhage reported that 1.9% (346) of patients developed CDI. In this population, CDI was not associated with a higher mortality but with a longer hospital stay. A CDI prevalence of 0.4% was reported in a neurointensive care unit in another study[23]. In that population, 77% of patients received antibiotic treatment previous to CDI diagnosis. The most frequently prescribed drugs before CDI were cephalosporins (71%), piperacillin/tazobactam (28%), vancomycin (28%), gentamicin (14%), and meropenem (14%). Only one-third of those patients developed fever and leukocytosis at the onset of CDI. In our case series, vascular disease was associated with a long-term hospital stay, while the most prescribed antibiotics were cephalosporins (second, third, and fourth generation) in 12 patients (75%) and carbapenems in four. As a part of CDI treatment, the discontinuation of the wide-spectrum antibiotics that disrupted the intestinal microbiota is mandatory. Antibiotic treatment for mild/moderate or severe CDI is associated with a recurrence rate of 20-30%. In our study, almost one-quarter (23%) of patients developed recurrent CDI (rCDI). In our series, these patients received rifaximin along with FMT. In this context[24], demonstrated in a meta-analysis that fidaxomicin provided higher cure rates than vancomycin. Unfortunately, fidaxomicin was not administered to our patients due to its high cost and lack of availability in our institution. FMT was provided to our severe CDI or rCDI patients after antibiotic treatment, leading to clinical improvement with no secondary effects. Several reports have confirmed that FMT is a highly effective and safe therapeutic tool for rCDI[25-29]. It should be noted that some patients failed to achieve cure after a single FMT course. The number of previous CDI-related hospitalization events seems to be strongly associated with an early therapeutic failure[30,31]. Despite these findings, FMT is a suitable alternative to antibiotic treatment for rCDI, with a high success rate, low cost, and no severe secondary effects[32]. Novel antibiotics, monoclonal antibodies, and FMT have been recently proposed to reduce the incidence of rCDI, while approaches such as vaccines and a reduction of intestinal dysbiosis have been proposed to prevent CDI. These strategies are required to cope with C. difficile, a resilient pathogen that can persist in the environment and in the host, perpetuating its dissemination and the recurrence of infections.

Conclusion

Despite the limitations of this study (a small number of patients with confirmed CDI and a diagnosis based only on immunological test instead of a molecular method to detect ribotypes), it showed that the neurological population is particularly predisposed to develop CDI due to the concomitant presence of corticosteroid use, obesity, and/or diabetes (before the use of extended-spectrum antibiotics). Considering the severe clinical and economic impact of CDI in healthcare settings, antibiotic stewardship programs must be enforced, ensuring the rational use of antibiotics, to decrease the risk of CDI.

Conflict of interest

The authors declare that there is no conflict of interest with respect to the publication of this article.This article has no financing support.

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Authors'contributions

Conception and design of the study, TEI, AMV, CG. Acquisition of data, TEI and AMV. Analysis and interpretation of data, CG and SHJ. Drafting the article, TEI, AMV, CG, SHJL. Critical revision of the manuscript content, CG and SHJL.

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