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ORIGINAL ARTICLE

Characteristics of Inflammatory Bowel Disease in Three Tertiary Health Centers in Southern Nigeria

Caractéristiques des maladies inflammatoires de l'intestin dans 3 centres de santé de niveau 3 au sud du Nigeria

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ABSTRACT

BACKGROUND: **Inflammatory bowel disease (IBD) refers to two chronic inflammatory disorders of the gastrointestinal tract which is generally believed to be rare in most African countries. The objectives of the current study were to present the experience of three tertiary gastroenterology centers in southern part of Nigeria on IBD, highlighting the age distribution of the patients seen, management and the impact on the quality of their life in university-based community-type practices in Nigeria.**

METHODS: **This was a retrospective review of charts of inflammatory bowel disease seen between January 2007 and June 2010 at three teaching hospitals in Southern Nigeria. Diagnosis of IBD was made from clinical manifestations, colonoscopic and histopathological findings.**

RESULTS: **During the study period, 12 patients presented with clinical features consistent with inflammatory bowel disease. There were 8 (66.7%) males and 4 (33.3%) females and had ages ranged from 18 years to 80 years with a median of 26.5 years. Eight (66.7%) patients had ulcerative colitis while 4(33.3%) had Crohn's disease. Ten {83.3%) patients had severe disease with main clinical features being recurrent diarrhoea and passage of mucoid bloody stools. All the patients had treatments with sulphasalazine or mesalazine, steroids and antibiotics with good responses. One patient died following the occurrence of toxic megacolon.**

CONCLUSION: **Although IBD is uncommon in Nigeria, high index of suspicion is necessary by attending physicians managing patients with recurrent passage of mucoid bloody stools. Prompt gastroenterological referral and judicious use of colonoscopy and biopsy will assist in making the diagnosis.**
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Key words: Inflammatory bowel disease, colonoscopy, Nigeria, treatments, Sulphasalazine.

RÉSUMÉ

CONTEXTE: Les maladies inflammatoires de l'intestin (MII) sont constituées par des anomalies inflammatoires chroniques du tractus gastro intestinal et sont supposées rares dans beaucoup de pays Africains.

Les objectifs de cette études étaient de présenter l'expérience de 3 centres de gastro entérologie de niveau 3 au sud du Nigeria sur les MII en mettant en exergue la distribution de l'âge des patients suivis, la prise en charge et l'impact sur la qualité de leur vie dans un contexte de pratiques de type communautaire par l'Université au Nigeria.

MÉTHODES: Il s'agissait d'une revue rétrospective de dossiers médicaux de patients présentant une maladie inflammatoire intestinale suivis entre Janvier 2007 et Juin 2010 au niveau de 3 hôpitaux universitaires du sud du Nigeria. Le diagnostic de MII était posé sur la base de manifestations cliniques, de la colonoscopie et des résultats de l'histopathologie.

RÉSULTATS: Durant la période d'étude, 12 patients étaient suivis pour des manifestations cliniques évoquant une maladie inflammatoire intestinale. On comptait 8 hommes (66,7%) et 4 femmes (33,3%), la médiane d'âge était de 26,5 ans pour des extrêmes de 18 et 80 ans. Huit (66,7%) patients présentaient une colite ulcérée tandis que 4 (33,3%) présentaient une maladie de Crohn. Dix {83,3%) patients étaient sévèrement atteints avec comme manifestations principales des diarrhées récurrentes et des selles glairo sanglantes. Tous les patients ont été traités par du sulphasalazine ou du mesalazine, des stéroïdes et des antibiotiques avec de bonnes réponses. Un patient est décédé au décours d'un mégacolon toxique.

CONCLUSION: Bien que les MII soient rares au Nigeria, un haut niveau de suspicion est nécessaire de la part des praticiens hospitaliers prenant en charge des patients présentant des selles glairo sanglantes. Une prompte référence en gastro entérologie et l'utilisation judicieuse de la colonoscopie avec biopsie permettront de poser le diagnostic.
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Mots clés: Maladie inflammatoire intestinale, colonoscopie, Nigeria, traitements, Sulphasalazine.

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Abbreviations: CD, Crohn's disease; **ESR,** Erythrocyte sedimentation rate**; IBD,** Inflammatory bowel disease; **UC,** Ulcerative colitis;

INTRODUCTION

Inflammatory bowel disease (IBD) refers to two chronic inflammatory disorders of the gastrointestinal tract with recognizable phenotypic differences between them. They have uncertain etiology and are not infrequently associated with extra intestinal manifestations.[1,2] Knowledge of the prevalence of IBD in different geographic areas or among different ethnic groups may provide insights into possible aetiologic factors.[3,4] Similarly, temporal trends in the prevalence rates in a given area can provide valuable clues about etiology.

The highest incidence and prevalence rates for ulcerative colitis (UC) and Crohn's disease (CD) are reported from Israel, North America and northern Europe.[5,6] Prevalence rates of 200 for the more frequently encountered UC and 90 for the less frequent CD per 100,000 have been reported in the United States.[6] The lowest prevalence rates are reported from South America, southeast Asia, Africa (with the exception of South Africa), and Australia.[2,5,6] Although these data suggest that a gradient exists from north to south, they could also indicate variation in access to, and quality of health care, as well as, different extents of industrialization, sanitation, and hygiene.[2]

Different prevalence rates could also result from different genetic backgrounds of the residents of these parts of the world. Genetic studies highlight the importance of host–microbe interactions in the pathogenesis of these diseases.[1,2] Prominent among these genetic findings are genomic regions containing nucleotide oligomerization domain 2 (NOD2), autophagy genes, and components of the interleukin – 23 – type 17 helper T-cell (Th17) pathway.[1] The NOD2 protein is an intracellular sensor of bacterial peptidoglycan, and autophagy enables cells to regulate and degrade diverse intracellular components including pathogens. The autophagy gene, *ATG16L1,* has been associated with Crohn's disease but not, thus far, with ulcerative colitis.[2] The interleukin – 23 – Th17 pathway mediates microbial defense and intestinal inflammation. Multiple genes regulating this pathway have been associated with both CD and UC.

More important factors, however, seem to be environmental factors. This hypothesis is supported by increasing prevalence rates among immigrants from low-incidence regions moving to developed countries and a correlation of prevalence rates with industrialization in Hong Kong and mainland China.[7,8]

In Nigeria, only sporadic case reports have been published.[9,10] This study is a case series of inflammatory bowel disease seen in three leading tertiary gastroenterology centers in the southern part of Nigeria with the aim of highlighting the clinical feature and the impact of the disease on the quality of life of the affected patients.

SUBJECTS, MATERIALS AND METHODS

This was a retrospective review of cases of inflammatory bowel disease seen between January 2007 and June 2010 at Obafemi Awolowo University Teaching Hospitals Complex, University College Hospital, and Nnamdi Azikiwe University Teaching Hospital. Obafemi Awolowo University Teaching Hospitals complex, Ile-Ife, Osun State, southwest Nigeria, is a referral tertiary health facility that provides specialized and comprehensive medical care to the immediate community and beyond. University College Hospital is a 1000 bed tertiary healthcare institution in Nigeria offering curative services in several disciplines of medicine located in Ibadan, Oyo state, southwest Nigeria. Nnamdi Azikiwe University Teaching Hospital is one of the leading referral teaching hospital in Anambra state, southeast Nigeria. The hospitals have active medical and surgical gastroenterology unit with functioning endoscopy suite.

Diagnosis of IBD was made by review of the patients' original medical records including ileocolonoscopies. Diagnosis of CD was confirmed when at least two of the criteria published by Landers et al. were fulfilled (Table 1).[11] Diagnosis of UC was based on barium enema findings, endoscopic appearance and continuity of inflammation, histology, and proven exclusive involvement of the colon. Both clinical conditions were further substantiated by histopathology. The data extracted from patients' record such as age of onset of symptoms, age at time of diagnosis, location of disease, severity of the disease, current treatment, incidence of relapse and treatment since diagnosis were recorded in a standard proforma. The severity of the disease was graded according to Truelove and Witts classification, as well as, Sutherland *et al.*classification (Table 1).[12,13] Thus severe disease was present if diarrhea stool were passed more than six times per day, constitutional signs were present, hemoglobin level was less than 10gm/dl and the erythrocyte sedimentation rate (ESR) was greater than 30mm/hr. Mild disease was characterized by passage of less than 4 diarrhea stools per day, no constitutional symptoms, anemia or elevated ESR. Moderate severe disease falls in between the two grades. The physicians' opinions of the severity were also noted. Data entry and analysis were carried out through the use of SPSS version 16.0. Univariate analysis was carried on all the socio-demographic, clinical, investigative and treatment variables.

RESULTS

Patients' Characteristics

During the study period, 12 patients were diagnosed with inflammatory bowel disease; these consisted of eight (66.7%) males and four (33.3%) females. The patients' ages ranged from 18 years to 80 years with a median of 26.5 years. The ages fell into two groups which are 18 to 40 years (nine; 75%) and 60 to 80 (three; 25%) years (Table 2). All the patients had at least primary school education. About two thirds [seven (58.3%)] of the patients were undergraduate students, two (16.7%) patients were civil servants, and one patient each was a farmer, retiree and a house wife.

Clinical Manifestations

The duration of symptoms and signs ranged from 1 to 22 years. The median delay of treatment was five years. The main presenting complaints in all the patients were diarrhea and passage of mucoid bloody stools. Other symptoms

Table 1: Diagnostic and Severity Criteria for Inflammatory Bowel Disease

A. Diagnostic criteria for Crohn's disease adapted from Landers et al. 2002[11]

1. Clinical – perforating or fistulizing disease, obstructive symptoms secondary to smallbowel stenosis, or stricture;
2. Endoscopic – deep linear or serpiginous ulcerations, discrete ulcers in normal-appearing mucosa, cobblestoning, or discontinuous or asymmetric inflammation;
3. Radiographic – segmental disease (skip lesions), small-bowel or colon strictures, stenosis, or fistula; and
4. Histopathologic – submucosal or transmural inflammation, multiple granulomas, marked focal cryptitis or focal chronic inflammatory infiltration within and between biopsies, or skip lesions, including rectal sparing in the absence of local therapy.

*Diagnosis of CD was defined by the presence of a combination of established features from at least 2 of the above categories.

B. Disease Activity in Ulcerative Colitis (adapted from Truelove and Witts[12])

	Mild	Moderate	Severe
Bloody stools/day	< 4	4 or more if	≥ 6 and
Pulse	< 90 bpm	≤ 90 bpm	> 90 bpm or
Temperature	< 37.5 °C	≤ 37.8 °C	> 37.8 °C or
Hemoglobin	> 11.5 g/dL	≥ 10.5 g/dL	< 10.5 g/dL or
ESR	< 20 mm/h	≤ 30 mm/h	> 30 mm/h or
or CRP	Normal	≤ 30 mg/L	> 30 mg/L

**CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.*

C. Sutherland Disease Activity Index for ulcerative colitis (requires sigmoidoscopy or colonoscopy)[13].

Score	0	1	2	3
Stool frequency	Normal 1–2 ×/day	> Normal	> Normal 3–4 ×/day	5 ×/day
Rectal bleeding	None	Streaks	Obvious	Mostly blood
Mucosal appearance	Normal	Mild friability	Moderate friability	Exudation, spontaneous bleeding
Physician's rating	Normal	Mild	Moderate	Severe

**Total disease activity score (= sum of the item scores): 2 = remission; 3–5 = mild; 6–10 = moderately active; 11–12 = severe.*

at presentation include weight loss [eight (66.7%)], tenesmus [five (41.7%)], abdominal pain [five (41.7%)], and fever [three (25%)]. No extra intestinal manifestation was seen in all the patients. None of the patients had family history of inflammatory bowel disease. No history of cigarette smoking in all the patients. Prior to presentation, patients had been on various regimens of antidiarrhea and antibiotics. Two patients had been treated for abdominal tuberculosis while one patient had had appendectomy on account of same symptoms. Only seven patients had record of their body mass index (BMI) at presentation. The range of the BMI was 12.5 to 19.4 with a median of 16.0. All the patients had reduced body mass indexes compared with the average for the age and sex of the patients.

Laboratory, Radiological and Colonoscopic Findings

The pack cell volumes (PCV) of the current cohort range from 15 to 44% with median of 27%. Seven out of nine of the patients had PCV were less than 30%, while the white blood counts and the platelet counts were all within normal limits. Six of eight patients had serum potassium less than three. Of the eight patients that had record of serum protein, only one patient had normal serum protein, others had hypoproteinemia. Stool for ova of parasite demonstrated positive cysts of entamoeba histolytical in four (33.3%) patients. Only three patients had barium enema done. The finding on barium enema include thickening colonic wall in one patient, narrowing of sigmoid colon in another and tram-line appearance of the descending and sigmoid colon in the third patient. Only one patient had computerized tomography scan done and the essential finding was thickening colonic and rectal wall. Eight (66.7%) patients had colonoscopic features suggestive of ulcerative colitis while four (33.3%) had features suggestive of Crohn's disease. The colonoscopic findings were presented in Table 3. Mucosa biopsies were congruent with the endoscopic diagnosis in eight (66.7%) patients while the histopathological diagnosis in the other patients were none specific colitis.

Table 2: Socio-demographic data and diagnosis of patients with IBD in Nigeria

Variables	Frequency	Percentages
Sex		
Male	8	66.7
Female	4	33.3
Age		
< 30	7	58.3
31 – 40	2	16.7
41 – 50	0	0.0
51 – 60	0	0.0
61 – 70	1	8.3
71 – 80	2	16.7
Diagnosis		
Ulcerative colitis	8	66.7
Crohn's disease	4	33.3

Treatment

All the patients had treatments with sulphasalazine or mesalazine, steroids and antibiotics with good responses as evidenced by reduction in frequency of

Table 3: The Distribution of the Bowel Involved, Colonoscopic Findings, Histological Diagnosis. Treatment and Outcome of Treatment in Patients with IBD in Nigeria

Serial No	Patient Identification	Part of bowel affected	Colonoscopic finding	Histological diagnosis	Drug used	Outcome
1	OO	Ileum,,entire colon, rectum, anal canal	Loss of mucosal fold, Ulceration, cobbleliness,	Nonspecific colitis	Sulphasalazine Steroids	Relapse once
2	SA	Sigmoid colon	Hyperemia, ulceration, bleeds on contact	Ulcerative colitis	Sulphasalazine Steroid	No Relapse
3	OE	Rectum, sigmoid colon	Hyperemia, ulceration, bleeds on contact	Ulcerative colitis	Sulphasalazine Steroid	No Relapse
4	ES	Entire colon	Loss of vascular pattern, ulceration, hyperraemia, granularity	Nonspecific colitis	Sulphasalazine Mesalazine Steroid	Relapse twice
5	OS	Rectum, sigmoid colon	Hyperemia, ulceration, bleeds on contact	Ulcerative colitis	Sulphasalazine Steroid	No Relapse
6	AA	Rectum, sigmoid colon	Loss of vascular pattern, ulceration, hyperraemia	Nonspecific colitis	Sulphasalazine Steroid	Relapse once
7	OO	Rectum, sigmoid colon	Hyperemia, ulceration, bleeds on contact	Nonspecific colitis	Sulphasalazine Steroid	No Relapse
8	OI	Descending, sigmoid colon	Spasticity and hyperaemia of the mucosa, ulcers, sloughs and purulent exudates	Crohn's disease	Sulphasalazine Steroid Antibiotics Infliximab	Relapse once
9	UH	–	Showed Edematous, granular mucosa with ulcerations, erosion and obliteration of the vasculature	Ulcerative colitis	Mesalazine Antibiotics Steroid	Relapse once
10	BG	Entire colon	Hyperemia, ulceration, bleeds on contact, granularity	Ulcerative colitis	Sulphasalazine Steroid	No Relapse
11	LL	Descending, sigmoid colon, rectum	Erythematous mucosa with multiple polyps	Crohn's disease	Sulphasalazine Steroid	Died
12	CN	Descending, sigmoid colon, rectum	Loss of haustration, erythrema	Crohn's disease	Mesalazine Antibiotics Steroid	No Relapse

bowel movement and the abdominal pain. After stability, patients were weaned off steroids. One patient died following a relapse and an episode of toxic megacolon which did not respond to routine treatment. Patients had had right hemicolectomy about 22 year ago when he had similar severe attack. Infliximab was prescribed but was not available anywhere in the country at the time. Before the drug could be sent from abroad, patient deteriorated and died. Six (50%) patients had at least one episode of relapse which was managed by the addition of steroid. During these periods of relapses, these patients missed schools or work frequently.

DISCUSSION

IBD is generally believed to be rare in most African countries except South Africa.[2] Several reasons have been adduced for the rarity of the disease. These include good breast feeding culture, low antibiotic exposure, exposure to sunlight, lower birth rank, absence of tap water, large or poor families with several children, crowded living conditions and consumption of contaminated foods.[2,3,14,15] Most of these factors are changing in Nigeria. There is improved sanitation, change in breast feeding pattern and adoption of western lifestyle.[16,17] Excessive sanitation might limit exposure to environmental antigens and impair the functional maturation of the mucosal immune system and induction of immune tolerance, which ultimately result in inappropriate immune

responses when re-exposed to these antigens later in life. Defects in the innate immune system allow bacteria to invade the gut mucosa, resulting in an exaggerated adaptive immune response, which leads to extensive bowel damage.[1] However, some believe that the rare nature of the disease may be apparent and not real due to lack of specialized personnel with appropriate equipment to make such diagnosis, difficulty in monitoring continuity in the care of the individual patients, sketchy nature of medical record, relative commonness of other causes of bloody diarrhea.[18] This index report from three large gastroenterology units in Nigeria showed that IBD may not be uncommon as it was previously stated. With increasing availability and accessibility of specialized personnel equipped with technical ability to make the diagnosis in Nigeria, more of such diagnosis will be made. It then implies that high index of suspicion should be entertained by physicians attending to patients that present with recurrent diarrhea and prompt referral should be done so that prompt diagnosis and treatment could be instituted.

In the context of Africa where there are several other causes of mucoid bloody stool, the diagnosis of IBD can only be made as a diagnosis of exclusion. In this cohort, the natural history of the disease, as well as response of the patients to treatment was highly in keeping with IBD. Unfortunately, a third of the patients' stools were positive for cysts of entamoeba histolytica at presentation and they were all treated for amoebiasis with metronidazole with no relief of symptoms. Recent studies from Turkey showed similarly high prevalence of Amoebiasis in patients with IBD.[19,20] Though the role of Entamoeba is not known, it has been suggested that it plays a role in exacerbation of IBD.[21]

The ages of the patient in this study fell into two categories, the young adult and the elderly. Most of the young adults developed the disease either in childhood or adolescence. However, unlike data from the developed countries where early onset IBD account for only 25% of cases, early onset IBD was seen in 75% of our study population.[22] Reasons for this disparity is not very obvious. As shown in this report, the uniqueness to early-onset disease is the potential for linear growth impairment as evident by low body mass index and reduced serum protein as a complication of under treated inflammation.

Diagnosing IBD and differentiating between UC and CD is not an easy task because of overlapping and distinct clinical and pathological features. In this study, colonoscopy supported by histopathology was used to differentiate the conditions. Colonoscopic features in ulcerative colitis include continuous involvement from the anus and extending proximally, diffuse cryptitis, erosions, loss of vascular pattern, normal ileocecal valve, and occasional periappendicular inflammation.[23,24] In Crohn's disease, skip lesions, cobblestoning, aphthous ulcers, longitudinal ulceration, ileocecal involvement, and anal lesions are seen.[24] CD generally involves the ileum and colon and it can also affect any region of the intestine, UC involves the rectum and may affect part of the colon or the entire colon (pancolitis) in an uninterrupted pattern. In CD the inflammation is often transmural, whereas in UC the inflammation is typically confined to the mucosa. Crohn's disease can be associated with intestinal granulomas, strictures, and fistulas, but these are not typical findings in UC.

Though none of our patients had serology testing done, serology antigen and antibody test are also useful in resolving some of the gray areas. Several studies have shown that perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) is a marker for UC while anti-*Saccharomyces cerevisiae* antibodies (ASCA) is a serology marker for CD.[25,26] These test were not done for any of our patient because the facility to perform the test were not available during the study period.

All of our patients presented with severe disease following Truelove and Witt's criteria. This is due to the fact that the disease had been neglected due to inaccurate diagnosis and inappropriate treatment. All this patients had received different forms of trado-medical and orthodox treatment prior final diagnosis. Prompt diagnosis and treatment have been shown to improve the quality of life in patients with this condition.[18,27] We suggest prompt referral of patients with recurrent bloody mucoid stool for colonoscopic assessment. The presence of severe disease among our patients may also suggest that those with mild to moderate disease are undetected because of low index of suspicion. Hence the actual prevalence of IBD may be higher than found in this study.

Follow up in these patients has presented a big challenge. Patients only presented to the hospital when they have relapse of symptoms. While one of the patients had died from the disease, the others were only seen during flares of the disease. Proto-colectomy would be the available therapy for our young patients with ulcerative colitis who have high chances of developing colorectal cancer from the condition.[9,18,27] None of these patients had surgical intervention. This may be due to the dread of surgery in most of our patients. We suggest better education of the patients on the disease and treatment.

This study did not show any patient with extra intestinal manifestation. The literature is replete with many such features such as erythema nodosum, psoriasis, Sweet's syndrome (acute neutrophilic dermatosis), primary sclerosing cholangitis (manifestations of chronic liver disease), ankylosing spondylitis, uveitis, episcleritis, and metabolic bone disease.[10,28] These extra intestinal manifestation can be a pointer to the presence of IBD. We hope that the more we diagnose the disease, the better the chances of identifying the possible pattern of extra intestinal manifestation common in our environment.

All our patients were treated with sulphasalazine and steroids. While these drugs had been shown to be useful in the management of IBD, recent introduction of cyclosporin and infliximab had revolutionised the treatment of active severe IBD.[27-29] These drug would have been used in the patient that died from the disease, but for the cost. Currently, medical treatment in Nigeria is based on out of the pocket payment due to fact that the National

health Insurance Schemes does not cover majority of the people as well as the bulk of chronic diseases. Further efforts should be made by the government to ensure the provision of the drugs for the few helpless patients.

This study have a major drawback because it is hospital based, however, it is a multi-centered study presenting the largest series in Nigeria. We hope this collaborative surveillance for the disease will encourage further study on this disease in Nigeria.

In conclusion, although IBD is still rare in Nigeria, high index of suspicion is necessary by the attending physicians who are managing patients with recurrent passage of mucoid bloody stool. Prompt gastroenterological referral and judicious use of colonoscopy and biopsy will assist in making the diagnosis. Since most of our patients are young, surgical intervention seems the available option to prevent the occurrence of malignant transformation.

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