Ulcerative Colitis and Crohn Disease in Cuban Pediatric Patients

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Abstract

Introduction: Inflammatory bowel disease includes ulcerative colitis and Crohn Disease (CD). About 25-30% of diagnosed patients correspond to pediatric age, with an increasing prevalence.

Objective: To characterize children with ulcerative colitis and Crohn disease.

Material and Method: A descriptive cross-sectional study was carried out that included 31 children with confirmed diagnoses of both entities according to the Lennard-Jones criteria, attended in the pediatric consultation of the Institute of Gastroenterology between 2017 and 2019. The variables were measured: age, sex, clinical manifestations, location, endoscopic and histological signs when diagnosing the disease and the current humoral immune response.

Results: A higher proportion of colitis (61.3%) than Cohn's disease (38.7%) was observed, but in the latter there was an increase of 25% of new diagnosed cases. The average at diagnosis is 10 years. It was predominantly male. The most frequent digestive clinical manifestations were diarrhea (83.9%) and abdominal pain (71%), as well as rectal bleeding in colitis ulcerative and enterocutaneous fistulas in the Cohn's desease. Nutritional status was affected in 29% of cases. The endoscopic study in colitis showed pancolitis (57.9%) and a degree II of activity (52.6%), while the Cohn's affected the terminal ileum in 58.4% with discontinuous and segmental lesions. Histological signs confirm the diagnosis in both entities. Crohn disease with 41.7% presented greater compromise of the humoral immune response.

Conclusions: The most frequent inflammatory bowel disease was ulcerative colitis, but there is a tendency to increase the cases diagnosed with Crohn disease, showing this greater compromise of the humoral immune response. A low frequency of complications and the affected nutritional status was found possibly at the appropriate time of diagnosis and treatment of the children studied.

Introduction

Inflammatory Bowel Disease (IBD) comprising mainly Ulcerative Colitis (UC), Indeterminate Colitis (IC), and Crohn Disease (CD). It is chronic and incurable with periods of relapse and remission. It has been postulated as a multifactorial disease, because genetic, immunological and environmental factors are involved in its pathogenesis [1,2].

After Burrill Bernard Crohn's publications in 1932, several studies have shown that lesions can spread anywhere in the digestive system, including extra-intestinal manifestations. IBD is increasingly diagnosed in pediatric age, and its incidence, especially CD, has increased worldwide [3].

Between 20% and 30% occur before the age of 20, preferably in adolescence, and only 4% debut before the age of five [1,2,4]. CD is more frequent in men and there are no differences in UC. The IBD mortality rate is low and is directly associated with the complications of UC and CD [2].

IBD in children has clinical and psychosocial peculiarities that differentiate it from adults, conditioning different therapeutic approaches. Long-standing CD, upto 40% presents growth retardation when adequate nutritional treatment is not established, and may be the initial symptom and even in 5% be the only sign of the disease [5,6].

A multicenter study, carried out in Cuba for 20 years, covered both diseases in children 4 and showed that they are not so infrequent in our setting and that there must be a high index of clinical suspicion to make an early diagnosis.

The literature reviewed shows few studies in Cuba that broadly address both diseases, with the largest number in the adult population [4,7]. Hence the importance of this study to help characterize these diseases in pediatric patients at the institution.

Material and method

A cross-sectional descriptive study was carried out with the aim of characterizing pediatric patients with UC and CD treated at the pediatric consultation of the Institute of Gastroenterology of Cuba, between the years 2017 and 2019. The sample consisted of 31 minor patients 18 years of age who were under follow-up at the institution in this period, with a clinical, endoscopic, histological and/or radiological diagnosis of Ulcerative Colitis or Crohn disease according to the widely accepted criteria of LennardJones [8,9,10] (Supplementary Tables).

In it, the following variables are evaluated at the time of diagnosis: age, sex, clinical manifestations, nutritional assessment using the Cuban anthropometric graphs in relation to sex and percentiles [7]: Weight/height (W/H), Height/Age (H/A), Weight /Age (W/A) and Body Mass Index (BMI) [weight (kg)/ Height (m)^2] /age, was evaluated, maximum extension according Montreal classification, [8,11] endoscopic signs according to the Mayo classification, [8,12] histological signs according Flore`n classification [13].

Associated immunological disorders: Immunoglobulins (Ig) according to cut-off points: Immunoglobulins (IgG): low<3.70, normal=3.70-14, high>14, Immunoglobulins (IgA): low <0.50, normal=0.30-1.70, high>2.3, Immunoglobulins (IgM): low <0.30, normal=0.50-2.3, high>1.70, C-reactive protein (CRP): semi-quantitative method of CPR- LATEX Agglutination, Rheumatoid factor (RF): [14] positive >15 negative ≤15, and ASCA Combi ELISA: [15] positive o negative.

All the patients included in the study, after communicating with the child, parent or guardian and after obtaining their authorization, underwent a review of the medical history in order to obtain the necessary data for the investigation, and immunological studies were indicated. The information obtained was recorded in a data collection notebook prepared for this purpose and processed in a Microsoft Excel database. For the descriptive analysis of the data, measures of absolute frequencies and percentages were used, for qualitative variables, and for quantitative variables, the mean, median and standard deviation were used. The results are presented in tables and graphs.

The study was carried out in accordance with the principles established in the Declaration of Helsinki [16]. The confidentiality of all personal information collected from medical records in the development of the investigation was ensured. The research project was approved by the Scientific Council and the Institution's Ethics Committee.

Results

In this study, 31 children with a diagnosis of IBD were included (Figure 1 & Table 1); with UC being the most frequent 61.3% with respect to CD, which resulted in 38.7%. Five new cases were diagnosed, 16.1% of all affected patients, with a greater increase in CD compared to UC with 25% and 10.5%, respectively.
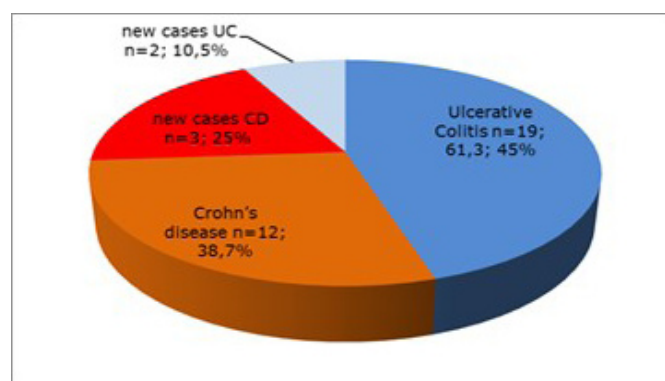

Figure 1: Pediatric patients according to the diagnosis of Ulcerative colitis and Cohn disease.

Table 1: Pediatric patients according to the diagnosis of Ulcerative colitis and Cohn disease.

Diagnosis	No (%)	New Cases No (%)
Ulcerative colitis	19 (61,3)	2 (10,5)
Crohn disease	12 (38,7)	3 (25,0)
Total	31 (100)	5 (16,1)

In Table 2. At the time of diagnosis, the age group of 5 to 9 years prevailed in UC with 52.6% and a mean age of 7.9 ± 4.4 years, while in CD the ages between 15 to 18 years for 75%, the mean age being 13.7 ± 5.5 years. In general, it was observed that the average age at diagnosis is approximately 10 years. Predominant in both entities, the male sex was more evident in UC with a 2:1 ratio. In CD there were no differences between both sexes.

Among the main clinical manifestations, UC presented a similar proportion of diarrhea and rectal bleeding (84.2%), sub-

sequently abdominal pain (73.7%). Also in CD, diarrhea (83.3%) and abdominal pain (66.7%) predominated, in addition to the enterocutaneous fistula (33.3%). There were extra-digestive manifestations that marked the debut of the disease such as weight loss in both entities, with 26% in UC and 33.3% in CD. Together, anemia and arthralgia were observed in UC with 26.3% and 21.1%, respectively, while aphthous stomatitis was found in 4 children (33.3%) with CD. On the other hand, 29% had an impact on nutritional status, five with malnutrition for 16% and three of them with a diagnosis of UC. 13% were thin with the same number of patients in both diseases. Only three children were affected by height, all diagnosed with UC; one with malnutrition and two with a normal weight. Adequate weight predominated in 71% of the children studied, and there were no overweight or obese children.

Table 3 shows the endoscopic and histological changes. According to endoscopy, pancolitis prevailed with 57.9% and grade II activity in 52.6% of all cases with UC. On the other hand, CD was located mainly in the terminal ileum, representing 58.4%, and discontinuous and segmental endoscopic lesions were seen in 100% of the patients, while fistulas and stenosis were observed in only three children (25%). Histologically according to the Floren [13] Classification for UC, grade 2 of activity was the one with the greatest impact with 57.9%, followed by grade 3 with 26.3%. Furthermore, CD confirms, mainly in 11 patients (91.7%), the presence of ulcers in the mucosa that settle on lymphoid aggregates and a transmural inflammatory infiltrate, predominantly macrophages, plasma cells, histiocytes, and lymphocytes that invade the lamina propria.

To a lesser extent, non-caseous granulomas were found in 3 children for 15.8%.

Table 2: Patients with Ulcerative Colitis and Crohn disease according to demography, digestive, extra-digestive clinical manifestations and nutritional status at the time of diagnosis.

		UC (n=19) No (%)	CD (n=12) No (%)	IBD (n=31) No %
Mean age at diagnosis (years)		5-9 (7,9 ± 4,4)	15-18 (13,7 ± 5,5)	10
Sex				
Female		6 (31,5)	6 (50)	12 (38,7)
Male		13 (68,4)	6 (50)	19 (61,3)
Digestive clinical manifestations Diarrhea		16 (84.2)	10 (83.3)	26 (83.9)
Rectal bleeding Diarreas		16 (84.2)	3 (25.0)	19 (61.3)
Abdominal pain		14 (73.7)	8 (66.7)	22 (71.0)
Stool mucus		9 (47.4)	2 (16.7)	11 (35.5)
Abdominal distension		1 (5.3)	2 (16.7)	3 (9.7)
We have		1 (5.3)	2 (16.7)	3 (9.7)
Vomiting		1 (5.3)	1 (8.3)	2 (6.5)
Anal fissure		0 (0.0)	2 (16.7)	2 (6.5)
Enterocutaneous fistula		0 (0.0)	4 (33.3)	4 (12.9)
Extradigestive clinic Systemic	al manifestations Decay	0 (0.0)	3 (25.0)	3 (9.7)
	Fever	2 (10.5)	1 (8.3)	3 (9.7)
	Weightloss	5 (26.3)	4 (33.3)	9 (29.0)
Orales	Aphthous stomatitis	3 (15.8)	4 (33.3)	7 (22.6)
Cutaneous	Erythema nodosum	0 (0.0)	1 (8.3)	1 (3.2)
Articular	Peripheral arthritis	0(0.0)	1 (8.3)	1 (3.2)
	Arthralgia	4 (21.1)	0 (0.09	4 (12.9)
Liver	Hypertransaminasemia	3 (15.8)	0 (0.0)	3 (9.7)
Hematological	Anemia	5 (26.3)	6 (50.0)	11 (35.5)
Nutritional assessment / Size impairment * Normal		14 (73,5)	8 (66,6)	22 (71)
Of it: with size involvement		2	-	-
thin		2 (10,5)	2 (16,7)	4 (13)
Malnutrition		3 (16.0)	2 (16,7)	5 (16.0)
Of it: with size involvement		1	-	-

UC: Ulcerative Colitis; CD: Crohn Disease; IBD: Inflammatory Bowel Disease.
* Note: Anthropometric Charts for nutritional assessment of 0-19 years in Cuba were used for nutritional assessment and height involvement for age [7]. The table shows the absolute frequency (relative frequency), except for the sex that shows the mean ± the standard deviation

Table 3: Patients with Ulcerative colitis and Crohn disease according to endoscopic and histological alterations.

	UC (n=19) No (%)	CD (n=12) No (%)
Initial disease location (UC) E1: Proctitis	7 (36,8)	
E2: Left-sided UC; E3: proximal extent of inflammation is distal to the rectosigmoid	1 (5,3) 11 (57,9)	
Degree of endoscopy activity Grade I (Erythema, decreased vascular pattern, edema, and slight friability (bleeding from rubbing) of the mucosa.)	3 (15,8)	
Grade II (Marked erythema, absence of vascular pattern, friability and erosions. Presence of small amount of blood.)	10 (52,6)	
Grade III (Severe involvement, spontaneous bleeding and presence of discrete ulcers.)	5 (26,3)	
Grade IV (Significant amount of blood, large, irregular, confluent ulcers, stenosis, pseudopolyps, mucous bridges, grafted neoproliferative processes, fistula, microcolon)	1 (5,3)	
Initial disease location L1: Terminal ileum L2: Colon L3: Ilecolon		7 (58,4) 4 (33,3) 1 (8,3)
Endoscopic Changes Discontinuous, segmental and asymmetric involvement		12 (100)
Canker sores and linear ulcers		10 (83,3)
Mucosa with a paved appearance		7 (58,3)
Eritema focal no friable		4 (33,3)
Degree of histological activity Grade 1 (normal mucosa) Grade 2 (isolated inflammatory cells or aggregates of lymphoplasmocytic or eosinophil cells)	3 (15,8) 11 (57,9)	
Grade 3 (marked increase in inflammatory cells with some changes in secretory cells, mild atrophy)	5 (26,3)	
Histological alterations Transmural inflammatory infiltrate with a predominance of macrophages, plasma cells, histiocytes and lymphocytes that invade the lamina propria.		11 (91,7)
Mucosal ulcerations that settle on lymphoid aggregates.		11 (91,7)
Mucosa and submucosa with prominent lymphoid aggregates		7 (58,3)
Epithelioid macrophages		5 (41,7)
Multinucleated giant cells en mucosa y submucosa.		5 (41,7)
Non-caseous granulomas.		3 (15,8)

UC: Ulcerative Colitis CD: Crohn Disease. The table shows the absolute frequency (relative frequency).

As shown in Table 4, the humoral immune response was compromised in 35.5% of the total cases studied, of which 31.6% corresponded to UC and 41.7% to those with CD. The most compromised variable in UC was IgG in 15.8% and in CD ASCA in 25%.

Table 4: Immunological disorders according to diagnosis.

	UC (n=19)	CD (n=12)	Total (n=31)
IgA altered	1 (5,3)	1 (8,3)	2 (6,5)
IgG Altered	**3 (15,8)**	0 (0,0)	3 (9,7)
Positive PCR	0 (0,0)	1 (8,3)	1 (3,2)
ASCA positive	2 (10,5)	**3 (25,0)**	5 (16,1)
Total	6 (31,6)	5 (41,7)	**11 (35.5)**

UC: Ulcerative Colitis; CD: Cohn Disease.

Discussion

Currently, despite the few epidemiological studies that exist in the pediatric age and in Cuba, an increase in the incidence and prevalence rates of this disease has been observed, and most suggest that 20%-30% of patients are diagnosed during the childhood and adolescence, UC being more common than EC [1-4].

During the study period, the current situation of the 31 children diagnosed with IBD is evaluated; identifying a higher proportion of UC (61.3%) than CD (38.7%) and 5 new cases were diagnosed with a greater increase in EC (3) with respect to UC (2). Similar results evidenced by Vicentín R, in Argentina, (n=50) children with a diagnosis of IBD, of them with CD (40%), UC (50%) and 5 unclassified cases [16,17]. However, there are series that show a predominance of CD, such as that of Sýkova J, in the Czech Republic, which in 15 years included (n = 170) resulting in CD (105), UC (48) and 17 without classification [18,19].

The age distribution of the patients at the time of diagnosis was consistent with reports from other pediatric series that infer that UC is more common in preschoolers, while CD is more common in older children, with the most frequent average age being adolescence approximately 12 years [1-4]. In Cuba (year 2000), in a multicenter study in children with UC, the average age at diagnosis was 10-14 years, [4] in addition, in studies carried out by Gasparetto M et al., It was between 11 and 16 years [20].

In the children studied, the mean age at diagnosis in both IBD was 10 years, being higher than the studies seen in Argentina (9.7 years) [16]. and lower than that reported by Sýkova J et al. (14.2 years) [18]. These results could be directly related to the possibilities existing in the different regions of the country to make an early diagnosis of these diseases and not precisely because of delay in the appearance of symptoms. In general, the male sex predominated, mainly in UC with a 2:1 ratio, similar to most of the publications that have shown its relevance. Also the series of patients studied in the reports by Sýkova J, and Gasparetto M, in Italy [18,20]. Inverse situation to that described in series of adults 1-4 and to the reports in Cuba of Fragoso Arbelo T, García Bacallao in a pediatric series of UC, which found a predominance of the female sex [4].

The clinical manifestations are varied in IBD and depend on: the location of the disease, the intensity of the inflammation and the presence or absence of intestinal and extraintestinal complications [21-23].

The results obtained are similar to reports carried out internationally and to what has been described in the literature, with diarrhea and abdominal pain prevailing in both diseases, in addition to rectal bleeding in UC and the presence of enterocutaneous fistulas in CD in 33.3%, unlike what was reported by Vicentín R, which raises the presence of perianal fistulas more frequently [16,21-23]. Of the reports in Cuba, with a series of cases in 20 years, Fragoso Arbelo T et al. Found, in UC, the rectal bleeding (35) and diarrhea (17) of the cases studied, on the other hand, abdominal pain presented in 53.3%, diarrhea in 33.3%, and perianal disease in 46.6% of them [4].

IBD is considered a multisystemic disease in such a way that up to 30% of patients develop some type of extra-digestive manifestation throughout its evolution. In the children evaluated, the highest percentages are reported for weight loss in 26% of cases with UC and 33.3% of those with CD. Together, anemia and arthralgia were observed in UC with 26.3% and 21.1%, respectively, while aphthous stomatitis was only found in four children (33.3%) with CD. These reports are in agreement with what is stated in the literature and international publications. [1-5,21-24], However, Vicentín R found five cases of UC, two of them with autoimmune liver disease, two with Autoimmune Sclerosing Cholangitis and one with arthritis, also in CD four patients presented arthritis and one had erythema nodosum [16]. Hano García OM in Cuba found in 74 studied patients (28.9%) joint manifestations, followed by hepatobiliary manifestations in 33 patients (12.9%) and the hematological ones with 30 (11.7%) [25]. The impact on nutritional status usually occurs between 15 and 40% of children with IBD at some point in their evolution, correlating with growth retardation and suggesting that its etiology is multifactorial [5,22-23,26,27].

One of the most important concerns to consider for IBD in the pediatric population is the impact it has on growth. This study reports that height was only affected in UC patients,

three of the children studied affected growth and of these only one had malnutrition, the results not coinciding with that reported in the literature [21-23]. 29% of the patients at the time of diagnosis affected nutritional status, the highest percentage being in the CD (33.4%) with respect to UC (26.5%), coinciding with that proposed according to the literature, which estimates between 25%-42% of children with CD may be nutritionally affected and will even appear months prior to the digestive clinic [26,27]. Similar statistics were reported by Buderus, in a study of 1257 children who found nutritional status impairment in 38.8% of diagnoses with UC, while 60.3% belonged to those with CD [19].

Contrary to Vicentín R, information that only 12% of the patients studied were nutritionally affected [16].

In multiple cohort studies or pediatric IBD registries coincide at the time of disease debut, pediatric patients have a more extensive commitment than adults, with ileocolonic inflammation (L3 +/- L4) according to the Montreal classification., 8 the most frequent in EC and pancolitis for UC. [5,24,26-28].

The current study presented similar results, since CD was mainly located at the level of the terminal ileum followed by colic. Similarly, Vicentín R reported, children with UC (n=25), pancolitis (19) and CD (n=20) were detected ileocolic extension (16) [16]. Different results were those reported by Buderus S et al. In Germany, who reported the predominance of ileocolic localization (62.5%) in patients with CD and more than half of the involvement of the upper gastrointestinal tract, however, the pancolitis (71%) of those who lost UC [19]. Similar results were those of Gasparetto, in Italy he studied a pediatric population of 160 children, [20] and Oliva-Hemker in several centers in North America [17].

It is suggested that patients with UC diagnosed at a younger age have a more severe course of the disease, compared to those who start it at a later age [5,8,26,27]. In this study, the greatest number of children were diagnosed before 10 years of age and, coincidentally, most of them presented grade II and III endoscopic activity as established in the Mayo classification [8].

In CD, endoscopic lesions were observed discontinuously and segmentally in all the patients studied, and aphtoid and serpinginous ulcers predominated, with cobblestone appearance and focal erythema, and to a lesser extent fistulas and stenosis. The results obtained in this study coincide with those mentioned in the literature to confirm the diagnosis of this disease and at the same time agree with the established endoscopic criteria of Lennard-Jones [1,8].

The histological signs in UC cases also coincided with grade 2 given by isolated inflammatory cells or aggregates of lymphoplasmocytic or eosinophil cells. In CD, there were mucosal ulcers that settle on lymphoid aggregates and the transmural inflammatory infiltrate, predominantly macrophages, plasma cells, histiocytes, and lymphocytes that invade the lamina propria, as well as mucosa and submucosa with prominent lymphoid aggregates, epithelioid macrophages, and granulomas. non-cheesy in 25.0% of patients. These results coincide with those defined by the literature to confirm the diagnosis of these diseases and at the same time agree with the established histological criteria of Lennard-Jones [1,8] and those of Florén for UC [13].

The most widely studied serological markers are pANCA (neutrophil perinuclear anticytoplasmic antibody) and ASCA

(anti-Saccharomyces cerevisiae antibody). They are not routinely recommended, only in cases of difficult diagnosis. Its absence does not exclude the presence of IBD, especially in children. ASCA IgA and IgG have been found in most clinical series, with a specificity for CD of (95% one of the two or 100% both) and pANCA has a specificity of 92% for UC, which limits its usefulness as an independent diagnostic marker [1-4,15,22,26].

Both markers could not be measured in this study. However, the humoral immune response was little compromised in 35.5% of the total cases studied, in both diseases, which shows little dangerous results. In the EC there is a greater number of immunocompromised patients, with ASCA being the most compromised variable in 25%, while in UC, IgG is in 15.8%, these data agreeing with those shown in the literature for the EC, specifically related to positive ASCA that has a higher sensitivity for CE than for UC [15,27]. In this center, in 2016, Hano OM and collaborators in a study with adult patients diagnosed with UC, described the behavior of these immunological variables and did not obtain significant results, apparently because most of the patients were compensated for his illness [25]. Dubinsky M, in a study of 1928 children over a 10-year period (2002-2012) detected positive ASCA with a sensitivity of 41-76% and a specificity of 86%-98% for the diagnosis of CD [28]. While other studies do not demonstrate changed changes due to the low number of samples taken [16].

Most of the cases studied are under follow-up by outpatient consultation, where the pertinent measures are taken dynamically and individually to maintain adequate and affected intestinal flora, since this factor does not constitute a trigger for humoral decompensation, for which reason the behavior of the immunological variables, the fact that most of the patients were compensated at the time of taking the blood samples.

Conclusions

The most frequent inflammatory bowel disease was UC, but currently there is a tendency to increase cases diagnosed with CD, showing greater compromise of the humoral immune response. A low frequency of complications and the affected nutritional status was found possibly at the appropriate time of diagnosis and treatment of the children studied.

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