Inflammatory Bowel Disease

Chapter 3

# Early Diagnosis of Pediatric Crohn's Disease - Pointing Problems and Suggestions

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## 1. Introduction

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC) and can be diagnosed in childhood and adolescence in 25% of cases [1]. Children that contract IBD before 10 years of age almost always present with extensive colitis that cannot be classified as either UC or CD, and remain colitis not determined (IBD-U) until several years later [2].

Data from the literature on the time of diagnosis vary considerably. A pediatric IBD study in Germany found that the average time for CD diagnosis was 5 months (2-10 months), for the UC was 3 months (1-6 months) and IBD-U was 4 months (2-11 months) and the growth deficit was the most common sign in cases with late diagnosis [3]. Compared to this study, the time interval between the onset of symptoms and the diagnosis was 4 and 2 months in a recent French study (EPIMAD) [4,5] and 4 months in Noroega [5], 10 and 6 months in Italy [6] respectively for CD and UC.

The European study group recently published the record of new diagnoses of pediatric IBD, EuroKids aged 0-18 years between the years 2004-2009. This study gathered in 2087 patients, of which 59% were diagnosed with CD, 32% with UC and 9% as IBD-U. The mean age at diagnosis was 12.1 years (0.6-17, 9 years), and 56% boys [7].

Pediatricians should become familiar not only with the typical but also a typical presentations of IBD because 22% of children present with growth failure, anemia, perianal disease, or other extra-intestinal manifestations of the predominant only initial feature. A detailed fam-

ily history should be obtained because 20% of children with IBD have an affected relative [2].

This section will be discussed the diagnosis of pediatric CD.



## 2. Gastrointestinal Manifestations in Children and Adolescents With CD

The clinical manifestations of CD depend on the site of affected bowel, if it is in the upper gastrointestinal tract, the small intestine or colon, in the latter case simulating UC. The highlight of the clinical manifestations of CD is the presence of abdominal pain associated with warning signs such as fever, growth retardation, pubertal delay, weight loss, pallor and perianal involvement (fistulas, fissures and abscesses). Sometimes, the picture begins acutely with symptoms of inflammatory acute abdomen, mimicking acute appendicitis. Pediatric patients with CD exhibit more ilealdiseaseat the onset of disease than adult.Throughout evolution, complications may occur as stricture bowel loops manifested with symptoms of occlusion or entero-enteric, enterocutaneous, perianal fistulas or fistulas between bowel loops and adjacent organs such as the bladder and genital [1,2,8].

The growth deficit that precedes the diagnosis is the biggest difference in the child's presentation of CD when compared to adults. The delay of puberty and decreased final adult stature can occur when the disease occurs in adolescence and there is delay in the diagnosis of CD. Furthermore, persistence of the growth deficiency may be the only signal to the diagnosis and disease activity, not only in performance but during the course of disease [1.2].

To evaluate these aspects of pediatric CD, we prospectively selected 22 patients with mildly to moderately active CD, 29 patients with inactive CD and 35 controls, undergoing regular treatment at the Clinical Gastroenterology Outpatient Clinical of the University of Sao Paulo School of Medicine Hospital das Clinicas, Sao Paulo, Brazil. The mean values for lean body mass, Tanner stage, height-for-age Z score and BMI-for-age Z score were lower in the active CD group than in the inactive and control groups ($p < 0.05$ for both). When compared individually, 2 (9.1%) of the patients with active CD and 1 (3.4%) of those with inactive CD had short stature (height-for-age Z score <-2). In addition, 7 (31.8%) of the patients with active CD and 3 (10.3%) of those with inactive CD were malnourished (BMI-for-age Z score <-2). It is of note that some (4.2%) of our CD patients had a BMI-for-age Z-score> 2 standarddesviation [9].

It is important to note that the very early on set of IBD (younger than 2 years of life), is characterized by severe progressive colitis that can start before three months of life with failure to thrive, extensive colonic inflammation, perianal involvement, arthritis, folliculitis usually not compromising the small bowel, imposing differential diagnosis with monogenetics disease [10,11,12,13]. **Table 1** summarizes the main differences of the clinical picture between

CD and UC.

**Tabel 1:** Percentage of Clinical Presentation Inflammatory Bowel Disease in Children and Adolescents.

| Presenting Symptom | Crohn disease (% of patients) | Ulcerative Colitis (% of patients) |
|---|---|---|
| **General** | | |
| Weight loss | 55-80 | 31-38 |
| Fever | 38 | NA |
| Anorexia | 2-25 | 6 |
| Growth retardation | 3-4 | 0 |
| Lethargy | 13-27 | 2-12 |
| **Gastrointestinal tract** | | |
| Abdominal pain | 67-86 | 43-62 |
| Diarrhea | 30-78 | 74-98 |
| Rectal bleeding | 22-49 | 83-84 |
| Nausea/vomiting | 6 | <1 |
| Constipation | 1 | 0 |
| Perianal disease | 6-15 | 0 |
| Mouth ulcers | 5-28 | 13 |

**Abbreviations:** NA: not applicable. Range are derived from data reported by Kugathasan et al [14], Griffiths [15] and Sawczenko and Sandhu [16].

## 3. Extra-Intestinal Manifestations in Children and Adolescents with CD

Despite its name, IBD is not limited to the intestine and about 30% of patients develop a previous extra-gastrointestinal manifestation or during evolution of their disease [17].
The extra-intestinal manifestations of IBD can be divided into a few categories:

• Related colitis (skin, eyes, joints and mouth) that occur in parallel with disease activity

• Hepatobiliary

• Deceleration of growth

• Secondary complications of the disease (nephrolithiasis, obstructive uropathy, and gallstone pancreatitis)

• Other events, which do not meet any previous criteria (amyloidosis, cancer, vascular, hematologic, pulmonary, cardiac and neurological)

**Table 2** summarizes the main extra-intestinal manifestations in IBD in children and adolescents

**Table 2:** Prevalence of intestinal manifestations in children and adolescents with IBD

| Extra-intestinal manifestation | Prevalence in CD (% of patients) | Prevalence in UC (% of patients) |
|---|---|---|
| Pyoderma gangrenosum | | CR* |
| Joints/arthritis | ----- | 3.8 |
| Osteoporosis and osteopenia | 8-41 | 24-25 |
| Growth delay | 81 | 28 |
| Nephrolithiasis | CR | 3.2 |
| Autoimune hepatitis | ----- | 1.3 |
| Uveitis | ----- | 0.63 |
| Amyloydosis | | CR |
| Vascular damage | 4.2 | 0.63 |
| Pancreatitis | 3.9 | 2.5 |
| Anemia | 69 | 40.5 |

*Except where noted by CR (case report) CD total N in children ranges from 21 to 26 and UC total N ranges from 21 to158. Data from: Jose FA and Heyman MB [17].

## 4. Differential Diagnosis

The clinical presentation of mucous and bloody discharge diarrhea may cover several etiologies [1,2,8]:

• Infectious Colitis (Salmonella, Shigella, Yersinia, Campylobacter, Aeromonas, Mycobacterium tuberculosis and Entamoebahystolitic)

• Pseudomembranous colitis (Clostridium difficile)

• Hemolytic uremic syndrome (Escherichia coli 0157: H7)

• Parasitic (amebiasis, strongyloidiasis)

• Viral (cytomegalovirus and herpes simplex)

• Vasculitis (Henoch-Schönlein and Behcet's disease)

• Familial Mediterranean Fever (autosomal recessive disease)

• Acquired Immunodeficiency Syndrome (AIDS)

• Primary Immunodeficiency

**Table 3** summarizes the main symptoms and alarm signals to the primary immunodeficiency

**Table 3**: Alarm signs and symptoms for primary immunodeficiency

| |
|---|
| Positive family history of primary immunodeficiency |
| Consanguineous parents or > 2 family members with early-onset IBD Infantile (< 2 years) IBD |
| Severe, therapy-refractary IBD, particularly with perianal/rectovaginal disease/abscesses |
| Recurrent infections in the absence of immunosuppressant drugs (particularly pulmonary disease and skin abscesses) |
| Neutropenia, thrombocytopenia, or abnormal immune status (Ig levels) in the abcense of immunosuppressant drugs |
| Nail dystrophy and hair abnormalities (trichorrhexisnodosa) |
| Skin abnormalities (congenital eczema, albino) |

**Abbreviations:** IBD:inflammatory bowel disease; Ig: immunoglobulin. Data from: Levine et al [1]

The children with rectal bleeding can present ulcerative proctitis, which must be differentiated from other causes, such as anal fissure, hemorrhoids, polyps, and depending on the intensity of the intestinal bleeding, Meckel's diverticulum [1,2,8].

In children with pain in the lower right quadrant should be excluded acute appendicitis possibilities, tuberculosis and lymphoma. In patients with abdominal abscess, the differential diagnosis includes appendix or perforated vasculitis and trauma. In adolescents, should remember the gynecologic causes.

Moreover, it is necessary to differentiate the CD from UC, not always possible task when one does not have definitive pathologic findings of each disease, staying for some time Colitis denomination not determined (IBD-U) in 15% of cases [18].

When recurrent abdominal pain is the main symptom in children, it should be considered the possibility of dealing with functional gastrointestinal disease (FGID), especially if there is intestinal and extra-intestinal symptoms unspecific. Thus, the identification of critical features or "red flags" can help pediatricians recognize the patient with FGID abdominal pain or CD, avoiding tests unnecessary diagnoses in patients with FGID and on the other hand, to prevent the delay diagnosis of CD [19].

In the study by El-Chammas et al characteristics of abdominal pain patient FGID were distinct from abdominal pain in patients with CD: (1) greater stress reports and headache ($p < 0.001$), (2) higher prevalence of FGID in family (irritable bowel syndrome or constipation, $p < 0.05$) and (3) lower reporting hematochezia, weight loss, difficulty gaining weight and greater presence of vomiting ($p < 0.05$). However, waking up at night and joint pain did not differ between the two groups. In contrast, the presence of anemia, hematochezia, and weight loss was more predictive of CD (sensitivity 94%) [19].

## 5. Diagnostic approach of CD in children and adolescents

### 5.1. Clinical symptoms

The diagnosis of IBD consists of a few steps, starting from the initial clinical suspicion pediatrician, based on clinical symptoms and physical examination with the referral of suspected cases to the Pediatric Gastroenterologist [1,2].

### 5.2. Physical exam

The previous history data of height and weight are essential for detecting deceleration of the growth rate and weight loss. Furthermore, it should be observed if there is the presence of delayed pubertal development by Tanner scale [20].

Examines the color of mucous membranes to detect pallor (anemia), clubbing of finger nails and watch glass (present in chronic disease). The oral examination may show aphthous ulcers, angular cheilitis and tongue with a reduction of the papillae (iron deficits, vitamin $B_{12}$, folic acid, zinc, etc.). Skin changes should be recorded (vitiligo, erythema nodosum and pyoderma gangrenosum).

Examination of the abdomen may show the tense wall, painful, and the presence of mass (suggestive of ileocecal abscess or infiltration). The evaluation of the joints can find signs of low back pain, arthritis or sacroiliitis. The anal area should be inspected to detect fissure, fistulas and perianal abscesses are more common in CD [1,2].

## 6. Laboratory tests

Initially, they must be rejected major diseases that mimic IBD through exams:

• Feces: stool culture and testing for toxin A and B of *Clostridium difficile*, to the exclusion of other causes of colitis

• Test of the purified protein derivative of tuberculin (PPD, purified protein derivative of tuberculin) to ward off tuberculosis

• General Immunological evaluation to rule out the presence of primary immunodeficiencies

• Serology for AIDS

After this initial step, ask to laboratory tests related to inflammation, such as erythrocyte sedimentation, C-reactive protein (CRP), platelet, acid alpha-1-glycoprotein; if the results are high, reinforcing the diagnosis of IBD. One should also ask cell blood count (CBC), with attention to the presence of hypochromic anemia and leukocytosis; and iron dosing and protein electrophoresis for detection of iron deficiency and secondary loss or hypoalbuminemia did

not absorbed by inflamed intestinal mucosa. Among the serum electrolytes, the most common is the hypokalemia against attributed to chronic diarrhea [1,2].

The patient will be referred to the pediatric gastroenterologist for definitivediagnosis of IBD.

Some non-invasive laboratory tests can increase the CD detection probability, such as lactoferrin and calprotectin in the faeces [21].

According to the study-level meta-analysis, in high-prevalence circumstances, faecal calprotectin can be used as a non invasive biomarker of pediatric IBD only with a small risk of missing cases, and it can help in selecting patients for endoscopic evaluation and has the high over all sensitivity and the specificity for diagnosing IBD [22]. Another application of this method was the differentiation between functional disease and IBD [23].

The use of serological markers in children with suspected IBD is a non invasive test application attempts to shorten the diagnosis, differentiate the CD from UC and correlates them to prognosis of the disease. Many antibodies against microbial components are found in CD, including the antibody against outer membrane porin-C *Escherichia coli* (anti OmpC), against the sequence I2 associated *Pseudomonas* (anti-I2) and against bacterial C Bir1 flagina (anti-CBir1 ). It was found the prevalence of 11% and 56% of anti-anti-OmpC and I2 respectively in children with CD, with differences according to age at diagnosis. Other markers are anti-glican antibodies, results from the interaction between immune cells and glycosylated cell wall components of fungi, yeast, and bacteria are found in CD: mannobioside anti-carbohydrate antibodies (AMCA), anti-laminaribiose carbohydrate antibodies (FTAA), anti-carbohydrate antibodies chitobioside (ACCA), antilaminarim carbohydrate antibodies (anti-L), and anti-chitin (anti-C) carbohydrates antibodies. Only 16.9% -30.5% of patients were positive for each of then in pediatric CD [24].

Anti-glicoprotein 2 (GP2) IgG and IgA, constituting novel CD specific autoantibodies, appears to be associated with distinct disease phenotypes Identifying patients at a younger age, with ileocolonic location, and structuring behavior with perianal disease [25].

Dosages of liver enzymes, bilirubin and amylase are intended to detect liver and pancreatic involvement in IBD, the disease itself or secondary to the use of drugs to treat the disease.

Recent meta-analysis determined the accuracy of diagnosis symptoms, signs, noninvasive tests, and test combinations that can assist the clinician with diagnosis of IBD in symptomatic children. The conclusions were children in the symptoms are not accurate enough to identify low-risk patients in whom an endoscopy can be avoided. Assessment of fecal Cal-

protectin (FCAL), C-reactive protein (CRP), and albumin findings are potentially of clinical value, given their ability to select children at low risk (negative FCAL test result) or high risk (positive CRP or albumin test result ) is IBD [26].

One such promising test, the polymorphonuclear CD64 index capitalizes on inflammation-induced expression of Fcy receptor I (CD64 markers) on neutrophils and has a high sensitivity and specificity for CD in children [27].

Normal laboratory evaluation result does not exclude the diagnosis of IBD because approximately 10% to 20% of children with IBD will have standard laboratory results [28]. If it persists the suspected diagnosis of IBD, even with regular screening tests, should continue the investigation, requesting to upper and lower endoscopy with serial biopsies.

### 6.1. Endoscopy

Upper endoscopy and ileocolonoscopy with serial biopsies of the different segments of the digestive tract are the tests considered the gold standard for the diagnosis of CD, and definitely excludes other viral, bacterial and fungal etiologies. Macroscopic characteristics of the luminal pediatric untreated DC are summarized in **Table 4**.

### 6.2. Histology

Early manifestations of pediatric IBD can be relatively nonspecific. Initial mucosal biopsies may not be conclusive, delaying the diagnosis until subsequent biopsies typical histologic features of IBD.

In contrast to the findings of IBD, acute self-limited colitis (CALA) does not show the architectural distortion of the crypt, basal linfoplasmocitose and Paneth cell metaplasia. The combination of three parameters - increase of plasma cells in the lamina propria, crypt distortion and atrophy - represents 94% sensitivity and 96% specificity to distinguish IBD from other non-specific colitis [18].

In a recent study investigating potential of early histologic markers of pediatric IBD, the authors concluded that the distortion of colonic crypts, gastritis and the average density of eosinophils in the rectosigmoid were increased significantly in the IBD group compared to the group with functional abdominal pain. Immunohistochemistry staining for tumor necrosis factor-α and matrix metalloproteinase-9 was performed on the stomach and rectosigmoid areas did not reveal any significant differences between the groups of the initial endoscopic evaluation [29].

Microscopic characteristics of the luminal pediatric untreated CDare summarized in **Table 4**.

**Table 4:** Macroscopic and microscopic features of DC pediatric luminal untreated.

| Typical macroscopic findings of CD | Typical microscopic findings of CD |
|---|---|
| Mucosal aphthous ulcers | Noncaseating granuloma (s)- must be remote from ruptured crypt |
| Linear or serpentine ulceration | Focal chronic inflammation, transmural inflammatory infiltrate, submucosal fibrosis |
| Cobblestoning | |
| Stenosis/structuring of bowel with prestenotic dilatation | **Nonspecific microscopic findings of CD** |
| Imaging ou surgical-bowel wall thickening with luminal narrowing | Granuloma adjacent to ruptured crypt |
| Perianal lesions- fistula(s),abscesses, anal stenosis, and canal ulcers, large and inflamed skin tags | Mild nonspecific inflammatory infiltrate in lamina propria |
| Skip lesions | Mucosal ulceration/erosion |
| Jejunal or ileal ulcers | Signs of chronicity (eg.crypt architectural changes, colonic Paneth cell metaplasia and goblet cell depletion) |
| Nonspecific macroscopic findings of CD: oedema,erythema,friability, granularity | |
| Exudate: loss of vascular pattern, isolated aphthous ulcers, perianal lesions- midline anal fissures, small ski tags | |

**Abbreviations:** CD: Crohn disease. Modification of Levine A et al [1].

## 6.3. Radiology

The imaging method for the evaluation of the small intestine is very important to evaluate the extent of disease, assess the severity, differentiate between CD and UC, and identify complications such as fistulae, abscesses and intestinal strictures. The current trend is to replace the intestinal transit by Computed Tomography Enterography (CTE) or Magnetic Ressonance Enterography (MRE). Both techniques provide a perfect image enterography of the lumen and wall structures adjacent to the intestine. MRE advantages are the superior contrast resolution and the lack of ionizing radiation, although it is possible to maintain the quality of the image by CTE through interactive image reconstruction [30]. Some pediatric MRE protocols are available radiological studies should include Magnetic Resonance Pelvic to evaluate cases accompanied by perianal abscesses and fistulas [31].

## 7. Further investigation

The realization of Endoscopy Capsule is authorized by the Food and Drug Administration (FDA) in the US for children above 10 years, but there are reports of children younger than held this diagnostic method by introducing the capsule endoscopically. This test allows evaluation of the entire small bowel mucosa, and is useful in children with persistent high di-

gestive symptoms and radiological assessment of seemingly normal small intestine. The Endoscope Capsule may not be performed in the presence of intestinal stenosis, as in these cases the capsule can be retained in place. To rule out this possibility, one can use prior to the examination, a composite of biodegradable material capsule, the same size as used for the examination. If it is excreted intact, the patency of the intestinal lumen will be confirmed, enabling the final completion of the capsule endoscope, on the other hand, if there is impaction of the capsule in a stenosed intestinal segment, it will disintegrate in 40 hours due to the action of intestinal fluid [1].

The exploratory laparoscopy may be useful in selected cases patients, for example, when there is possibility of intestinal tuberculosis [1,2].

## 8. The classification of Paris

The classification of Paris [32], recently updated, to characterize the patient with CD according to age at diagnosis, location of the disease, inflammation behavior. It should be applied in the initial staging and progression of the disease, and this detailed in **Table 5**. As an adaptation to pediatric practice, was added to the discriminatory phenotype characteristic it was subdivided according to whether the disease was diagnosed before or after the patient was 10 years old, the presence or absence of growth failure, also introduced subdivision of upper gastrointestinal disease into jejunal versus oesophago-gastro-duodenal disease. The demarcation of the disease territory should be guided by inflammation observed at endoscopy or imaging and not by microscopic Involvement.

**Table 5:** Paris Classification for Crohn's disease

| |
|---|
| **Age Diagnosis**<br>• A1a: 0- aged <10 years<br>• A1b: 10- <17 years |
| **Location**<br>• L1: 1/3 distal ileum ± limited to the cecum<br>• L2: Colonic<br>• L3: ileocolônica<br>• L4A: TGI proximal to the high angle of Treitz<br>• L4B: TGI high distal to Treitz angle and proximal to the distal third of the ileum |
| **Behavior**<br>• B1: not stenotic and non-penetrating<br>• B2: stenotic<br>• B3: Penetrating<br>• B2B3: both penetrating and stenosing<br>• p: perineal disease |
| **Growth**<br>• G0: no evidence of stunting<br>• G1: with evidence of growth deficit |

The phenotype pediatric CD Characterized by more widespread intestinal inflammation, often Involving the large and small bowel as well as the upper gastrointestinal tract (pa-

n-enteric disease) [8].

## 9. Conclusion

The CD has become an increasingly diagnosed in children of all ages. This condition is of particular clinical picture in children compared with adults. Perform early diagnosis is crucial to avoid an additional impact on the nutritional status, growing and pubertal development. It also requires attention to the consequences of CD on the psychosocial aspect of children and adolescents, as is common in CD school break and social activities, especially in those patients with unstable or severe disease, requiring psychological intervention.

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