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Clinical presentation of Crohn's, ulcerative colitis, and indeterminate colitis: Symptoms, extraintestinal manifestations, and disease phenotypes

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ABSTRACT

The incidence of inflammatory bowel disease (IBD) is rising with 25% of IBD diagnosed in children under 18 years of age. The clinical presentation of IBD in children is often vague leading to initial misdiagnosis as infectious colitis or irritable bowel syndrome. When IBD is identified, overlap in histologic and endoscopic features may lead to difficulty distinguishing Crohn's disease from ulcerative colitis, resulting in a higher frequency of the diagnosis indeterminate colitis or IBD unspecified. Recognizing the common and the atypical presentation of pediatric IBD and extraintestinal manifestations will aid in expeditious referral and early diagnosis. Activity severity scoring tools and more specific classification systems for pediatric IBD direct therapeutic algorithms and allow for improved longitudinal assessment since disease severity and location have been shown to be associated with outcome.

Introduction

Inflammatory bowel disease (IBD) encompasses a spectrum of diseases, with Crohn's disease (CD) and ulcerative colitis (UC) representing the two broadest subtypes of IBD. Crohn's disease is characterized by transmural inflammation involving any part of the gastrointestinal tract while UC typically involves superficial inflammation of the rectum with extension into adjacent mucosa in a continuous fashion. Indeterminate colitis (IC) represents a third subtype of IBD involving mucosal inflammation with features that cannot be distinguished between UC and CD.[1] Recent reviews have demonstrated a rising incidence of IBD internationally. Incidence in North America has risen as high as 11.4 new cases per 100,000 individuals each year.[2,3] A quarter of all IBD cases are diagnosed in children under the age of 18 years.[4] Pediatric inflammatory bowel disease is often more extensive and severe than adult-onset IBD.[5] Moreover, atypical presentations are often found in the pediatric population. The purpose of this article is to review the clinical presentations of the diverse phenotypes found in pediatric inflammatory bowel disease.

Clinical presentation

Overall, Crohn's disease is the predominant IBD subtype comprising 59–73% of pediatric IBD, while UC comprises 24–32% of pediatric IBD (Table 1).[6–9] However, clinical presentation for Crohn's disease and ulcerative colitis can be highly variable with enormous diversity in disease phenotypes.[10] Often, clinical symptoms may be similar to those seen in irritable bowel syndrome, allergic gastroenteritis, and infectious gastroenteritis. CD and UC both commonly present with abdominal pain and diarrhea. Rectal bleeding occurs more frequently with UC (83–95%) compared to CD (40%).[11] On the other hand, patients with CD often have weight loss and perianal disease. Physical examination is fundamental to the diagnosis of IBD. On general assessment, any evidence of growth failure or pubertal delay as well as pallor suggestive of anemia should be noted. In additional to an abdominal exam for tenderness and palpable masses, a careful perianal examination should be performed to examine for perianal disease. Evidence of occult or gross blood in the stool merits further investigation. Additionally, 17% of pediatric IBD have extraintestinal manifestations at baseline.[12] Joint disease and mucocutaneous disease are common extraintestinal manifestations. Thus, clinicians should search for findings of tender swollen joints, apthous stomatitis, and erythema nodosum (tender red nodules typically on extensor surface of lower extremities).

Due to the clinical diversity and sometimes vague symptoms of children presenting with IBD, delays in diagnosis are common.

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Table 1
Differences in clinical presentations between ulcerative colitis, Crohn's disease, and indeterminate colitis. Histologic features for indeterminate colitis are according to the ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents[39].

Presentation	Ulcerative colitis[6–8]	Crohn's disease[6–9]	Indeterminate colitis[6–8,22]
Pediatric IBD (%)	24–32	59–73	3–13
Clinical features			
Abdominal pain	Common	Common	Common
Rectal bleeding	Common	Occasionally	Variable
Diarrhea	Common	Common	Common
Anemia	Common	Occasionally	Variable
Weight loss/growth failure	Infrequent	Common	Variable
Disease extent	Limited to colon, spreads proximally from the rectum in a continuous fashion	Rectal sparing, anywhere from mouth to anus	Variable
Perianal involvement	Infrequent	Common	Variable
Stenosis	Infrequent	Common	Variable
Abscess	Infrequent	Common	Variable
Fistula	Infrequent	Common	Variable
Endoscopic features	• Diffuse continuous inflammation from rectum extending proximally • "Sandpaper" appearance of mucosa • Friable mucosa • Small superficial ulcers • Gastritis may be present	• Patchy inflammation with aphthous or linear ulcers • Active ileitis • Fissures, fistulization and strictures • Cobblestoning • Gastritis may be present	Variable
Histologic features	• Crypt abscesses • Crypt architectural distortion • Inflammation limited to mucosa • Periappendiceal inflammation alone with distal colitis is frequently seen	• Granulomas • Crypt architectural distortion • Transmural inflammation • Colitis with granulomatous inflammation of esophagus, stomach, or duodenum • Absolute rectal sparing	• UC features with absence of severe colitis but transmural inflammation present • UC features with significant growth delay • UC features with presence of ileitis atypical for backwash or discontinuous inflammation • Pancolitis with anal fissures or anal tags • UC features with macroscopic and microscopic rectal sparing • Reverse gradient of mucosal inflammation

These delays may be due to non-classical presentations which occurs in 21% of pediatric IBD.[13] Non-classical presentations include growth failure as the only sign of illness in 5% of patients,[14] extraintestinal manifestations as the presenting sign in 6–35% of patients,[15–17] and perianal disease as the only predominant initial feature in 4% of patients.[13] Kwon et al.[18] report an average diagnostic lag time of 3.4 months for children with Crohn's disease. Children who are previously healthy without GI symptoms who suddenly become severely ill have the shortest time lag until diagnosis (1.2–1.5 months). However, patients with a history of pre-diagnostic GI symptoms such as abdominal pain, diarrhea and weight loss can have a diagnostic lag time of up to 26 months prior to definitive diagnosis of Crohn's disease. Similarly, they found an average diagnostic lag time of 2.2 months in children with ulcerative colitis. Children presenting with a history of pre-diagnostic GI symptoms such as abdominal pain, constipation, or bloody stools can have up to 12 months lag time prior to definitive diagnosis of ulcerative colitis.[18] Thus, when evaluating children with persistent abdominal pain and chronic diarrhea associated with rectal bleeding or weight loss, IBD should be considered high in the differential diagnosis and referral to pediatric gastroenterology should be made in a timely manner in order to minimize the lag time prior to treatment.

Another contributing factor to delays in diagnosis may be uncertainty with classifying patients as either CD or UC. Inability to determine IBD subtype may lead to delays in therapy and difficulty in providing long-term prognosis for pediatric IBD patients. Indeterminate colitis (IC) is defined as "patients with colonic disease who cannot be classified into one of the two major forms of IBD [UC or CD]."[11,19] This third subtype of IBD was introduced by the Montreal working group in 2005. Typically, IC will contain features of overlap with both CD and UC. Due to varying degrees of uncertainty with pediatric IBD classification, prevalence of IC is reported to range between 5% and 33% in pediatric series.[1,11,20] Higher rates of uncertainty are seen in the younger pediatric age groups, with rates of IC as high as 33% being diagnosed in young children under 2 years of age.[1,21,22] Incidence of IC decreases with increasing age, with IC diagnosed in only 9% of adolescents ages 13–17 years old.[20] Over a mean 2 years of follow-up, 15% were reclassified to CD while 6% were reclassified to UC.[9] Over 30% of children initially categorized as IC will be reclassified into either CD or UC on longer follow-up.[1] While use of IC in the youngest subgroups may be unavoidable, widespread use of this diagnostic category should be avoided.

Age of onset has been shown to have a profound impact on clinical presentation and disease course, especially in terms of extent of disease.[10,20] In children younger than 6 years of age at disease onset, ulcerative colitis is the predominant form of pediatric IBD (31–47%) while in children 6 years of age and older Crohn's disease (60–66%) is predominant. Younger children also have a higher rate of isolated colonic disease (41–69%) compared to older children (24–46%).[9,20] While younger children tend to have isolated colonic disease, older children more frequently present with terminal ileum involvement.[9] Pediatric-onset UC is often more extensive and more severe than the disease phenotypes seen in adult-onset UC.[23,24] In fact, 61–90% of pediatric UC