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Review

Early onset inflammatory bowel disease: manifestations, genetics and diagnosis

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Crohn's disease and ulcerative colitis are immunologically mediated chronic inflammatory conditions, collectively referred to as inflammatory bowel diseases (IBD). While most studies have described the condition in the adult population, recent evidences suggest that IBD in children may represent an etiologically distinct disease from the adult onset IBD. Since a significant proportion of patients diagnosed with IBD demonstrate their clinical manifestations during childhood, knowledge about the disease progression, severity and diagnosis in this particular patient population is crucial. Therefore, in the present study, the clinical manifestations, recent advancements in the genetics of early onset IBD and the clinical approach to diagnoses of IBD in children are described.

Key words: Crohn's disease, inflammatory bowel diseases, interleukin-10.

Crohn's disease (CD) and Ulcerative colitis (UC) are two distinct types of gastrointestinal disorders, collectively defined as inflammatory bowel disease (IBD). IBD is an idiopathic, life-long, destructive chronic inflammatory disease of the gastrointestinal tract. Deregulated balance of immune response, environmental triggers and genetic susceptibility are among the essential contributors in the development of IBD.[1-3] As a consequence, every group of ages, races, gender and socioeconomic are at risk of developing to IBD.[4]

Population based studies have revealed that a large proportion of patients diagnosed with IBD develop their symptoms before 30 years of age.[2,5] In addition, there are several studies that have shown an estimated 10% to 15% of patients are diagnosed with IBD under the age of 18.[6-8]

Therefore early-onset IBD is likely to represent a specific disorder with particular gene defects and phenotypic appearance compared to the adult population.[9] Recently, IBD demographics have been changed due to the increasing rate of IBD onset that occur in childhood. Over the last 4 decades there has been an internationally increasing trend in the incidence of early onset IBD in pediatrics, according to European report.[10-13] The rise in the incidence of childhood IBD could also have an impact on both emotional and physical development.[14,15] In contrast to adults, children with early-onset IBD appear to have a more severe intestinal involvement and clinical course.[16] Moreover, a positive family history of IBD is more common among children, suggesting a genetic association for IBD in this population.[17,18]

Among these patients with early onset IBD, a subset has recently been identified with the onset of disease occurring before 6 years of age. This group of very–early-onset IBD (VEOIBD) have shown to have unique clinical presentations with greater duration of disease, extensive colonic inflammation, and poor response to standard therapies, including biologic agents.[19] Also, a much stronger family history of the disease is present in this subset of pediatric IBD. In addition to the different disease phenotype between patients with early onset IBD and VEOIBD, the latter group has also been associated with distinct genetic variants, often involving genes associated with primary immunodeficiencies.[19,20]

Manifestations

In general, IBD manifestations are highly dependent on the areas of gastrointestinal tract involvement. UC and CD may present with similar clinical complains and symptoms among both children and adults. Although UC and CD are two distinct GI disorders, both of them could be presenting with symptoms such as abdominal pain, vomiting, diarrhea, rectal bleeding and abdominal cramp. Also, there are a number of clinical, endoscopic and histopathological factors that can help in distinguishing between these two major forms of IBD.

UC is limited to large intestine and involves in superficial inflammatory process, while, CD can affect any part of the gastrointestinal tract, from mouth to anus. UC only affects colon and rectum.[21-23] In the pediatric population, the most prominent feature is bloody diarrhea, also known as “Hematochezia”. The severity of its clinical presentations is based on the extent of the disease process.[23] UC typically begins in the rectum and it can be continuously extended to terminal ileum which is termed backwash ileitis.[24,25] UC symptoms may be varied from mild abdominal discomfort to painful bowel movements and abdominal cramping. Increasing rate of anemia is noted in patients with UC as a result of inflammation along with chronic blood loss (84%).[26,27] In almost all cases of UC, inflammation of anorectal region (also known as proctitis) results in urgency of defecation which is called "Tenesmus". Pancolitis is defined as the involvement of the entire colon, may occur in severe forms of UC. In one study, 74.7 % of children with early onset IBD presented with pancolitis at the time of diagnosis.[17]

In contrast to UC, CD is characterized by discontinuous and transmural nature with inflammation extending from mucosa to serosa which could affect any part of gastrointestinal tract.[17] The initial manifestations of CD may be abdominal pain (44%) which is usually accompanied by diarrhea.[28] In one study only 25% of pediatric patients present with classic triad of abdominal pain, weight loss and diarrhea.[29] Diarrhea is often in large-volume, intermittent and non-bloody, depending on which part of the small or large intestine is involved. In severe cases, bowel movements could be exceeding more than 20 times per day. The most common symptom of CD in pediatrics is weight loss occurred in 90% of cases.[30,31] One of the most commonly observed regions in gastrointestinal tract that is affected by CD is terminal ileum (71% of pediatrics patients) and right colon (71%).[17] This involvement usually presents with symptoms such as malabsorption which could be resulting in weight loss and anorexia. Limbergen et al.[17] demonstrated that childhood-onset CD is more likely to progress to more extensive anatomic involvement including small bowel, large bowel, and upper GI tract. Other common symptoms such as persistent vomiting and severe abdominal pain are caused by small intestinal stenosis involving the pylorus or duodenum. Perianal complications (29% in pediatric population) such as fistulae, abdominal abscesses and intestinal strictures are also commonly seen in CD.[32] The incidence of strictures have been shown to be similar to adults with approximately 30% of patients experiencing this complication during the course of their disease.[33]

Extraintestinal manifestations of both UC and CD include liver involvement (primary sclerosing cholangitis), arthritis and skin rashes such as erythema nodosum and pyoderma gangrenosum. Arthritis is the most common extraintestinal manifestation among pediatric population (32, 34-36) (Table I).

Table I. Clinical and Histologic Characteristic of CD and UC in Children.

	CD	UC
Clinical Manifestation		
Abdominal pain	++	+++
Diarrhea	++++	++
Hematochezia	++	++++
Weight loss	++	++
Extra-intestinal manifestations		
Toxic megacolon	+	+
Primary sclerosing cholangitis	+	Rare
Erythema nodosum	+	+
Arthritis	+++	++
Pyoderma gangraenosum	Very rare	Rare
Fistula/abscess/stricture	++	+
Distribution of the disease in gastrointestinal tract	Mouth to anus (ileum the most common)	Colon and rectum
Location	Transmural	Mucosal
Histology	Tissue granuloma	Crypt abscess

+ indicates presence in 0–25% of patients; ++ indicates presence in 26–50% of patients; +++ indicates presence in 51–75% of patients; ++++ indicates presence in 76–100% of patients.

Table II. Differences in the Clinical Manifestations Between Early and Late Onset IBD.

Clinical Manifestation	Early Onset IBD	Late onset IBD
Severity of disease		
Ulcerative colitis	Higher	Lower
Crohn's disease	Higher	Lower
Requirement for surgery		
Ulcerative colitis	Higher	Lower
Crohn's disease	Lower	Higher
Nutritional Impairment		
Ulcerative colitis	Higher	Lower
Crohn's disease	Higher	Lower

Differences between early and late onset IBD

The clinical manifestations of early-onset IBD may be different than adult onset disease (Table II).[37] Among the UC population, it has been shown that extensive colitis is found to be twice more common among children than adults.[9,38] Also, the median time to operation in the pediatric population is significantly shorter than in adults.[18,39] Among patients affected by CD, those with early-onset disease are shown to have a much more extensive disease involvement than adult-onset IBD.[40] However, fewer patients in the early-onset group require surgery compared with adult-onset CD patients. These distinct phenotypic characteristics suggest that pediatric-onset IBD may have different pathogenic mechanisms from adult-onset IBD.[17,41] This notion has been supported by the findings in

recent years that specific mutations are present in many cases of early-onset IBD which points to pathogenic mechanisms affecting this group of patients.[42,43] Since many of these mutations have been shown to harbor a recessive mode of inheritance, parental consanguinity can potentially increase the susceptibility of these individuals to manifest the disease in young age. This notion, however, has not been confirmed by larger studies to date.

Nutritional impairment is among the common clinical manifestations of early-onset IBD.[14,44,45] Loss of appetite and impaired absorption are seen in both early-onset CD and UC with up to three quarters of patients with active disease experience some degree of malnutrition during their course of disease. However, delay of growth and puberty secondary to malnutrition is mostly seen in CD, and less frequently encountered in pediatric onset UC.[29] Enteral nutrition, defined by liquid formula diet by mouth or nasogastric tube, has been used for over 30 years in the CD population.[46-48] While limited evidence exists regarding the role of enteral nutrition in the early onset UC population, provision of adequate nutrition still remains important in this patient population.[49,50]

It has been suggested that patients affected by early-onset IBD have lower response rates to conventional anti-inflammatory and immunomodulatory therapy. However, there is a paucity of well-designed studies to support this hypothesis.

Histological investigation is paramount in the work up of patients suspected to have early-onset IBD, not only to differentiate IBD-like features, but also to exclude other established pathologies such eosinophilic or allergic gastrointestinal disease and infection.

Laboratory tests such as immunoglobulin measurements, flow cytometry and oxidative burst assays could be utilized as an important tool in differentiating different subgroups of IBD[51,52], such as those who develop the disease before the age of 2 years old, those with excessive autoimmunity, or those with severe perianal disease. For instance, flow cytometry analysis of XIAP and FOXP3 expression can assist in the diagnosis of significant proportion of patients with XLP2 and IPEX. Flow cytometry can detect functional defects in signaling pathways of MDP among patients with XIAP deficiency.[53,54] Detection of antibodies against enterocytes can be useful in the diagnosis of autoimmune enteropathy, particularly among patients with IPEX syndrome.[52] Additional tests for other rare genetic defects may also help in the detection of subgroups of early-onset IBD, but are usually only available at specialized laboratories, often as part of research projects.[55]

Among patients with early-onset IBD, approximately one fifth under the age of 6 and one third of patients under 3 years of age are labeled as unclassified IBD[56], which reflects a lack of a refined phenotyping tool to categorize all patients affected by IBD at a young age. Incomplete diagnostic workup is also partly responsible for the lack of better characterization of this group of patients.

Genetics

Single nucleotide polymorphism (SNP) has tremendously helped in understanding the genetics of human IBD (57, 58), providing insights into the genetic complexity underlying these inflammatory conditions. However, the functional relevance of most of these susceptibility genes is unclear.[59,60]

Several pathways have been discovered by analyzing genetic loci implicated in patients with IBD, that are crucial for intestinal integrity and homeostasis such as, epithelial barrier function, innate and adaptive immune regulation, reactive oxygen species (ROS) generation and autophagy[42,61-63] (Table III).

Very early onset IBD and PIDs: IL-10, IL-10Ra, IL-10Rb, NFAT5, TTC7A

IL-10, IL-10Ra, IL-10Rb

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that has several pleiotropic effects on immunoregulatory cells including T cells, B cells and monocytes.[64] This cytokine is encoded by IL-10 gene, located on chromosome 1.[65] The receptor for IL-10 is consisted of two subunits including IL-10 receptor-1(IL10Ra) and IL-10 receptor 2 (IL10Rb) proteins.[64] IL10R1 is

Table III. Genes with Functions Associated with Early vs Late Onset IBD.

Gene	Chromosome	Associated with Early-onset IBD	Associated with Late-onset IBD	Function
NOD2	16	Yes	No	killing of intracellular pathogens, Innate immune recognition
CARD 9	9	Yes	Yes	NFκB activation and/or regulation, positive regulator of apoptosis
Interleukin-10	1	Yes	No	maintaining intestinal homeostasis
TTC7A	2	Yes	Yes	modulating immune homeostasis, cell cycle control
NFAT5	16	Yes	Yes	regulate immune response including cytokine production
LRBA	4	Yes	No	activation of receptor complexes, secretion of immune effector molecules
MEFV	16	Yes	No	regulating of the inflammasome platform
XIAP	X	Yes	No	inhibits apoptosis

CD: Crohn's Disease UC: Ulcerative Colitis NOD2: Nucleotide-binding oligomerization domain-containing protein 2
CARD9: Caspase recruitment domain-containing protein 15 TTC7A: Tetratricopeptide repeat domain 7A
NFAT5: Nuclear factor of activated T-cells 5 LRBA: LPS responsive beige-like anchor protein
MEFV: Familial Mediterranean fever XIAP: X-linked inhibitor of apoptosis protein

unique to the interleukin-10 receptor, while, IL10R2 is a subunit of the receptors for several additional cytokines (e.g., interleukin-22 and interleukin-26).[65,66] Interleukin-10 is a cytokine synthesis inhibitory factor (CSIF) and limits the secretion of proinflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin-12.[67]

Deficiency in interleukin-10 results in prolonged activation of mononuclear cells on exposure to bacterial particles, which in turn augments the efflux of inflammatory cytokines such as TNF-a, causing damage to the intestinal mucosa.[68] The presence of severe inflammatory bowel disease is the most prominent phenotype in patients with IL10Ra or IL10Rb deficiency.[69]

TTC7A

Tetratricopeptide repeat domain 7A (TTC7A) is a gene present on chromosome 3 that encodes a protein that has shown to have diverse functions in cell cycle control such as protein transport, phosphate turnover, and protein trafficking or secretion. This protein also has a role in acting as chaperones or scaffolding proteins.[70,71]

Recently, mutations in the TTC7A gene were found to cause multiple intestinal atresia (MIA). Mutation in this gene has also shown to be associated with severe infantile or very early onset IBD.[70,72]

NFAT5

Nuclear factor of activated T-cells 5, also known as NFAT5, is a human gene located on chromosome 16 that encodes a transcription factor that play a central role in inducible gene transcription during the immune response including cytokine production.[73] In addition, this protein has shown to regulate gene expression induced by osmotic stress in mammalian cells.[74] Recent studies indicate that mutations in this gene can cause hyperosmolarity and hyperosmotic stress within the colon, which in turn triggers inflammation.[75] Observational studies in human patients with IBD have shown elevated osmolarity in fecal fluid within the colon in these patients.[76,77] Moreover, elevated fecal osmolarity has shown to closely correlate with disease severity in these patients.[77,78]

PIDs associated with IBD: LRBA, FMF, XIAP, Blau syndrome

Primary immunodeficiency disease (PID) are a group of more than 150 genetically heterogeneous disorders involving innate and adaptive immune system which include antibody production defects (B-cell defects), cellular or combined defects (T-cell defects or B-cell and T-cell defects), phagocytic cell defects and complement defects.

Gastrointestinal manifestations are a hallmark of patients with PID. Given the fact that the intestine is the largest lymphoid organ in the body, any dysregulation in the humoral or cell-mediated immunity could affect the integrity of the gastrointestinal tract resulting in a diverse range of manifestations. A number of PID disorders have been linked with the presence of IBD.[79]

LRBA deficiency

Deficiency in the "Lipopolysaccharide (LPS)-responsive vesicle trafficking, beach- and anchor-containing" gene is a rare genetic disorder of the immune system characterized by autoimmunity, lymphoproliferation, and immune deficiency.[80] The gene encodes a protein that plays a major immuno-regulatory role in the expression, function, and trafficking of cytotoxic T lymphocyte-associated protein 4 which acts as an inhibitory checkpoint for the immune response.[81] Patients with LRBA deficiency present with infections occurring in the eyes, skin and gastrointestinal tract. Many patients also present with chronic diarrhea and inflammatory bowel disease. Other clinical features can include hepatosplenomegaly, reoccurring warts, growth retardation, allergic dermatitis, and arthritis.[80,81]

FMF

Familial Mediterranean fever (FMF), is a hereditary inflammatory disorder caused by mutations in the gene MEFV, located on chromosome 16.[82] The gene encodes pyrin, a protein playing a major role in the regulation of the inflammasome platform in addition to interacting with the gene product of NLRP3, an important active member of the inflammasome.[83] The NLRP3 region was recently reported to be associated with Crohn's disease (CD) susceptibility.[84]

XLAP

X-linked inhibitor of apoptosis protein (XIAP), is a protein produced by *XIAP gene* located on the X chromosome and plays a major role in inhibiting apoptotic cell death induced by viral infection or overproduction of caspases.[85,86] The protein functions by binding to caspase 3, 7 and 9 and inhibiting these factors.[87] Deregulation of XIAP can result in tumorogenesis, neurodegeneration and autoimmunity as well as to a rare and severe type of IBD.[88,89]

Blau Syndrome

Blau syndrome (BS) is a rare systemic inflammatory disease characterized by pediatric onset granulomatous arthritis, uveitis and skin rash.[90] The syndrome is caused by mutations in the *NOD2 gene* (16q12), which causes activation of nuclear factor kappa B which in turn up-regulates pro-inflammatory cytokine transcriptions. This results in alterations in the innate immune response causing inflammation, cell death and IBD.[91,92]

Other gene variations, associated with IBD: NOD2, CARD9

NOD2

The first gene polymorphism recognized to be related to IBD was NOD2 located on chromosome 16. Also known as caspase recruitment domain-containing protein 15 (CARD15), the gene encodes a protein which plays a critical role in the innate immune system by recognizing bacterial peptidoglycan product muramyl dipeptide (MDP) and initiating an immune response.[93] Expression of NOD2 induces autophagy by MDP stimulation, resulting in the luminal bacterial replication regulation.[94,95] Mutations in CARD15 gene have also shown to cause an impairment in the clearance of salmonella from epithelial cells.[96]

CARD 9

CARD9 is a member of the caspase-associated recruitment domain (CARD) protein family. It encodes an adaptor molecule signal which is critical for NF-kB activation and participation in apoptosis signaling.[97] This gene also plays an important role in modulating innate immune

responses to intracellular pathogens such as viral, bacterial and fungal motifs.[98-100] A defect in CARD9 function can lead to immune disorder and increased susceptibility to intracellular pathogens such as candidiasis.[101] It has been suggested that defects in this gene may be implicated as a predisposition factor for developing IBD.

Diagnosis

IBD is diagnosed by the confirmation of chronic inflammation in the gastrointestinal (GI) tract and ruling out other causes of inflammation such as infectious diseases, primary immunodeficiency disorders (PIDs) and allergic diseases.[102]

The accurate diagnosis for all patients with suspected IBD should be based on a full medical history including intestinal and extra-intestinal manifestations. Physical examination should include growth velocity, anthropometric measurements and the inspection of oral and perianal involvement.[103] Laboratory investigation should comprise ESR, CRP and platelet count (as a sign of inflammation), anemia workup and signs of malnutrition.[51] Growth retardation may be the only initial symptom at the time of diagnosis.[14,29,104] Endoscopic and histological assessment of the both small bowel and large bowel mucosal pinch biopsies should be performed.[105-107] Stool examination and fecal cultures are needed in order to exclude infectious causes of diarrheal illness.[51]

Previously, performing small bowel imaging has been recommended for all cases of IBD particularly in patients suspected with Crohn's disease, atypical presentations of ulcerative colitis and unclassified IBD.[108]

Despite recent endeavors in standardization of definitions and classifications of pediatrics IBD as well as advances in diagnostic imaging modalities, the exact diagnosis of pediatric IBD is still highly dependent on choosing the best diagnostic tests and appropriate interpretation of the results of the workup.[108]

The diagnosis of UC is based on the identification of continuous inflammation of the colon by colonoscopy and colonic biopsies. Macroscopic features of UC include diffuse mucosal granularity, friability, purulent exudates, edema, and erythema with or without ulceration.[109] Histological evaluations can reveal the presence of active inflammation defined as neutrophils infiltrations within the crypt lumen as well as crypt forming abscesses.[110] Chronic features of UC include crypt architectural distortion with an increase in chronic inflammatory cells in the lamina propria and increased lymphocytes and plasma cells between crypt bases and the muscularis mucosae (termed as plasmacytosis).[8] Macroscopic rectal sparing may be seen in about 10% to 30% of children diagnosed with UC.[111] on the other hand microscopic rectal sparing is infrequently seen in UC.[112]

A single gold standard for the diagnosis of CD has not yet been introduced. CD is diagnosed by a combination of clinical evaluation and histological and radiological findings. The diagnosis of CD is based on findings of discontinuous involvement of GI tract.

According to the Paris classification, typical features of pediatric CD are as follows: Macroscopic features such as mucosal aphthous ulcers, fat wrapping, stenosis, structuring, skip lesions, bowel wall thickening and perianal lesions such as fistula, abscesses and skin tags. Microscopic features include non-caseating granuloma, transmural infiltration of inflammatory cells and submucosal fibrosis.[111] The presence of any well-formed non-caseating granuloma anywhere in the gastrointestinal tract should prompt the diagnosis of CD.[111]

Pediatric IBD represents a specific disorder with distinct clinical manifestations, genetics and diagnostic criteria that differ from adult onset disease. The number of susceptibility genes related to pediatric onset IBD continues to increase, leading to a deeper understanding of the pathogenesis involving this distinct clinical entity. Identification of the responsible genetic variants could help in defining specific disease phenotypes as well as novel therapeutic targets. Future studies are required to identify the interactions between genes and environmental factors that could play a role in the pathogenesis of these diseases and provide optimal medical therapy.

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