DIAGNOSIS AND THERAPEUTIC MANAGEMENT OF VERY EARLY ONSET INFLAMMATORY BOWEL DISEASE

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Abstract
The relation between the age at diagnosis and the evolution of pediatric inflammatory bowel disease (IBD) is not well known. However, it is obvious that IBD has particular characteristics in pediatric patients. For the first time, Montreal classification delimited patients whose disease started under age 17, as a distinct group of patients – pediatric IBD. Recently there were proposed IBD subgroups according to age: very early onset IBD - (<6 years), infantile IBD (<2 years) and neonatal IBD (<28 days). An increasing incidence of IBD in pediatric patients was noticed; affected children are increasingly younger. Over 163 associated genetic loci have been identified. This could be explained by a particular genetic predisposition to develop IBD, and also by changes in environmental factors that initiate the disease. There are at least 50 monogenic defects responsible for an IBD-like pathology.

Patient history, physical examination, endoscopic investigations, imaging, are required to establish the diagnosis of IBD. Gastrointestinal infections are frequent in pediatric patients and are excluded by stool culture and virology tests. Cow’s milk protein allergy and celiac disease should be excluded. Several studies reported an increasing incidence of very early onset-IBD, frequent pancolonic ulcerative colitis, children presenting with severe ulcerative colitis disease activity. Very early onset IBD has a severe prognosis and often needs an aggressive therapeutic approach.

Keywords: very early onset inflammatory bowel disease, ulcerative colitis, Crohn’s disease, immunodeficiency, genetics, diagnosis, treatment

Introduction
Inflammatory bowel disease (IBD) develops during childhood in 25% of patients. The relation between the age of onset and the phenotype of pediatric IBD is incompletely known. However, it is obvious that IBD has particular characteristics in pediatric patients.

For the first time, Montreal classification delimited patients whose disease started under age 17, as a distinct group of patients – pediatric IBD. Paris classification has defined a group of patients with early onset IBD, under the age of 10. Recently there were proposed more IBD subgroups according to age: very early onset inflammatory bowel disease (VEOIBD) (<6 years), infantile (and toddler) IBD (<2 years) and neonatal IBD (<28 days). An increasing incidence of both ulcerative colitis (UC) and Crohn’s disease (CD) in pediatric patients was noticed; affected children are increasingly younger.

A report which included 1370 patients from six centers in North America found that in 15% of the patients, IBD presented before the age of 6. A population-based retrospective cohort study of the Canadian children diagnosed with IBD, showed that the incidence increased by 7.4% per year among children younger than 6 years old. Increasing incidence could be explained by a particular genetic predisposition to develop IBD, and also by changes in environmental factors that initiate the disease. Intestinal flora changes, resulting from the change in dietary habits associated with sterile living conditions, have increased the risk of IBD.

Monogenic forms of IBD
The genetics of IBD is complex and incompletely elucidated. Over 163 associated genetic loci have been identified but most of them have a small genetic contribution; these variants commonly implicated in IBD pathogenesis account for only 25% of the heritability.

A high-density Immunochip genotyping was performed on 1008 pediatric patients with IBD (801 children with CD, 121 children with UC and 86 children with IBD undetermined) and could not identify additional common variants for early onset IBD. The researchers concluded that with the exception of infantile IBD, no overt differences in genetic susceptibility have been identified.

More than 50 monogenic defects responsible for IBD or IBD-like pathology were found. Three-fourths of these genetic defects are associated with primary immunodeficiency: neutrophil (and other phagocyte) dysfunctions, various defects of adaptive immunity (including regulatory T cells and anti-inflammatory cytokines) and innate immunity.
Defects in T cell and B cell function

Autoinflammatory disorders are characterized by the inability of the innate immune system to produce superoxide. It is caused by mutations in genes that encode the subunits of the NADPH oxidase.

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Defects effecting the inflammasome include familial Mediterranean fever, pyogenic arthritis, pyoderma gangrenosum, and peritonitis (FAPA syndrome). These disorders are characterized by the inability of the innate immune system to produce superoxide. It is caused by mutations in genes that encode the subunits of the NADPH oxidase.
Clinical characteristic and diagnosis of VEOIBD

UC is more frequent in VEOIBD, and CD is often diagnosed in older children. The study performed in Grigore Alexandrescu Emergency Children’s Hospital, Bucharest included 41 patients diagnosed with IBD between January 2004 and December 2013. We found an increased frequency of cases with VEOIBD – 14 (34%) cases. Most of the patients under 6 years (71%) were diagnosed with UC.

Several studies support the suggestion that IBD phenotype differs in very early-onset disease. Children with VEOIBD may have a mild disease with isolated colitis and bloody stools; whether Crohn disease, ulcerative colitis, or indeterminate colitis.

The patients with very early onset CD have perianal disease and a severe inflammatory disease presentation. In a cohort of 1928 children with IBD from multiple centers of North America, 112 children with VEOIBD (<5 years) were identified: children with very early onset CD had a mild disease and presented with a colonic phenotype. The presenting colon phenotype changed to ileo-colonic phenotype at 6-10 years. Five years post-diagnosis, disease activity was similar regardless of patient age at onset. A more frequent isolated colonic and upper gastrointestinal involvement were noticed in a cohort of patients with CD diagnosed in Italy.

Very early onset UC is characterized by an extensive disease; proctitis is rarely described. A report which included 30 Australian children diagnosed with VEOIBD revealed that UC was characterized by less abdominal pain at presentation, but an aggressive course with and a significant reduction in weight-for-age.

If only consider infantile IBD, it is found that it has a poor prognosis. Cannioto et al. describe a group of 16 patients under 2 years old with a very severe IBD course and high mortality (3 patients died). Almost all infants with IBD have chronic diarrhea; a high proportion of very young patients have hematochezia, perianal disease and more severe extensive disease.

A significant proportion of children with VEOIBD have malnutrition. Growth failure is more severe at diagnosis in CD patients than in UC patients. It is known that pre-pubertal onset of IBD (especially CD) is a risk for lower final height.

Medical history, physical examination, laboratory tests (for anemia and inflammatory markers), imaging, and upper and lower gastrointestinal endoscopy with histological analysis should be performed in order to establish the diagnosis of IBD; it is also important to evaluate disease behavior and locations as well as disease activity. We have to classify the disease status according to the Paris Classification.

Investigations are also done to rule out certain diseases that are more common in this age, such as gastrointestinal infections (caused by Salmonella, Shigella, Yersinia, Campylobacter, Cytomegalovirus, Clostridium difficile, HIV, cow’s milk protein allergy, celiac disease.

The diagnosis of monogenic IBD is difficult in clinical practice. Functional screening is followed by genetic confirmation; whole-exome sequencing is recommended.

Therapeutic management

Children with VEOIBD often need aggressive treatment strategies. Frequently, VEOIBD is severe at diagnosis and treatment with corticosteroids is required. In steroid dependent patients or in patients who fail to respond to corticosteroids, immunosuppressive agents are used and sometimes decrease the need for surgery.

The recently described North American cohort included a high percentage of children 1 to 5-years-old with CD who received corticosteroids and methotrexate and a high percentage of children 1 to 5-years-old with UC who received mesalamine and thiopurine immunomodulators.

The group of children diagnosed with VEOIBD in Australia often required immunosuppressive treatment, and surgery.

Cannioto et al have remarked that patients with infantile IBD needed multidrug, immunosuppressive approach; 25% received total parenteral nutrition and 12.5% received colectomy.

A molecular diagnosis became an important stage in the diagnosis of all cases of therapy-refractory VEOIBD because it has a significant impact on patient management. Hematopoietic stem cell transplantation has been proposed as a curative treatment in patients with severe VEOIBD and IL-10 deficiency; it was performed in several cases and clinical remission was achieved in the majority of patients.

Conclusion

More than 50 monogenic defects responsible for VEOIBD or IBD-like pathology were identified and the majority is associated with primary immunodeficiency. IBD phenotype differs in very early-onset disease and children with VEOIBD often need aggressive treatment, early surgery. Hematopoietic stem cell transplantation has been performed in certain monogenic defects responsible for VEOIBD.

References

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