REVIEW ARTICLE

CONTENTS

Complex diagnostic approach in early manifestation of Crohn's disease in children

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ABSTRACT

Aim: To summarize current approaches to diagnosing and evaluating clinical features and disease course of Crohn's disease, and to provide competency-based practical recommendations for diagnostic assessment in children with early-onset disease.

Materials and Methods: Literature analysis was conducted using electronic databases (PubMed, Medline, the Cochrane Library) and the author's clinical cases of Crohn's disease in 7 children aged 1 year 10 months to 4.5 years. The diagnostic algorithm in young children included general clinical examination and laboratory and instrumental methods, including genetic testing and serological markers. Morphological verification of the diagnosis by histological examination of biopsy specimens is mandatory.

Conclusions: Delayed diagnosis of Crohn's disease in young children results from nonspecific symptoms, variable early manifestations, and prominent extraintestinal features. Early-onset disease poses a major diagnostic challenge and requires increased awareness of extraintestinal manifestations, perianal lesions, and growth failure. Serological tests serve as supportive tools and do not exclude the diagnosis when negative, particularly in children under 6 years. Genetic screening to rule out primary immunodeficiencies is an essential part of the diagnostic workup in this age group.

KEY WORDS: Crohn's disease, young children, clinical manifestations, diagnostic evaluation

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INTRODUCTION

Crohn's disease (CD) is a chronic transmural granulomatous inflammatory disease of the gastrointestinal tract (GIT) of multifactorial etiology, characterized by segmental involvement of various parts of the digestive tract. The disease may affect any segment from the oral cavity to the anal canal, leading to both local and systemic complications [1-3]. Particular attention of the global scientific community is focused on the phenotype with very early onset (Very Early-Onset Inflammatory Bowel Disease, VEO-IBD) occurring in children under 6 years of age. Within this group, infantile-onset disease (debut within the first 2 years of life) and neonatal-onset disease (debut within the first 28 days of life) are distinguished [4-7]. The incidence of CD in young children is estimated at 0.5–1.5 cases per 100,000 pediatric population, with a global trend toward increasing prevalence [8=10]. A distinctive feature of early-onset CD is not only the severity of gastrointestinal involvement but also a strong association with monogenic immune defects, positioning this pathology at the intersection of gastroenterology, immunology, and genetics [11-16]. Recently, an increasing proportion of CD has been observed within the structure of chronic inflammatory bowel diseases in early childhood [17].

At present, diagnosis of CD in young children remains challenging. An atypical clinical presentation, predominance of extraintestinal manifestations and growth retardation, and an aggressive disease phenotype often lead to delayed diagnosis [7, 18-20].

Delayed diagnosis increases the risk of severe disease course and development of serious complications [21]. *However, despite growing interest, the number of studies addressing this issue remains limited.*

Understanding the pathogenesis of CD in early childhood is essential for appropriate clinical management. Compared with older children, early-onset CD is characterized by a stronger genetic contribution, pronounced dysbiosis, and impaired immune regulation. Monogenic mutations affecting epithelial barrier function and immune response are frequently identified in children

under 6 years of age. Early-life dysbiosis is marked by reduced microbiome diversity. Impaired autophagy and phagocytic defects lead to ineffective pathogen elimination, resulting in chronic uncontrolled inflammation.

AIM

The aim of this study is to systematize current diagnostic approaches, assess clinical manifestations and features of the clinical course of CD, and provide practical recommendations using a competency-based approach for diagnostic evaluation in cases of early disease manifestation in children.

MATERIALS AND METHODS

A literature review was conducted using the electronic databases PubMed, Medline, and the Cochrane Library, as well as the author's own clinical cases of CD in young children. The clinical manifestations, disease course, and diagnostic findings were analyzed in 7 children aged from 1 year 10 months to 4.5 years, including 5 boys (71.43%) and 2 girls (28.57%). The study included patients with early-onset Crohn's disease who were monitored and treated in pediatric surgical departments in Kyiv and Vinnytsya during the period of 2020 – 2025.

The diagnosis of early-onset CD was based on the Porto criteria (ESPGHAN) adapted for early childhood [22-24]. Diagnostic evaluation included general clinical examination, laboratory tests, and instrumental investigations.

The general clinical examination included a thorough collection and analysis of anamnestic data, assessment and analysis of the clinical manifestations of the pathology, dynamic follow-up of patients with consideration of changes in gastroenterological and extraintestinal symptoms, evaluation of physical and somatic status, as well as the nature and frequency of bowel movements.

Laboratory investigations included assessment of general and specific inflammatory markers (fecal calprotectin, anti-Saccharomyces cerevisiae antibodies) [25], microbiological stool analysis [26, 27]. An extended immunological evaluation was performed to assess the status of all components of the immune system [28]. In cases of suspected primary immunodeficiency, genetic testing using targeted gene panel sequencing was performed [29].

A mandatory diagnostic measure was the use of endoscopic examination methods (esophagogastroduodenoscopy and ileocolonoscopy) with morphological verification of the diagnosis through histological examination of clinical biopsy specimens [30, 31].

The gold standard for the diagnosis of CD in young children for assessing the condition of the small intestine is magnetic resonance enterography, which provides optimal visualization, enables evaluation of bowel wall thickness and detection of fibrotic changes, while avoiding radiation exposure.

Radiological methods such as irrigography and fistulography were also applied.

In cases of perianal disease, examination under general anesthesia and perineal CT scanning were performed.

The work is a fragment of the scientific-technical work of the Department of Children's Surgery of National Pirogov Memorial Medical University, Vinnytsya «Development of modern and improvement of existing methods of diagnosis, treatment, prevention and rehabilitation of surgical pathology in children» (state registration number 0123U102436).

The research was carried out in accordance with the principles of the Helsinki Declaration of the World Medical Association on the ethical principles of conducting scientific medical research with human participation, approved by the ethics and bioethics committees of the University KROK, Educational and Scientific Institute of Medicine. and National Pirogov Memorial Medical

University, Vinnytsya.

Written informed parental consent for participation in the study was obtained.

REVIEW AND DISCUSSION

The main complaints included chronic diarrhea associated with recurrent respiratory infections, relapsing disease course with a short-term positive effect of conservative therapy, very early disease onset (within the first year of life), and a wide range of extraintestinal and systemic manifestations. Diarrhea in infants with CD persisted for more than 6 weeks, without blood admixture, and was accompanied by abdominal pain.

At admission, the children were in severe condition due to pronounced cramping abdominal pain, intoxication syndrome, and anemia. The abdomen was moderately distended and painful on palpation, with marked intestinal rumbling. Bowel movements occurred up to 10 or more times per day, both during the daytime and at night. Mucus admixtures in the stool were observed, without blood.

Extraintestinal manifestations (EIMs) were observed in all children included in the study and often preceded intestinal symptoms, complicating diagnosis. In one child, erythema nodosum (painful red nodules on

the anterior lower legs) was observed, which showed a close correlation with exacerbations of intestinal disease. In two children, EIMs included eye pain and redness, photophobia, which required urgent consultation with an ophthalmologist; anterior uveitis was diagnosed. Primary sclerosing cholangitis/autoimmune hepatitis occurred in association with ileocecal CD in one 3-year-old child [32]. In three boys (43%), perianal lesions were characterized by deep fissures, fistulas, abscesses, and skin tags. Perianal changes were the only manifestation of CD for a prolonged period, until colitis was detected 1.5–2 years after the onset of perianal lesions.

All patients exhibited growth retardation, which was caused not only by malabsorption but also by the direct effect of proinflammatory cytokines (TNF-α, IL-6) on the bone growth plate and the growth hormone axis, as well as by weight deficit and iron-deficiency anemia.

Laboratory findings showed significantly elevated inflammatory markers (CRP, ESR, thrombocytosis) in all patients. Complete blood count findings included severe anemia in all children, leukocytosis, toxic granulation of leukocytes, and increased ESR. Biochemical blood tests showed hypoproteinemia, elevated C-reactive protein levels, and decreased serum iron. When assessing fecal calprotectin levels, it is important to remember that normal values in infants during the first year of life are higher (<350 μg/g) than in adults (<50 μg/g). In the studied group, fecal calprotectin levels (measured by ELISA) were elevated in all children, ranging from 200 to 250 μg/g.

Serological markers assist in differentiating CD from ulcerative colitis and in predicting disease course; however, their informativeness in children under 6 years of age is limited due to immaturity of the immune response. The main laboratory marker of CD is antibodies to *Saccharomyces cerevisiae* (ASCA), represented by IgG and IgA classes. Positive ASCA results are associated with CD only when correlated with clinical presentation and endoscopic findings. In the studied group, positive ASCA results were obtained in only 4 of 7 children (57.1%). Serological diagnostics is an auxiliary tool; a negative result does not exclude the diagnosis, especially in children under 6 years of age.

Regarding genetic testing, all children with early disease onset underwent molecular genetic testing to detect specific gene mutations. However, the diagnosis was established comprehensively, taking into account clinical symptoms, laboratory findings, and results of instrumental investigations.

Microbiome studies in young children with CD revealed a reduction in bifidobacteria and lactobacilli, which directly correlates with inflammatory damage to the intestinal mucosa and leads to impaired protective mechanisms, increased intestinal permeability, and initiation of systemic inflammation.

Ultrasound examination of the abdominal organs revealed marked intestinal meteorism, moderate thickening, and infiltration of the wall of the descending and transverse colon as well as the cecum.

Esophagogastroduodenoscopy (EGD) and ileocolonoscopy with multiple biopsies are mandatory and constitute the basis for diagnostic verification. During EGD, the gastric mucosa was focally hyperemic, edematous, with isolated hemorrhages. Colonoscopy revealed hyperemic mucosa with an enhanced vascular pattern, fibrinous deposits in the lumen, moderate edema, and mucus clots; in three patients, multiple erosions of the distal colon were observed.

According to the diagnostic evaluation, lesion localization revealed ileocolitis in 4 children (57.1%) and pancolitis with perianal involvement in 3 children (42.9%). In all patients, the diagnosis was morphologically verified.

At present, the diagnosis of early-onset CD remains a challenging issue. The diagnostic findings indicate an aggressive disease phenotype in this patient population, with high inflammatory activity and extensive pathological involvement.

Timely and adequate diagnostic evaluation of CD in children with early manifestation is the basis for initiating treatment, as therapeutic strategy depends on diagnostic findings, taking into account age, phenotype, and the presence of complications. Achieving deep remission (clinical and endoscopic) is possible only with appropriate selection of therapy involving a multidisciplinary team of physicians.

CONCLUSIONS

- Delayed diagnosis of CD in young children is caused by the absence of specific symptoms, diversity of early clinical manifestations, and the presence of extraintestinal and systemic features.
- CD in early childhood represents a significant diagnostic challenge and requires heightened clinical awareness of extraintestinal manifestations (arthritis, erythema nodosum, growth retardation) and perianal lesions.
- Serological testing is an auxiliary diagnostic tool; negative results do not exclude the diagnosis, especially in children under 6 years of age.
- Genetic screening to exclude primary immunodeficiencies is a mandatory component of diagnostics in this age group.

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CONFLICT OF INTEREST

The Author declare no conflict of interest

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