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MONOGENIC IBD: DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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მონოგენური ნაწლავთა ანთებითი დაავადებები (MONOGENIC IBD): დიაგნოსტიკური და თერაპიული გამოწვევები

თსსუ, გ.ჟვანიას სახ. პედიატრიის საუნივერსიტეტო კლინიკა

რეზიუმე

ადრეული დებიუტის ნაწლავთა ანთებითი დაავადებები, შესაძლებელია იყოს დაკავშირებული ე.წ მონოგენურ ნაწლავთა ანთებით დაავადებასთნ. განსაკუთრებით მაშინ, თუ პირველი მანიფესტირება ხდება 6 თვის ასაკამდე. ეს არის იშვიათი გენეტიკური პათოლოგიები, ატიპიური კლინიკური მიმდინარეობით, მათ შორის ექსტრაინტესტინალური ართრიტით. მათი დიფერენცირება სხვა ინფექციური, თუ ალერგიული დაავადებებიდან წარმოადგენს მნიშვნელოვან გამოწვევას. ჩვენს მიერ წარმოდგენილია კლინიკური შემთხვევა: ჩვილი პერსისტიული ჰემატოქეზიით, რეკურენტული ართრიტით. კომპლექსური იმუნოლოგიური, გენეტიკური კვლევებით დადგინდა მონოგენური ნაწლავთა ანთებითი დაავადების (monogenic IBD) არსებობა.

Introduction. Inflammatory bowel disease (IBD) diagnosed in infancy is rare but increasingly recognized as a distinct clinical entity often underpinned by monogenic causes. Monogenic IBD, representing less than 5% of pediatric IBD cases, typically manifests in very early-onset forms (VEO-IBD; <6 years) or infantile IBD (<2 years), and even more rarely before 6 months of age [1]. These forms are frequently associated with immune dysregulation, defective epithelial barrier function, and altered microbial interactions [2]. Clinical overlap with food allergies, infections, and autoimmune diseases often delays diagnosis and appropriate treatment.

Case Presentation. The patient is a male infant born at term via spontaneous vaginal delivery following an uneventful pregnancy, except for maternal SARS-CoV-2 infection during the second trimester. Birth weight and Apgar scores were within normal limits. He was exclusively breastfed until the onset of symptoms.

At the age of 4 months, the infant presented with hematochezia - fresh blood streaks in stools occurring sometimes several times per day. Initially suspected to be food protein-induced allergic proctocolitis (FPIAP), the mother eliminated dairy and soy from her diet with no significant improvement. Over the following weeks, the patient continued to have blood-streaked stools with mucous, intermittent fussiness, poor weight gain, and abdominal discomfort.

At 6 months of age, he developed sudden swelling, warmth, and decreased movement of the left ankle without any preceding trauma or fever. Joint aspiration was sterile, and inflammatory markers were mildly elevated. The arthritis was recurrent, affecting the same joint over a span of two months.

Diagnostic workup included: complete blood count revealing microcytic anemia, elevated C-reactive protein (CRP), low serum iron, and hypoalbuminemia. Stool studies were negative for infectious pathogens. Fecal calprotectin was elevated. Serological tests showed elevated IgG anti-TTG but normal IgA levels. Fecal elastase was low, raising concern for pancreatic involvement.

An endoscopic examination revealed multiple discrete ulcers and patchy inflammation in the colon. Biopsies confirmed active chronic colitis with crypt abscesses and architectural distortion. Small bowel mucosa was intact, and no villous atrophy was seen. Imaging with abdominal ultrasound and MRI ruled out abscess or fistula formation.

Initial treatment with systemic corticosteroids led to partial remission of gastrointestinal bleeding and full resolution of arthritis. Sulfasalazine was added as a maintenance agent, and azathioprine initiation was planned pending TPMT activity. The clinical phenotype, early onset, steroid-responsive colitis with arthritis, and poor response to dietary restriction prompted referral for genetic testing. Whole-exome sequencing is underway in collaboration with international experts in monogenic IBD.

Discussion. Monogenic inflammatory bowel disease (IBD) represents a rapidly growing subset of early-onset IBD (EO-IBD), distinguished by single-gene mutations that disrupt mucosal immunity, epithelial barrier integrity, or microbial tolerance. These disorders are particularly prevalent in infants and young children, especially those who present with disease before the age of 2 years (very early-onset IBD, VEO-IBD) or even within the first months of life (infantile-onset IBD). Unlike polygenic IBD, monogenic forms often present with atypical, severe, or refractory clinical features and may be associated with systemic immune dysregulation [1,2].

In the presented case, the persistence of hematochezia despite elimination diets and the emergence of extraintestinal symptoms (arthritis) prompted reconsideration of the initial diagnosis of food protein-induced allergic proctocolitis. Allergic proctocolitis typically resolves with dietary management and rarely presents with systemic symptoms. The development of monoarthritis in an infant, particularly without evidence of preceding infection or trauma, strongly suggests an underlying immune-mediated process, which aligns with documented presentations of monogenic IBD [3].

The identification of colonic ulcerations on endoscopy and histopathologic evidence of chronic colitis further supported this suspicion. Colonoscopic findings in monogenic IBD can be indistinguishable from classic IBD (Crohn's disease or ulcerative colitis), but the rapid onset, early age of presentation, and systemic features (joint inflammation, anemia, immune markers) suggest a primary immunodeficiency or immune dysregulation syndrome.

Notably, the elevated IgG anti-TTG in this patient was interpreted cautiously. While suggestive of possible celiac disease, isolated IgG anti-TTG positivity in an infant without clear histological evidence of villous atrophy may also reflect generalized immune activation rather than true autoimmunity. In monogenic IBD, aberrant antibody production is a known phenomenon due to disrupted regulatory T cell function or defects in B cell maturation [4].

Therapeutically, the use of systemic corticosteroids led to significant clinical improvement in both gastrointestinal and joint symptoms, highlighting the immune-driven nature of the disease. However, steroid dependence or resistance is common in monogenic IBD, and long-term control often requires early introduction of steroid-sparing agents such as thiopurines, methotrexate, or biologics [5]. In this case, sulfasalazine was initiated with plans for azathioprine pending TPMT activity — a prudent strategy given the risk of severe myelosuppression in TPMT-deficient individuals.

Genetic testing is now a cornerstone of the diagnostic workup in suspected monogenic IBD, especially in infants with atypical presentations or treatment-refractory disease. More than 70 genes have been implicated, including those affecting regulatory T-cell function (FOXP3, IL2RA), epithelial barrier integrity (ADAM17, TTC7A), and autoinflammatory pathways (XIAP, NOD2, CYBB) [6]. Identifying a causative mutation can significantly influence management. For instance, IL10 or IL10R mutations may necessitate hematopoietic stem cell transplantation (HSCT), as conventional immunosuppressive therapies are largely ineffective.

The maternal history of COVID-19 during pregnancy in this case is noteworthy. While no direct causative link has been established between in utero SARS-CoV-2 exposure and monogenic IBD, there is emerging interest in how maternal infections and inflammation might influence neonatal immune

development and trigger disease expression in genetically susceptible individuals [7]. Further research is needed to elucidate these connections.

Ultimately, this case emphasizes the need for heightened clinical vigilance in infants presenting with refractory gastrointestinal symptoms and systemic features. Pediatricians and pediatric gastroenterologists must be aware of red flags for monogenic IBD, including:

- Onset of symptoms before age 2 (especially <6 months)
- Poor response to dietary or conventional IBD therapies
- Extraintestinal manifestations (arthritis, skin lesions, failure to thrive)
- Family history of consanguinity or autoimmune disease
- Evidence of immune dysregulation (e.g., elevated inflammatory markers, unusual antibody profiles)

Early recognition, comprehensive immunologic workup, and prompt genetic testing are critical to guiding therapy and improving long-term outcomes. In resource-limited settings, international collaboration—as demonstrated in this case—is essential for accessing advanced diagnostic tools and personalized treatment strategies.

Conclusion. Infants with persistent hematochezia and systemic manifestations such as arthritis should be evaluated for monogenic IBD. Early endoscopic and immunologic assessment, along with genetic testing, are crucial for diagnosis. Prompt initiation of immunomodulatory therapy may alter disease course and prevent long-term complications.

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SUMMARY

Early-onset inflammatory bowel disease (EO-IBD), especially when presenting before 6 months of age, raises a high index of suspicion for monogenic IBD. These rare, genetically driven disorders are associated with atypical presentations, including extraintestinal manifestations such as arthritis. Differentiating them from more common allergic or infectious conditions poses significant diagnostic and therapeutic challenges. We present a case of an infant with persistent hematochezia and recurrent arthritis, ultimately guiding immunologic and genetic investigation for monogenic IBD.

Keywords: monogenic IBD, diagnosis, therapy, challenges