

DIAGNOSTIC WORK UP IN VERY EARLY-ONSET IBD and IBD LIKE DISORDERS

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Background

Very early-onset Inflammatory Bowel Disease (VEOIBD) refers to children with IBD diagnosed before the sixth year of life ¹. This age group represents the minority of worldwide reported IBD cases with an estimated incidence of 4.37 and a prevalence of 14 per 100,000 children ². Similar to adults with IBD, young patients present with abdominal pain, intestinal bleeding, diarrhoea and weight loss. Of additional concern in young children however, are the effects of chronic inflammation on growth and global development. In paediatric patients it is therefore paramount to establish effective diagnostic and management strategies early in the disease course ³. IBD-like intestinal inflammation can also present as a feature of a phenotypically diverse group of monogenic conditions including primary immunodeficiencies affecting T- and/or B-cells, phagocyte defects, hyper- and autoinflammatory disorders, immune regulation- and epithelial barrier defects ⁴. To diagnose “monogenic IBD” can have far reaching consequences such as performing potentially curative haematopoietic stem cell transplantation in children with IL10 pathway deficiencies. Uhlig et al described all currently known monogenic diseases with IBD-like phenotype ³. Certain clinical and histological features and laboratory abnormalities can be suggestive for those conditions (see table 1).

Clinical history and examination

The mnemonic YOUNG AGE MATTERS MOST is a useful clinical approach to children with suspected monogenic IBD (for further details see: ³) as it highlights specific phenotypic features commonly seen in this cohort of patients.

YOUNG AGE onset

M ultiple family members affected and consanguinity

A utoimmunity (e.g. thyroiditis, haemolytic anaemia, thrombocytopenia, neutropenia, arthritis, hepatitis)

T hriving failure

T reatment with conventional medication fails

E ndocrine concerns

R ecurrent infections

S evere perianal disease

M acrophage activation syndrome / HLH

O bstruction and atresia of the intestine

S kin lesions, dental and hair abnormalities

T umors

Laboratory tests

A basic set of investigations as described in table 1 (FBC, Lymphocyte subsets, Immunoglobulins and neutrophil oxidative burst assay) may give further indication for underlying primary immune deficiency/dysregulation. Additional investigations to specifically assess the innate or adaptive immune function may be required and should be considered after discussion with a paediatric immunologist.

<p>1. Establish IBD-like pathology (as per BSPGHAN/ESPGHAN guidance):</p> <ul style="list-style-type: none"> - Endoscopy with Histology (OGD and ileo-colonoscopy) - Small bowel imaging - Biochemistry (FBC, CRP, ESR, Albumin, faecal calprotectin) <p>2. Exclude intestinal infections</p> <p>3. Consider other causes of intestinal inflammation such as coeliac disease or allergic gastrointestinal disease</p>
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TEST	DISEASE GROUP
Full blood count	Neutro-, Thrombo-, Lymphocytopenia (indicative of some monogenic IBD conditions – see ³)
Neutrophil oxidative burst assay	Chronic Granulomatous Disease
Immunoglobulins A, G, M, E	Common variable immune deficiencies Agammaglobulinaemia Hyper-IgM Hyper-IgE
Lymphocyte subsets	Severe combined immune deficiencies Agammaglobulinaemia
Specialist Laboratories for functional confirmation	
FOXP3+CD25+ T-Cells	IPEX
XIAP	XLP2
IL10 suppression of LPS induced PBMC activation	IL10 receptor defects
Genetic testing either to establish genetic diagnosis of functionally confirmed disease or as primary screening tool (subsequently requiring functional confirmation if possible)	
Single candidate sequencing, targeted gene panel sequencing, whole exome/genome sequencing	

Table 1. Pathway for investigating children with suspected monogenic IBD modified from Uhlig et al. ³

Genetics

Single gene testing (Sanger sequencing) as first line genetic screening tool is now less commonly deployed due to the improved availability of next generation sequencing (NGS) technologies. NGS enables us to screen for pathogenic variants in multiple genes (targeted gene panel) or the entire exome/genome. Broader screening tools are advantageous given that many monogenic conditions have overlapping phenotypes⁵. Gene panels have the advantage of producing more diagnostically reliable data for a specific list of genes whereas whole exome/genome platforms enable the discovery of mutations in novel genes⁶.

Children with VEOIBD should be managed in a multidisciplinary team involving local immunology and genetics services. For further information or additional advice please contact:

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