Genetics & Very Early-Onset Inflammatory Bowel Disease (VEO-IBD)

Professor Lee Way Seah
Department of Paediatrics
Faculty of Medicine
University Malaya
Kuala Lumpur
Definition of VEO-IBD
Epidemiology
VEO-IBD in Asia
Etiology of VEO-IBD
Differential diagnoses
Clinical approach
Implications to clinical practice
## Classification of PIBD according to Age Group

### Paris Modification of Montreal Classification

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Previous classification</th>
<th>Age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric-onset IBD</td>
<td>Montreal classification A1</td>
<td>&lt; 17 y</td>
</tr>
<tr>
<td></td>
<td>Paris classification A1b</td>
<td>10 – 17 y</td>
</tr>
<tr>
<td>Early-onset IBD</td>
<td>Paris classification A1a</td>
<td>&lt; 10 y</td>
</tr>
<tr>
<td><strong>Very early-onset IBD</strong></td>
<td>Paris classification A1a</td>
<td>&lt; 6 y</td>
</tr>
<tr>
<td>Infantile-onset IBD</td>
<td>Paris classification A1a</td>
<td>&lt; 2 y</td>
</tr>
<tr>
<td>Neonatal IBD</td>
<td>Paris classification A1a</td>
<td>&lt; 28 day of age</td>
</tr>
</tbody>
</table>

Ouahed J, et al. *Inflamm Bowel Dis* 2019
Shim JO. *Pediatr Gastroenterol Hepatol Nutri* 2019
Epidemiology of VEO-IBD

VEO-IBD
- Onset < 6y
- Heterogenous phenotype
- Mild disease to extensive, severe phenotype

A sub-set of VEO-IBD
- Early age of onset
- Positive family history
- Severe / atypical phenotype

Monogenic disease

VEO-IBD (< 6 y)
6 – 15% of all PIBD

PIBD (< 18 y)
15 – 20% of all IBD

IBD in all age groups
Incidence

- Rising incidence in Canadian study
  - 1.3 / 100,000 in 1994 vs. 2.1 / 100,000 in 2009
- Stable in France and Korea
- Better awareness? Improved diagnostic accuracy?

Contributing factors

- Genetic predisposition
- Early environmental exposure (gut microbiome developing in first 3y after birth):
  route of delivery, gestational age, maternal diet, infant feeding practice

Benhimol E, et al. Am J Gastroenterol 2017
Bequet E, et al. J Crohn’s Colitis 2017
## Epidemiology of VEO-IBD in Asia

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>VEO-IBD (%)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italian PIBD Network</td>
<td>2009–2014</td>
<td>688</td>
<td>11%</td>
<td>Extensive phenotype needing aggressive treatment</td>
</tr>
<tr>
<td>Canadian multi-center</td>
<td>2014–2017</td>
<td>1092</td>
<td>4%</td>
<td>Similar phenotype between &lt; 6y vs. 6-10 y</td>
</tr>
<tr>
<td>Japanese multi-center</td>
<td>2012-2015</td>
<td>243</td>
<td>11% (&lt; 5y)</td>
<td>Similar phenotype between &lt; 5y vs. 6-17 y</td>
</tr>
<tr>
<td>Southeast Asia PIBD-Network (7 countries from Southeast Asia)</td>
<td>2007-2017</td>
<td>227</td>
<td>30%</td>
<td>Not described</td>
</tr>
</tbody>
</table>

More research needed about epidemiology & phenotype of VEO-IBD in Asia.

Aloi M, et al. *Inflamm Bowel Dis* 2014  
Dhahliwal J, et al. *J Crohn’s Colitis* 2018  
Arai K, et al. *Intestinal Research* 2020  
Chew KS, et al. *International PIBD Congress; Budapest; 2019*
Etiology of VEO-IBD

Monogenic etiology of VEO-IBD

- Defects in epithelial barrier function
- Defects in adaptive immunity
- Impaired regulatory T cells
- Autoinflammatory & Hyperinflammatory defects
- Phagocytic & NADPH oxidase complex defects
- Others

Kelsen JR, et al; NASPGHAN Position Paper. JPGN 2020
<table>
<thead>
<tr>
<th>Epithelial barrier defect</th>
<th>Defects in adaptive immunity</th>
<th>Autoinflammatory and Hyperinflammatory defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTC-αa deficiency</td>
<td>IL-10 deficiency</td>
<td>Mevalonate kinase deficiency</td>
</tr>
<tr>
<td>NEMO (NF-κB essential modifier deficiency)</td>
<td>IL-10RA/RB deficiency</td>
<td>XLP-2 (X-linked lymphoproliferative syndrome 2)</td>
</tr>
<tr>
<td>Dystrophic epidermolysis bullosa</td>
<td>X-linked agammaglobulinaemia</td>
<td>Herman-sky-Pudiak syndrome</td>
</tr>
<tr>
<td>Klindler syndrome</td>
<td>Common variable immunodeficiency</td>
<td>Phosphorylase Cy2 defects</td>
</tr>
<tr>
<td>ADAM-17 deficiency</td>
<td>Dyskeratosis congenita</td>
<td>Familial Mediterranean fever</td>
</tr>
<tr>
<td>Familial diarrhoea</td>
<td>Hyper-IgE syndrome</td>
<td>Chronic enteropathy with SLCO2A1</td>
</tr>
<tr>
<td>Congenital diarrhoea</td>
<td>Leukocyte adhesion deficiency</td>
<td>Familial haemophagocytic lymphohistiocytisis type 5</td>
</tr>
</tbody>
</table>

Kelsen JR, et al; NASPGHAN Position Paper. JPGN 2020
<table>
<thead>
<tr>
<th>Impaired regulatory T cells</th>
<th>Phagocytic and NADPH oxidase complex defects</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPEX</td>
<td>Chronic granulomatous disease AR</td>
<td>MASP deficiency</td>
</tr>
<tr>
<td>LRBA deficiency</td>
<td>Chronic granulomatous disease XL</td>
<td>Trichohepatoenteric syndrome (SKIV2L, TTC7)</td>
</tr>
<tr>
<td>STAT1 deficiency</td>
<td>Congenital neutropenia</td>
<td>CHAPLE syndrome</td>
</tr>
<tr>
<td></td>
<td>Glycogen storage disease type 1b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukocyte adhesion deficiency 1</td>
<td></td>
</tr>
</tbody>
</table>
Review of VEO-IBD

Very Early Onset Inflammatory Bowel Disease: A Clinical Approach With a Focus on the Role of Genetics and Underlying Immune Deficiencies

Jodie Ouahed, MD, MMSc, Elizabeth Spencer, MD, Daniel Kotlarz, MD, PhD, Dror S. Shouval, MD, MMSc, Matthew Kowalik, MD, Kaiyue Peng, MD, Michael Field, MS, Leslie Grushkin-Lerner, PhD, Sung-Yun Pai, MD, Athos Bousvaros, MD, MPH, Judy Cho, MD, Carmen Argmann, PhD, Eric Schadt, PhD, Dermot P. B. McGovern, MD, PhD, Michal Mokry, MD, PhD, Edward Nieuwenhuis, MD, PhD, Hans Clevers, MD, PhD, Fiona Pownie, DPhil, Holm Uhlig, MD, DPhil, Christoph Klein, MD, PhD, Alexio Muise, MD, PhD, Maria Dubinsky, MD, and Scott B. Snapper, MD, PhD

Ouahed J, et al. Inflamm Bowel Dis 2019

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Evaluation and Management for Patients With Very Early-onset Inflammatory Bowel Disease


Very Early-Onset Inflammatory Bowel Disease: A Challenging Field for Pediatric Gastroenterologists

Katsuhire Arai

Center for Pediatric Inflammatory Bowel Disease, Division of Gastroenterology, National Center for Child Health and Development, Tokyo, Japan

Arai K. Pediatr Gastroenterol Hepatol Nutri 2020
Mutations Affecting IL-10 & IL-10 Receptor

- IL-10 produced by dendritic cells, macrophages & T-reg cells
- Maintains intestinal homeostasis
- IL-10 suppresses excessive pro-inflammatory (inhibits release of TNFα) response via binding to IL-10 receptor (IL-10R)
- IL-10 deficiencies or IL-10R mutation; IL-10 has no effect, resulting excessive inflammation

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10R</td>
<td>IL-10RA</td>
<td>AR</td>
<td>Crohn’s</td>
<td>Perianal fistula, arthritis, eczema, folliculitis, pyoderma, B-cell lymphoma</td>
</tr>
<tr>
<td>IL-10R</td>
<td>IL-10RB</td>
<td>AR</td>
<td></td>
<td>Perianal fistula, arthritis, eczema, AIHA, B-cell lymphoma</td>
</tr>
<tr>
<td>IL-10</td>
<td>IL-10</td>
<td></td>
<td></td>
<td>Perianal fistula</td>
</tr>
</tbody>
</table>

- Mutations in IL-10R more common than IL-10
- Asia: mostly IL-10R mutations (China, Japan, Korea)

- Mostly case report / series
- Exact prevalence unknown
- In UK; 8% (5/62) IBD < 2y confirmed IL-10 or IL-10R mutation.

Ouahed J, et al. Inflamm Bowel Dis 2019
Glocker EO, et al. NEJM 2008
Clinical Features of IL-10 & IL-10R Mutations

- (Previously intractable ulcerating enterocolitis of infancy)
- Consanguinity (Arabic or Pakistani origin)
- Onset < 3 m
- Crohn’s disease phenotype
- Severe perianal disease; recto-vaginal or perianal fistulae
- Recurrent skin folliculitis (~ 50%)
- Recurrent infections: pneumonia, otitis media, varicella, etc.
- Unresponsive to immunosuppression, i.e. steroids and biologics
- Surgical intervention

Glocker EO, et al. NEJM 2008
Therapy for IL-10 & IL-10R Mutations

- Severe & intractable phenotype
- Severe perianal disease
- Resistant to immunosuppressive therapy including azathioprine, MTX, steroids, biologics
- HSCT curative in several reports
- 3 patients had HSCT cured of colitis and immunosuppression discontinued.
- **Mutations must be confirmed**

Severe ano-cutaneous fistula
Before and after allogeneic stem cell transplant

Glocker EO, et al. NEJM 2009
X-linked Inhibitor of Apoptosis Protein (XIAP)

- XIAP gene associated with primary PID & Crohn’s disease phenotype (chronic intestinal inflammation)
- XIAP protein stops apoptotic cell death by inhibiting action of enzyme caspases (necessary for apoptosis)
- Clinically X-linked lymphoproliferative disease (XLP); 2 types
  - XLP1: SAP (SLAM-associated protein) deficiency; SH2D1A mutation
  - XLP2: XIAP (X-linked inhibitor of apoptosis) deficiency
2 Siblings with XIAP

- Elder brother, healthy parents, non-consanguineous
- Polyarthritis, uveitis, psoriasis
- Crohn’s disease at 2 y
- Partially controlled with IM & infliximab
- Cataracts - prolonged steroids
- Mutation: XLP2 (XIAP deletion)
- Haploidal SCT (father donor)
- Remission

- Younger brother
- Crohn’s disease onset 7 m
- Not responding to EEN, aza, combination antibiotics
- Homozygous deletion in XIAP (c.909_910delTG, p.Cys303TrpfsTer6)
- Matched HSCT (sister donor)
- Remission of Crohn’s disease
XLP2 Phenotype & Clinical Features

- Inheritance: AR
- Phenotype: Crohn’s like granulomatous colitis
- C/F: perianal fistulas, HLH, splenomegaly, cholangitis, skin abscess, arthritis, EBV & CMV infections, hypogammaglobulinemia
- Colon histology: ulcers, transmural inflammation, granulomas
- Raised IL-18, decreased XIAP protein expression, little expression of IL-8 and MDP-1 in response to MDP stimulation
- Management: stem cell transplant

China

- 1/22 patients with confirmed XIAP had CD phenotype
- Most common phenotype HLH (18/22)

Ouahed J, et al. Inflamm Bowel Dis 2019
Xu T; Eur J Pediatr 2020
Differential Diagnoses of VEO-IBD

Consider

- Infections
- CMPA & other food allergies
- Primary immune deficiency (PID) with intestinal inflammation
- Eosinophilic GE
- Coeliac disease (not common in many parts of Asia)

Considerable overlap between VEO-IBD and other differential diagnoses

Must exclude more common conditions before considering VEO-IBD

Ouahed J, et al. Inflamm Bowel Dis 2019
Differentiating VEO-IBD from Other Conditions

- Variable GI & extra-GI manifestations
- Systemic / extra-GI: fever, arthritis, arthralgias, folliculitis, uveitis, skin disease
- Chronic diarrhoea: exclude bacterial GI infections, TB, HIV, Clostridium difficile, etc.
- Young infants with bloody stools: cow’s milk / food protein allergies
- Look for growth faltering, recurrent infections
- Non-bloody diarrhoea, growth faltering, anaemia, appropriate setting – consider coeliac disease

Ouahed J, et al. IBD 2019
**Approach to VEO-IBD**

**History**
- Family history, consanguinity, other immune-mediated conditions, early unexplained deaths
- GI symptoms, growth faltering, peri-anal skin-tags or discharge
- Diarrhoea: bloody / mucus diarrhea, response to dietary change
- Intermittent fever, recurrent infections, vaccines history

**Remember:**
VEO-IBD can present with a wide variety of symptoms, both GI & extra-GI

Ouahed J, et al. *IBD* 2019
Approach to VEO-IBD

Physical Examination

❖ Growth parameters, finger clubbing, oral ulcers
❖ Systemic: skin (folliculitis), joints, eyes, signs of infections
❖ Signs of nutrients deficiencies
❖ Disease phenotype, anal ulcers
❖ Dysmorphic features, hepatomegaly, splenomegaly, hyperkeratosis, epidermolysis bullosa

Suspect monogenic VEO-IBD if:
• Wt loss, growth faltering
• Frequent infections, arthritis, folliculitis, fevers
• Severe perianal disease
• Refractory course
Approach to VEO-IBD

**Blood**
- FBC & differential; ESR & CRP, metabolic studies
- Coeliac serology (uncommon in Asia)
- Immunoglobulins classes (IgG, IgM, IgA, IgE), lymphocyte subsets, antibody response to vaccines (vaccination history), etc.
- HIV serology, TB testing (diagnosing TB may be challenging)

**Stools**
- Occult blood
- Bacteria, parasites (Giardia, Cryptococcus, etc.), viruses
- C. difficile (if > 12 months)
- Calprotectin

Ouahed J, et al. IBD 2019
### Specific Signs & VEO-IBD

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Signs, features</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10 signaling defects</td>
<td>Severe perianal disease, folliculitis, arthritis, onset first few months</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>Oral leukoplakia</td>
</tr>
<tr>
<td>CVID</td>
<td>Recurrent infections, organomegaly, autoimmune &amp; endocrine disorders</td>
</tr>
<tr>
<td>IPEX</td>
<td>Enteropathy, T1DM, eczema, food allergies, autoimmune features</td>
</tr>
<tr>
<td>Trichohepatoenteric syndrome</td>
<td>Syndromic features, hair abnormalities</td>
</tr>
<tr>
<td>SCID, CVID, CGD</td>
<td>Recurrent infections</td>
</tr>
</tbody>
</table>

Ouahed J, et al. *IBD* 2019
Investigating VEO-IBD

Investigations
- Stool electrolytes, stools fat (if non-bloody diarrhea)
- Small bowel imaging
  - MRE, capsule endoscopy
  - Small intestinal ultrasound, CT scan, small bowel follow-through
- EGD, ileo-colonoscopies, biopsies

Laboratory clues
- Hypoglycaemia: glycogen storage disease type 1b
- Thrombocytopenia: Wiskott-Aldrich syndrome

Ouahed J, et al. IBD 2019
Investigating VEO-IBD

Therapeutic trial
- Antibiotics, metronidazole for *Giardia*
- 2-week trial of elemental formula in <12 month if with bloody stools
- Remember: both CD and cow’s milk protein allergy may improve with elemental formula

Consult immunologist, clinical geneticist
Histology Suggestive of VEO-IBD

Histological features suggestive of VEO-IBD

- Deep ulceration of mucosa, crypt abscess (IL-10 signaling defects)
- Chronic inflammation (architectural changes, crypt branching, inflammatory cells in lamina propria, non-caseating granuloma)
- Epithelial cell apoptosis (epithelial barrier function)
- Villous atrophy, leukocytic & eosinophilic infiltration (IPEX)

Ouahed J, et al. IBD 2019
Genetics & VEO-IBD

- Diagnostic algorithm – helpful
- Consult expert
- Research collaboration

Arai K. Pediatr Gastroenterol Hepatol Nutri 2020
Prevalence of Monogenic VEO-IBD

- Toronto, Canada
- Age < 18y, all disease severity
- (Research)
- N=1005
- Monogenic = 31 (0.3%)
- More likely earlier age at onset, family history of autoimmune disease, extra-intestinal manifestations, progression to surgery
- XIAP = 5

Crawley E, et al. Gastroenterology 2020
Prevalence of Monogenic VEO-IBD

- Italian multicenter
- VEO-IBD (onset < 6y); 60% < 2y
- Severe / atypical phenotype:
  - Severe perianal disease, recurrent infections, skin disease
  - Abnormal immune status
  - Autoimmune disease, HLH, tumors, etc.
- Overall N=93
- Monogenic = 12 (~13%)
- Impact: BMT in 7 children

Lega S, et al. Inflamm Bowel Dis 2020
# VEO-IBD in Malaysia

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Onset</th>
<th>Phenotype</th>
<th>Mutations</th>
<th>Management</th>
<th>Final status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; wk</td>
<td>Eosinophilic colitis → UC</td>
<td>Not done</td>
<td>IM, elemental diet, total colectomy</td>
<td>Remission, off drug</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>12 mo</td>
<td>UC</td>
<td>Not done</td>
<td>IM</td>
<td>Remission, off drug</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>7 mo</td>
<td>CD</td>
<td>None</td>
<td>IM, biologics, hemi-colectomy</td>
<td>Remission</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>2 mo</td>
<td>CD</td>
<td>TGF β1 deficiency</td>
<td>IM, biologics</td>
<td>Palliative care</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>6 mo</td>
<td>CD</td>
<td>None</td>
<td>IM</td>
<td>Remission</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>4 mo</td>
<td>IBD-U</td>
<td>None</td>
<td>IM</td>
<td>Remission, off drug</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>2 y</td>
<td>CD</td>
<td>XIAP (XLP2)</td>
<td>IM, HSCT</td>
<td>Remission</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>7 mo</td>
<td>CD</td>
<td>XIAP (XLP2)</td>
<td>IM, HSCT</td>
<td>Remission</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>11 mo</td>
<td>CD</td>
<td>None</td>
<td>IM, biologics, ileostomy</td>
<td>Persistent disease</td>
</tr>
</tbody>
</table>
New Discovery of Genetic VEO-IBD

- CD-like disease, onset at 3m
- Severe perianal disease, abscess, fistulae
- Colonic ulceration, pseudo-polyps, eosinophilic esophagitis, esophageal candidiasis
- Extra-GI: history of CMV retinitis, generalized muscle atrophy, global development delay, global brain atrophy (MRI)
- Refractory disease: IM, biologics, total colectomy
- Mutation: human TGF-β1 deficiency
Conclusions

- Genetic basis of VEO-IBD increasingly recognized
- ~ 10 – 15% of severe / atypical phenotype may have genetic basis
- Epidemiology & etiology in Asian children: largely not studied

- Consider monogenic disease in severe / atypical phenotype (consanguinity; +ve family history, very early onset [< 2y], immune abnormalities, extra-GI, refractory, etc.)
- Important to exclude monogenic IBD: avoid unnecessary / ineffective / potentially harmful therapy
- HSCT curative
- Collaboration with expert
Daniel Kotlarz, Munich Children’s Hospital, Munich, Germany
❖ Genetic analysis for VEO-IBD
❖ Kotlarz.Daniel@googlemail.com

Professor Lau Yu Lung, University Hong Kong, Hong Kong SAR
❖ Primary Immune Deficiency
❖ lauylung@hku.hk