The child under age 5 with inflammatory bowel disease

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Overview

• IBD as a manifestation of immune deficiency
  – Chronic granulomatous disease
  – Glycogen storage disease 1b
  – Hermansky-Pudlak syndrome
  – NEMO
  – Wiskott Aldrich Syndrome
  – IPEX
• Idiopathic IBD under age 5 years
  – Phenotype, genetics, prognosis.
Immunodeficiency and IBD

• Perform baseline immune evaluation and consult immunology in:
  – Very early onset IBD (age 2 years or less)
  – Child with recurrent infections
  – Syndromic child
  – Child with other autoimmune manifestations
    • Hemolytic anemia
    • Eczema
    • Autoimmune enteropathy
    • High IgE levels
• Recognition is essential, as therapy for many of these conditions involves stem cell transplant rather than immune suppression.

Chronic granulomatous disease
Winkelstein et al 2000; Medicine 79:155

• Primary immunodeficiency characterized by inability of cells to kill bacteria and fungi.
  – Staphylococcus, Aspergillus cause serious infection
  – Catalase positive organisms
  – Pneumonia most common infection (80%)
• 75% of patients present under age 5 years
• Autosomal recessive or X-linked
• GI manifestations
  – Colitis present in approximately 20%
  – Perianal abscess
  – Gastric outlet obstruction
• Diagnosis – defective NADPH oxidase
  – Dihydrorhodamine test
**Chronic granulomatous disease**

- Mimics Crohn disease on endoscopy and histology
- Granulomas in only 34% (Levine, Histopathology 2005)
- Paucity of neutrophils compared to UC (Shappi JPGN 2003)
- Decreased CD68+ macrophages (Liu et al, IBD Journal 2009)
- Therapy – gamma-IFN, steroids, thalidomide, SCT

**Glycogen Storage Disease Ib**

- Fasting hypoglycemia, hepatomegaly, growth retardation, and neutrophil dysfunction
- GI complications
  - Diarrhea, anemia, high esr
  - Ileitis, Colitis
- Therapy
  - Granulocyte colony stimulating factor
  - Adalimumab (Davis et al 2007; JIMD)
Hermansky–Pudlak syndrome

- Autosomal recessive disorder best reported in the Puerto Rican population
  - Oculocutaneous albinism
  - Bleeding diathesis from platelet dysfunction
  - Accumulation of lipofuscin in RE system
  - Granulomatous colitis
- Crohn like enterocolitis reported as young as age 3 years (Mahadeo et al 1991; J. Pediatrics 118:904).
- Treatment
  - DDAVP before any diagnostic procedure
  - 6-mercaptopurine, infliximab (Grucela 2006; AJG 101:2090)

Nuclear factor kappa B essential modifier (NEMO) mutation

- X-linked ectodermal dysplasia
  - Males only, female mutation lethal
  - Sparse teeth, alopecia, hypohydrosis
  - Associated with osteopetrosis, lymphedema
  - Natural killer cell dysfunction
  - Poor antibody production
- GI manifestations
  - Crohn like colitis
  - Villous atrophy
- Therapy – stem cell transplant
  - Permaul 2009 Immunol Res 44:89
Wiskott-Aldrich Syndrome (WAS)

- Eczema, thrombocytopenia, recurrent infections
- Small platelets (low mean platelet volume)
- Autoimmune disease in up to 70% of patients
  - UC like colitis in early infancy
  - Hemolytic anemia
  - Arthritis
  - Vasculitis
- Mutation in WASP gene causes Treg dysfunction
- One study suggests alterations in a WASP like gene (WAFL) in patients with UC.
- Therapy – 5ASA, stem cell transplant

X-linked immune dysregulation, polyendocrinopathy, enteropathy (IPEX)

- Presents in first two years of life
- Watery or bloody diarrhea
  - Subtotal or total villous atrophy
  - Colitis
- Systemic disease
  - Eczema
  - High IgE, autoantibodies
  - Recurrent infections
  - Hyperglycemia
- Diagnosis
  - FOXP3 gene mutation, reduced Tregs
- Treatment
  - Immunosuppression (tacrolimus)
  - Stem Cell transplant
Summary of IBD and Primary Immune Deficiencies

• Classic “immunology labs” often will not help establish a diagnosis
  – Complete blood count
  – Immunoglobulins
  – B and T cell subsets by flow cytometry
  – Mitogen assays – PHA, PMA, proliferation

• Clinical symptoms essential
  – Eczema and skin infections – WAS, IPEX
  – Hypoglycemia – GSD 1b
  – Albinism – Hermansky-Pudlak syndrome
  – Ectodermal dysplasia, defective NK function – NEMO
  – Recurrent abscesses and pulmonary infections – CGD

• Diagnosis can only be made with a high index of suspicion and appropriate genetic testing.
  – www.genetests.org

“Idiopathic IBD” in children under age 5 years

• How common is IBD under age 5?
• Does IBD under age 5 have a different disease distribution?
• Is there a greater likelihood of a family history?
• Are there genes that explain “idiopathic IBD” under age 5?
• Do patients under age 5 have more aggressive or severe disease?
“Idiopathic” IBD is rare in the young child

<table>
<thead>
<tr>
<th>Pediatric Reference</th>
<th>Cutoff</th>
<th>Proportion of young children</th>
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<tbody>
<tr>
<td>Gupta 2008 (n=989)</td>
<td>5 yr.</td>
<td>10% (Crohn only)</td>
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<tr>
<td>Kugathasan 2003 (n=199)</td>
<td>10 yr.</td>
<td>20%</td>
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<tr>
<td>Cannioto 2007 (n=184)</td>
<td>2 yr.</td>
<td>9%</td>
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</tbody>
</table>

Both CD and UC can be seen in the child under 5 years

<table>
<thead>
<tr>
<th>Consortium</th>
<th>Age dx</th>
<th>CD</th>
<th>UC</th>
<th>IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heyman (n=1370)</td>
<td>0-2 years</td>
<td>n=31</td>
<td>n=27</td>
<td>n=29</td>
</tr>
<tr>
<td>(USA, J. Pedes 2005)</td>
<td>3-5 years</td>
<td>n=44</td>
<td>n=58</td>
<td>n=22</td>
</tr>
<tr>
<td>Castro (n=1445)</td>
<td>0-5 years</td>
<td>n=70</td>
<td>n=203</td>
<td>n=45</td>
</tr>
<tr>
<td>(Italy, IBD Journal 2008)</td>
<td></td>
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<tr>
<td>Van Limbergen (n=416)</td>
<td>0-8 years</td>
<td>n=53</td>
<td>n=19</td>
<td>n=10</td>
</tr>
<tr>
<td>(Scotland, Gastro 2008)</td>
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The IBD in young children predominantly involves the colon: UC or Crohn colitis (Montreal L2), and is less than 20% of the total number of pediatric cases.
IBD in children under age 5 years
(Paul et al 2006; J. Clin Gastro 40:583)

• 413 consecutive IBD outpatients
  – 8 patients with immune deficiency syndromes
    or indeterminate colitis excluded.

• 50 patients under age 5 years
  – 33 patients with ulcerative colitis
    • Pancolonic 67%, left sided 12%, rectosigmoid 21%
  – 17 patients with Crohn disease
    • Ileocolonic 24%, colonic 76%
    • No isolated ileal disease

Crohn’s disease in children
under 5 years (Gupta et al 2008; AJ Gastro 103:2092)

• Crohn’s patients under 5 years analyzed from a
  registry of 1,736 patients (989 with CD).
• Mean followup 5 years.
• Age 0-5 years - 98 patients with CD, 15% initially
diagnosed as UC or IC.
• Isolated colonic disease more common
• Risk of intestinal abscess or stricture, perianal
  fissure or fistula markedly less than in older
  patients.
• Granulomas in 17% of patients (not significantly
different from older patients).
Does family history differ?

- Heyman et al
  - 29% family history overall in pediatric (0-17 years) cohort
  - Only 12% of first degree relatives
  - In probands diagnosed under age 2 years
    44% overall had a family history in first degree relatives.

Do genetics differ?

- The genetic studies currently published are underpowered to conclusively identify a group of genes in the population of children under age 5 years.
- Most large genetic consortia do not contain enough children in this age group to distinctively characterize a unique early onset phenotype.
- Replication, validation, and accurate phenotyping will be essential in genome-wide association studies of these young children.
- Promising work
  - Kugathasan
  - Grimbacher
IBD and mutations affecting the interleukin-10 receptor  
(Glocker et al, NEJM Nov 2009)

• Early onset colitis (under 1 year of age)
• Four of nine patients had distinct homozygous mutations in IL10R genes (chromosome 21)
  – Deficient STAT3 phosphorylation when cells stimulated with IL-10
• Phenotype
  – Middle Eastern descent (Turkish, Lebanese)
  – Colitis, perianal abscesses
  – Enterocutaneous fistulizing disease
  – Colostomy or ileostomy required in 3 patients
  – Other infections
    • Folliculitis, pneumonia, renal abscess, otitis media, bronchitis

Does IBD under age 5 have a different behavior/prognosis?

• Not enough data to allow a conclusion
• Comparison of childhood onset vs. adult onset disease in Scotland  
  (van Limbergen 2008)
  – Childhood onset disease <=16 year
• Higher probability of surgery in:
  – adults with Crohn disease
  – Children with UC
Why?

- Different phenotype
- Different time of presentation
- **Different management**
  - Earlier IM use in children
  - Growth preservation
  - Different “risk tolerance” by parents

Conclusion

- Crohn’s disease and ulcerative colitis in the child under age 5 is infrequently seen, but not rare.  
  - 10-20% of all pediatric cases
- Serious consideration should be given to excluding primary immunodeficiency, especially if other organ systems are involved.
- Most “idiopathic IBD” in this age group involves the colon.
- Further genetic and natural history studies in this cohort are needed to determine if these very young children are indeed a unique phenotype.