Pathophysiology of diarrhea

- Inadequate absorption of water, due to:
  - Congenital transport defect
  - Lumenal fermentation of unabsorbed solute
  - Diffuse mucosal injury
- Acute
  - Usually infectious, + stool cult, rarely biopsied
- Chronic
  - > 2-3 weeks, often associated with FTT
  - May require biopsy, nutritional support, etc.
  - Congenital diarrheas
    - Osmotic - unabsorbed solute
      - Disorder of digestion or transport
      - Remits with removal of solute or NPO
    - Secretory - diffuse mucosal disease or injury
      - Does not remit when NPO

Outline of topics covered in this lecture

- Congenital Transport and Enzymatic Deficiencies
- Primary Enteropathies
- Autoimmune Enteropathy
- Allergic/eosinophilic Enteritides

Causes of chronic diarrhea and malabsorption in infancy and childhood

- Congenital transport and enzymatic deficiencies
- Severe (Primary) Enteropathies of Infancy
- Allergic enteropathies
- Metabolic disorders (GSD I, Wolman's, MPS)
- Motility disorders (Hirschsprung disease)
- Infections (bacterial overgrowth, Giardia, HIV)
- Anatomical Disorders (malrotation, short gut, lymphangiectasia)
- Tumors (direct infiltration, secretion of VIP)
- Pancreatic disorders
- Endocrine disorders – hyper/hypothyroidism

Table 1: Evolving etiologies of severe protracted diarrhea in children in Italy

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<td>4 (12)</td>
<td>2 (3)</td>
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<td>Food intolerance</td>
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<td>4 (12)</td>
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<td>Structural enterocyte defects</td>
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<td>Eosinophilic enteropathy</td>
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<td>Lymphangiectasia</td>
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<td>Motility disorders</td>
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<td>5 (16)</td>
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Intestinal Biopsy Findings in Enteropathies

- **Normal villous morphology**
  - congenital chloride diarrhea
  - carbohydrate malabsorption
  - sucrase-isomaltase deficiency

- **Villous atrophy +/- inflammation**
  - Autoimmune enteropathy and IPEX
  - Microvillus inclusion disease
  - Epithelial dysplasia (“tufting”)
  - Gluten-sensitive enteropathy
  - Eosinophilic gastroenteritis and dietary protein-induced enteropathy
  - Congenital immunodeficiency disorders

- **Specific or characteristic features**
  - Fat-filled enterocytes [abetalipoproteinemia, chylomicron retention]
  - Infectious agents
  - Absence of plasma cells – immunodeficiency
  - Lymphangiectasia
  - Metabolic storage disorders

Lipids

1. Abeta/hypobetalipoproteinemia
2. Chylomicron retention disease

- Fat malabsorption
- Low levels of serum lipids
- Failure to thrive
- Neurologic and visual problems

Congenital Transport and Enzymatic Deficiencies

- **Normal or slightly abnormal biopsy**
  - Carbohydrates
  - Aminoacids
  - Electrolytes and trace metals
  - Vitamins

- **Abnormal biopsy**
  - Lipids

Abetalipoproteinemia

- Deficiency of MTTP (Microsomal Triglyceride Transfer Protein)
- Chr 4q22
- Irregular vacuoles
- Non-membrane bound
- Absence of apo-B lipoproteins
- Acanthocytosis
Chylomicron Retention Disease

- **AR**
- **SAR1B**, chr 5q31 (Sar1-ADP-ribosylation)
- Codes for GTPase
- Chylomicron trafficking

Primary enteropathies of infancy

- Epithelial defects
  - Microvillus inclusion disease
  - Tufting enteropathy
  - Enteroendocrine cell deficiency
  - Autoimmune enteropathies
- Others

Microvillus Inclusion Disease (MVID), Microvillus Atrophy (MVA)

- Described in 1978 by Davidson et al
- Severe secretory diarrhea during 1st week of life
- Absence of infectious/enzymatic etiology
- Villous atrophy without significant inflammation
- Abnormal mucosal staining by PAS, CD10
- Abnormal mucosal ultrastructure
- **MYO5B** gene; 18q21
  - Encodes myosin Vb, regulates distribution of endosomes

Microvillus inclusion disease

- Normal
- Microvillus Inclusion Disease

“Tufting” Enteropathy

- Severe diarrhea 1st week
- Dysmorphic features in some infants
  - Choanal atresia
  - Esophageal/rectal atresia
  - +/- “tufting” in colon
- **AR**
- EpCAM gene mutations (chr 2p21)
- TPN dependent
- Clusters of cases described in families from Malta and from the Gulf states

Microvillus inclusion disease

- PAS
- CD10
- 18 day-old boy
Tufting enteropathy

Enteroendocrine cell dysgenesis – Neurogenin-3 mutation

- NEUROG 3 is a protein involved in gut and pancreatic endocrine development
- Pts with Neurogenin 3 mutations present with congenital diarrhea and eventually develop type I diabetes
- TPN-dependent; bowel transplantation

Duodenal biopsy, 5 months

Enteroendocrine cell dysgenesis – Neurogenin-3 mutation

- No enteroendocrine cells per IHC for chromogranin
- Neurogenin-3 -/- mice lack endocrine cells in pancreas and intestine, death from diabetes in the first days of life

Control

Case

Immunostaining for chromogranin A

Enteropathy with dysmorphic features “Syndromatic diarrhea”

Chronic diarrhea in first year of life
Facial dysmorphism
Trichorrhexis nodosa
Immunodeficiency
Poor prognosis
Similar patients described as tricho-hepato-enteric syndrome
Gene TTC37 (5q14) - Thespin

Autoimmune Enteropathy

- Most common severe enteropathy of childhood
- Rarely observed in adults, but may account for some cases of refractory celiac disease
- Heterogenous entity
- Severe early-onset diarrhea, male preponderance
- Concomitant colitis and gastritis present in majority
- Circulating gut-autoantibodies
- Autoimmune phenomena in majority of cases
- Favorable response to immunosuppression (Tacrolimus)
- BMT attempted in some cases

Autoimmune enteropathy - extra-intestinal manifestations

- Insulin-dependent DM
- Nephrotic syndrome, membranous GN with granular IgG deposits or interstitial nephritis
- Thyroid insufficiency
- Acute or chronic hepatitis
- Coombs –positive hemolytic anemia and thrombocytopenia
- Diffuse pulmonary interstitial infiltrates
- Autoantibodies: ASMA, AMA, ANA, anti-parietal cell antibodies
Autoimmune enteropathy (AE) — clinical conditions

- IPEX Immunodysregulation / polyendocrinopathy / enteropathy / X-linked.
  - Mutation in FOXP3 gene, Xp11.23-q13.3
  - FOXP3 codes for a protein called Scurfin which is predominately expressed in CD4+/CD25+ regulator T-cells
- 50% of patients with clinical features of IPEX have normal FOXP3 gene — “IPEX-like”
  - A few cases reported with specific CD 25 deficiency

Autoimmune Enteropathy

- Severe villous atrophy
- Marked inflammatory destruction of crypts
- Increased apoptosis
- Loss of Paneth and goblet cells
- Concomitant colitis and gastritis
- Few surface intraepithelial lymphocytes

Gut Autoantibodies

Anti-Enterocyte Antibodies

- Linear fluorescence pattern along the apex or brush border of enterocytes
- Also anti-goblet abs
- Predominantly IgG but IgA and IgM have been described

Autoimmune enteropathy in adults

- Protracted diarrhea, weight loss, malnutrition
- Absence of response to gluten-free diet and/or absence of typical celiac antibodies and/or characteristic HLA immunotype
- AEA + variety of autoantibodies
- T-cell rearrangement studies neg
- Good response to immunosuppression

Autoimmune enteropathy - differential diagnosis

- Celiac disease
- Enteritis in congenital immunodeficiencies
- Food allergy
- IBD
- GVHD
- Collagenous or lymphocytic enterocolitis
- Autoimmune polyglandular syndrome

Autoimmune enteropathy - 6 yr-old boy with chronic diarrhea and FTT

IgA deficiency - 6 yr-old boy with chronic diarrhea and FTT

Duodenum – celiac-like

Colon - focal marked lymphoid hyperplasia

Colon - focal crypt architectural distortion
Common Variable Immunodeficiency

Increased basal crypt apoptotic activity, or extensive loss of goblet and Paneth cells
GVHD-like or IPEX-like histology
Crohn’s-like enteritis, especially in younger age

Food Allergy
The New Epidemic

- Food hypersensitivity reactions affect up to 8% of children under 3 years of age and approximately 2.5% of the general population
- 3x increase in the prevalence of food allergies over the past 20 years
  - Changes in environment
  - Changes in the processing of foods
  - Alteration of immunologic recognition
  - Use of antibiotics
- Food intolerance (non-allergic food hypersensitivities) are adverse responses caused by metabolic or enzymatic disorder (lactose)

Eosinophilic Gastroenteropathies
The New Epidemic

Spectrum of disease or unique diseases
Codon

Allergic proctocolitis
Eosinophilic esophagitis
Eosinophilic gastroenteritis

Immunopathology of Food Allergic Disorders

- IgE mediated (Immediate hypersensitivity)
  - Oral allergy
  - Urticaria
  - Anaphylaxis
- Cell mediated (delayed onset/chronic)
  - Dietary protein enteropathy/enterocolitis
  - Dietary protein-induced proctocolitis
  - Gluten-sensitive enteropathy
- Mixed IgE and Cell mediated (delayed onset/chronic)
  - Atopic dermatitis
  - Eosinophilic gastrointestinal disease

**Allergic proctocolitis: key features**

- Usually presents by 6 months of life
- Blood streaked, loose stools +/- diarrhea in otherwise well-appearing infants
- Some may present with constipation, mimicking HD
- Usually occurs in breast-fed (50-60%) or cow/soy milk formula-fed infants
- Diagnosis is via clinical history; food prick skin tests negative
- Treatment via protein elimination; resolution of symptoms in 48–72 h
- Tolerance to allergen usually occurs by 1 yr of life

Adapted from Maloney, J. Pediatr Allergy Immunol 2007:18:360-367

**Allergic Eosinophilic Gastroenteritis in children: Key features**

- Usually occurs from infancy through adolescence
- Chronic symptoms of poor appetite, poor weight gain or weight loss, emesis, diarrhea, occult blood in stool
- Endoscopy and biopsy helpful in diagnosis with usually marked eosinophilic infiltration of mucosa and submucosa
- > 90% of cases have involvement of gastric antrum
- Approximately, 50% are atopic; 50% have peripheral blood eosinophilia
- Resolution of symptoms with removal of causal food within 6 wk
- Most common foods: cow’s milk, egg, soy, cereals, fish
- Excellent response to amino-acid-based formula
- Responsive to steroids
- Typically prolonged; natural history not well understood

Adapted from Maloney, J. Pediatr Allergy Immunol 2007:18:360-367
Eosinophilia in the GI Tract

- Allergy ≠ Eosinophilia
- Eosinophilia ≠ Allergy

Dietary protein-induced enteropathy/enterocolitis

- Dietary protein-induced enteropathy/enterocolitis
  - Infancy to school age
  - Cow’s milk, soy, wheat, rice, chicken and fish
  - Malabsorption and osmotic diarrhea
  - Biopsy: flat villi, +/- increased eosinophils; diff dx: celiac disease

2 month-old with malabsorption; improved on elemental formula

Eosinophilic Gastroenteritis – Differential Diagnosis

- Infections, particularly parasitic
  - Stool ova and parasite study may be diagnostic
- Drug reactions
  - Check drug history – Azathioprine, NSAIDS, tacrolimus
- Crohn’s disease
  - May primarily show eosinophilic abscesses
  - Typically more of a focal lesion
- Some primary immunodeficiencies
- Connective tissue disorders
  - Consider lupus, polyarteritis, and Wegener’s
  - Are fibrinoid changes present in vessels?
- Inflammatory fibroid polyps
  - Check configuration of lesion on endoscopy
- Hyperesinophilic syndrome.
  - Are tumorous lesions present, particularly in soft tissue?
- Post-transplant eosinophilic gastroenteritis
  - Check transplant history, immunomodulatory drugs

Post-Liver Transplant Eosinophilic Gastroenteritis

2yr-old girl 18 months post-O LT with weight loss, food refusal, peripheral eosinophilia