Congenital Diarrhea (Intractable diarrhea syndrome)

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Objectives

- General approach of congenital diarrhea
- Tufting Enteropathy
- MVID
- DDx
Types of diarrhea

• Diarrhea can be divided: secretory, osmotic, inflammatory or secondary to altered motility.

• **Secretory diarrhea** results from a disturbance in the balance between absorption (primarily via villous epithelial cells) and secretion (primarily via crypt cells).

  • **This is caused by** the activation of intracellular mediators like cyclic AMP, cyclic guanosine 5’-monophosphate, and intracellular calcium $\rightarrow$ stimulate active chloride secretion from crypt cells.

• Various bacterial enterotoxins (*Cholera, Escherichia coli, Shigella* and *Salmonella*), Vasoactive Intestinal Peptides (VIPomas), Ion transport defects (congenital chloride diarrhea (CCD) and congenital sodium diarrhea (CSD)).
Types of diarrhea

- **Osmotic diarrhea** is caused by ingestion of non-absorbable solutes or by disease states that interfere with normal solute absorption.

- A typical example is lactose intolerance.

- The colonic bacteria ferment the non-absorbed sugar to short chain organic acid → generate an osmotic load resulting in diarrhea.
Types of diarrhea

- **Inflammatory diarrhea:**
  - Characterized by the presence of blood, mucus and leukocytes in the stool → an infective process, allergic colitis (CMPA, EE) or inflammatory bowel disease (IBD).

- **Diarrhea due to motility disturbances:**
  - It can be either hypermotility as in hyperthyroidism or hypomotility as in pseudo-obstruction) tends to produce loose or normal looking stools.
  - **Stasis** predisposes to bacterial overgrowth, leading to diarrhea and malabsorption.
DDx of Diarrhea in the 1st 6 months of life

• **Congenital abnormalities of gut**: Short gut (NEC, atresias, gastroschisis)

• **Allergic enteropathy/enterocolitis**: Cow’s milk, Soya protein intolerance

• **Chronic diarrhea of neonatal onset**: Tufting Enteropathy (TE), Micro-Villous Inclusion Disease (MVID), Ion Tp defects

• **Congenital pancreatic insufficiency**: CF, Shwachman–Diamond syndrome, isolated pancreatic insufficiency

• **Immunodeficiencies**

• **Acrodermatitis enteropathica**

• **Autoimmune enteropathy**

• **IPEX syndrome**: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked

• **Abetalipoproteinemia**

• **Lymphangectasia**
DDx according to Bx findings

**TABLE 1. Causes of protracted diarrhea beginning during the first six months of life**

<table>
<thead>
<tr>
<th>Normal villus-crypt architecture:</th>
</tr>
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<tbody>
<tr>
<td>Transport defects</td>
</tr>
<tr>
<td>chloride-bicarbonate exchanger (chloride-losing diarrhea)</td>
</tr>
<tr>
<td>sodium-hydrogen exchanger (congenital sodium diarrhea)</td>
</tr>
<tr>
<td>ileal bile acid receptor defect</td>
</tr>
<tr>
<td>sodium-glucose cotransporter (glucose-galactose malabsorption)</td>
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<table>
<thead>
<tr>
<th>Micronutrient deficiency</th>
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<tbody>
<tr>
<td>acrodermatitis enteropathica (zinc deficiency)</td>
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<table>
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<tr>
<th>Enzyme deficiency</th>
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<tr>
<td>enterokinase deficiency</td>
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<tr>
<td>Congenital short bowel</td>
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<table>
<thead>
<tr>
<th>Villus atrophy:</th>
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<tbody>
<tr>
<td>microvillus inclusion disease</td>
</tr>
<tr>
<td>tufting enteropathy</td>
</tr>
<tr>
<td>autoimmune enteropathy</td>
</tr>
<tr>
<td>IPEX syndrome</td>
</tr>
<tr>
<td>infectious enteropathy</td>
</tr>
<tr>
<td>post-infectious enteropathy</td>
</tr>
<tr>
<td>allergic enteropathy</td>
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<tr>
<td>idiopathic</td>
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## Clues in the history and clinical examination towards specific diagnostic entities

<table>
<thead>
<tr>
<th>History</th>
<th>Diagnostic consideration</th>
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<tbody>
<tr>
<td>Polyhydramnios</td>
<td>Congenital chloride diarrhoea, sodium diarrhoea</td>
</tr>
<tr>
<td>Onset with gastroenteritis episode</td>
<td>Post-enteritis syndrome</td>
</tr>
<tr>
<td>Bowel surgery</td>
<td>Short gut, bacterial overgrowth</td>
</tr>
<tr>
<td>Association with specific food</td>
<td>Intolerance, allergy</td>
</tr>
<tr>
<td>Excessive fruit juice intake</td>
<td>Chronic non-specific diarrhoea</td>
</tr>
<tr>
<td>Recurrent infections</td>
<td>Immunodeficiency – congenital or acquired</td>
</tr>
</tbody>
</table>

Bulky, oily, malodorous stools: Exocrine pancreatic insufficiency
Explosive, watery stools: Carbohydrate intolerance
Family history of chronic diarrhoea: Genetic causes e.g. Cf, coeliac disease, IBD
Atopy: Food allergies
Autoimmunity: Coeliac, autoimmune enteropathy
Recurrent aphthous ulcers: Coeliac disease, Crohn's disease
Extra intestinal manifestations – e.g. rash, arthritis: IBD
Blood and mucus in the stool: Infective colitis, allergic colitis, IBD
Bone marrow transplant: Graft versus host disease
Multi-organ or neurological involvement: CDG, mitochondrial disorders
Investigations in chronic diarrhoea

Baseline investigations
- Stool microscopy: ova, cysts, parasites, fat globules
- Stool microbiology
- Stool pH, reducing substances, electrolytes
- Full blood count and differential
- U&E, CRP and ESR
- Liver function tests including albumin
- Coeliac serology

Subsequent investigations
- Stool elastase-1
- Stool alpha-1-antitrypsin
- Vitamins A, D, E, coagulation, B12, folate levels, Ca, Mg, phosphate, ferritin
- Endoscopy, colonoscopy and biopsies for histology, disaccharidases, bacterial culture, Electron microscopy
- Imaging studies: x-ray, ultrasound, barium, MRI
- Sweat test
- Immunoglobulins, subclass, lymphocyte and neutrophil function test, complements
- Zinc level
- Cholesterol, triglycerides, low-density lipoproteins
- Autoantibodies including anti-enterocyte antibodies
- Isoelectric focussing of transferrin
- Gastrin, secretin, calcitonin, VIP
- Manometric studies
- Urinary laxatives
- Breath hydrogen tests
- Plasma and urinary bile acids and salts
- Response to dietary modifications
## Differentiation of osmotic and secretory diarrhea

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Osmotic Diarrhea</th>
<th>Secretory Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool volume</td>
<td>Small (generally $&lt; 200$ ml/24 hours)</td>
<td>Large ($&gt; 200$ ml/24 hours)</td>
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<tr>
<td>Responding to fasting</td>
<td>Diarrhea reduced significantly</td>
<td>Diarrhea continues</td>
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<tr>
<td>Stool osmotic gap</td>
<td>$&gt; 135$ mOsm/l</td>
<td>$&lt; 50$ mOsm/l</td>
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<tr>
<td>Stool Na</td>
<td>$&lt; 70$ mmol/l</td>
<td>$&gt; 70$ mmol/l</td>
</tr>
<tr>
<td>Stool K &amp; Cl</td>
<td>$&lt; 35$ mmol/l</td>
<td>$&gt; 40$ mmol/l</td>
</tr>
<tr>
<td>Stool pH</td>
<td>$&lt; 5.5$</td>
<td>$&gt; 6$</td>
</tr>
<tr>
<td>Stool reducing substance</td>
<td>Positive ($&gt; 0.5%$)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Paediatrics and Child Health 2008;18 (10): 441-447
- Secretory
- Osmotic

**Intestinal Biopsy**

- Normal
- Abnormal

**Secretory**

- Ion Tp defects:
  - Congenital Ch Diarrhea
  - Congenital Sodium D

- Ultra-structural abnormalities of enterocytes:
  - MVID
  - Tufting Enteropathy

**Osmotic**

**Congenital Lactase deficiency**
**Congenital Enterokinase def**

**Tufting Enteropathy**
**Phenotypic diarrhea**

**AIE, IPEX**
Severe and Protracted Diarrhea: Results of the 3-Year (1993-1996) SIGEP Multicenter Survey in Italy

<table>
<thead>
<tr>
<th>Cause</th>
<th>Patients (n)</th>
<th>Recovered (n)</th>
<th>Persisting diarrhea (n)</th>
<th>Deceased (n)</th>
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<td>Autoimmune enteropathy</td>
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<tr>
<td>Others</td>
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<td>Multiple food intolerance</td>
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<td>Chronic intestinal pseudo-obstruction</td>
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<tr>
<td>Undefined</td>
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<td>0</td>
<td>3</td>
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</table>

<sup>a</sup> Outcome was not reported in one of these three cases.

32 patients from 26 centers in 3 years

Protracted diarrhea: results of the five-year survey in a tertiary hospital in Korea

Table 1. Clinical features and outcomes observed in 25 patients with protracted diarrhea

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (day)</th>
<th>Sex</th>
<th>Group</th>
<th>Diagnosis</th>
<th>TPN duration (day)</th>
<th>Vilous atrophy (grade)</th>
<th>Outcome</th>
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<td>1</td>
<td>F</td>
<td>ED</td>
<td>MVID</td>
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<td>1</td>
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<tr>
<td>2</td>
<td>1</td>
<td>M</td>
<td>ED</td>
<td>MVID</td>
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<td>4</td>
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<td>Tufting enteropathy</td>
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<td></td>
<td>149</td>
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<td>recovered</td>
</tr>
</tbody>
</table>

TUFTING ENTEROPATHY (TE)
= INTESTINAL EPITHELIAL DISPLASIA (IED)

MICROVILLOUS INCLUSION DISEASE (MVID) =
MICROVILLOUS ATROPHY
Clinical presentation of MVID & TE

- Sever watery diarrhea observed from the 1st few days-weeks of life
- Stool volume 50-300 mls/kg/day while NPO & up to 100-500 mls/kg/day while feeding
  

- Significant dehydration with electrolytes disturbances & acid base balance changes (metabolic acidosis)
- Impaired growth
- Not respond to Enteral elemental diet → TPN dependant (variable)
- Associated anomalies (Tufting Enteropathy)
- FHx of consanguinity
- Hx of Polyhydromions (diarrhea started in utero)- Cong. Chloride Diarrhea
Tufting Enteropathy

- First described in 1994
- TE is characterized by clinical and histological heterogeneity and association with malformations
- It constitutive epithelial disorder involving both small intestine and colon that

- AR

Epidemiology

• Incidence is estimated at 1/50,000 - 100,000 live births in Western Europe (Goulet O, Salomon J, Ruemele F, et al. Orphanet J Rare Dis 2007;2)

• More common than microvillous inclusion disease (MVID)?

• The prevalence is higher in countries with high degree of consanguinity (Middle-East, Turkey and North Africa)
Pathology of TE

• Tufts correspond to non-apoptotic epithelial cells at the villous tips that are no longer in contact with the basement membrane = abnormal adhesion of the enterocytes to the BM).

• Gene mutation: decreased expression of EpCAM (Epithelial Cell Adhesion Molecule)

• EpCAM function may be important for the development of the crypt villus axis (where epithelial cells originate from stem cells in the crypt and migrate distally to the tip of the villus prior to shedding).

Gastroenterology. 2008 August ; 135(2): 429437
Pathology of TE

• An abnormal basement membrane & its components (integrins and laminins) thought to play a role in the pathogenesis of TE → dysfunctional epithelial cell interactions and adhesion

Associations

- **Dysmorphic features**: like esophageal atresia, choanal atresia, or unperforated anus.

- **Phenotypic abnormalities** eg: Dubowitz syndrome (microcephaly, growth retardation and a characteristic facial appearance)

- **Punctuated keratitis** is observed in more than 60% of patients → important in differentiating TE from MVID

- **Chronic arthritis**


Histology

- Histological abnormalities in TE are seen in both SB & colon:
  - **Total or partial villus atrophy**: present in all patients but is variable in severity
  - **Crypt hyperplasia**
  - **Normal or slightly increased density of inflammatory cells** in the LP
  - **Disorganization of the surface epithelium**: disorganization of surface enterocytes with focal crowding, resembling tufts (may affect up to 70% of villi → may not always seen esp. early in life --> repeated biopsies are required)
Histology

Villous atrophy with crypt hyperplasia without marked inflammatory cells in LP

Surface epithelial tuft formed at the top of blunted villi (may not be seen early in life)

Sherman P et al. JPGN 2004; 38:16–26
EM

• Disruption of desmosomal and integrin-mediated contacts between enterocytes

• On EM, the cytoplasmic organelles of enterocytes appear well preserved. There is an absence of microvillus inclusions or vesicular bodies
EM

Normal BB microvilli, normal cytoplasm & nucleus

Sherman P et al. JPGN 2004; 38:16–26

Normal deposition of laminin in a control patient

Goulet et al. Orphanet Journal of Rare Diseases 2007 2:20

Patient with TE with very faint and lamellar laminin
Px

• The long-term prognosis is variable & in general better than MVID.

• Most affected individuals depend on TPN to acquire a caloric intake sufficient for normal growth and development.

• TPN requirements may decrease in later childhood → TPN – related liver disease seems to be less in compare to MVID

• 3-year survival rates for recipients after intestinal transplant approaching 30% .

Microvillus Inclusion Disease (MVID) = Congenital Microvillus Atrophy = Familial Microvillous Atrophy = Davidson's syndrome

• MVID described first in 1978

• MVID manifests with severe secretory diarrhea either in the first few days of life (early-onset form) or in the first two months of life (late-onset form)


• The diagnosis is based on typical morphological abnormalities detected through a combination of light and electron microscopic (EM) analyses of small bowel & colon biopsies
Pathology

• The precise etiology of MVID is still unknown.

• The occurrence among siblings → raised the possibility that it is a genetic defect inherited in an autosomal recessive manner (Genetic defect has not been identified)

• ? Genetic defect → Altered structure of the cytoskeleton → defect in the trafficking of membrane proteins to the apical surface of differentiated epithelia

Carruthers L et al. *Clin Gastroenterol* 1986, 15:105-120
Pathophysiology- orph

- Recent observations indicate a selective defect in glycoprotein exocytosis in patients with MVID.
  

- Another hypothesis suggesting a defect in the auto-phagocytosis pathway was proposed to explain the morphological and functional abnormalities in MVID
  
  Reinshagen K et al. *Gut* 2002, 51:514-521
Presentation

- Significant diarrhea becomes so abundant → children can lose up to 30% of their body weight within 24 hrs → resulting in severe dehydration & profound metabolic acidosis

- No additional clinical signs are associated with MVID (e.g., malformations or associated anomalies)
Histology

• Standard histology reveals:
  1- A variable degree of villous atrophy without marked crypt hyperplasia

  2- Abnormal periodic-acid schiff (PAS) positive secretory granules accumulating in the apical cytoplasm of mature enterocytes (highly characteristic)

  3- An altered (atrophic) brush border membrane of the enterocyte (CD 10 immunostaining)
MVID

- Villus atrophy
- Relatively little crypt hyperplasia
- An absence of marked inflammatory infiltrate in the LP

Sherman P et al. JPGN 2004; 38:16–26
PAS) positive secretory granules accumulating in the apical cytoplasm of mature enterocytes (highly characteristic)

Sherman P et al. JPGN 2004; 38:16–26
Histology

- Microvillus inclusions can also be identified in colonocytes and in epithelial cells lining the stomach, renal tubules and gall bladder

- Microvillus inclusions are not found in every enterocyte → an extensive search on multiple blocks must be undertaken → Dx need skilled pathologist
These findings are completed by EM with the detection of:
1- Atrophic or completely absent microvilli on mature enterocytes
2- Microvillous inclusions (vacuoles lined by microvilli)
• Children with MVID are dependent on exclusive parenteral nutrition throughout their lives.

• Appropriate oral caloric intake are almost impossible → long term survival is extremely rare in compare patients with TE → early intestinal/combined transplantation is recommended

• A large number of patients do not survive the first three years of life as a result of infectious complications or rapid evolution of liver failure.

• Those children with MVID who survive often have mental and statural retardation, and renal complications.

Transplantation. 2004 Apr 15;77(7):1024-8
Treatment .. General principles

• **Supportive Mx:** Correction of dehydration, electrolyte & AB balance disturbances

• **Nutrition support (TPN):** Infants with partial intestinal function and a limited amount of stool output require only partial long-term PN infusions 3–4 times per week.

• **Careful monitoring** should be performed to avoid progressive growth retardation.
Treatment .. General principles

• In infants with MVID and TE, immunosuppressants therapies options are usually unsuccessful and the long-term prognosis is more guarded.

• Intestinal Transplantation (isolated small bowel or combined liver-small bowel transplantation): esp in patients with progressive liver disease, the loss of vascular access, and recurring life-threatening sepsis and poor quality of life)
DDx: Ion Transport defects

- **Chloride loosing diarrhea:**
  - Disorder of intestinal Cl/HCO3 exchange caused by mutations in the *SLC26A3* gene
  - It is characterized by persistent Cl- rich diarrhea from birth
  - Patients with CLD present with lifetime watery diarrhea with a high Cl content causing dehydration and hypochloremic metabolic alkalosis.
  - Chloride is low in urine and very high in stools (Chloride > 150 mmol/L > Sodium).
DDx: Ion Transport defects

• **Congenital Sodium Diarrhea:**
  - CSD is caused by defective sodium/proton exchange with only few sporadic cases reported.
  - The genetics of the disease have not yet been established.
  - Patients with CSD have acidosis and hyponatremia.
  - Stools have high concentrations of HCO3 and sodium (150 mmol/L).
DDx: CHO malabsorption

- **Glucose-galactose malabsorption (GGM):**
  - AR, rare, life threatening diarrhea
  - Defect in **SGLT-1** (SLC5A1 mutation)

- **Dx: 3 key features:**
  1. Elimination of Glucose & Galactose from diet → disappearance of sx
  2. +ve Glucose H2 BT
  3. Normal intestinal Bx- no mucosal disease

- Intestinal Bx can be used to measure Lactase & Sucrase activities to differentiate GGM from primary lactase or sucrose deficiency

- Responding well to fructose containing formula or diet

- Sx improve with age despite persistence of the Tp defect.
Syndromic (phenotypic) diarrhea in early infancy = Tricho-Hepato-Enteric syndrome (THE)

- Sever diarrhea in the 1st month of life
- SGA
- Facial dysmorphism (prominent forehead and cheeks, broad nasal root and hypertelorism)
- Hairs are woolly, easily removed and poorly pigmented.
- Liver disease affects about 50% of patients with extensive fibrosis or cirrhosis.
- A functional T-cell immune deficiency with defective antibody production was reported.
Syndromic (phenotypic) diarrhea in early infancy = Tricho-Hepato-Enteric syndrome (THE)

- Microscopic analysis of the hair shows twisted hair and **trichorrhexis nodosa**.
- Histopathological analysis of SB biopsy shows non-specific villous atrophy with low or no mononuclear cell infiltration of the lamina propria, and no specific histological abnormalities involving the epithelium.
- Variable phenotype with variable Px (EF → TPN)
Conclusions

• Till you find the Dx, adequate support of total caloric intake and nutritional rehabilitation is very crucial & has dramatically improved the survival of affected infants

• Identifying an underlying etiology of protracted infantile diarrhea is very important to allow appropriate management & counseling of parents, families, referring physicians and other health care professionals about long-term prognosis and therapeutic options.