Congenital and Genetic chronic Diarrhea

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Definition of acute and chronic Diarrhea

Acute: up to 5(7) Days

Chronic (Persistent): longer than 2 weeks

Prolonged: longer than 5(7) days
Classification of Chronic Diarrhea

1. **Infectious**: Cryptosporidium, Giardia, Entamoeba, Schistosoma, HIV
2. **Chronic bloody diarrhea**: IBD (Crohn’s, Ulcerative Colitis, Indeterminate colitis)
   Polyposis, TB
3. **Functional**: Irritable bowel syndrome, Toddler’s diarrhea
4. **Genetic** chronic diarrhea with **accompanying symptoms**: Coeliac disease, CF, Shwachman, Acrodermatitis enteropathica, early onset IBD,
5. **Congenital**: Osmotic / secretory Diarrhea, structural Defects, immune dysregulation,
   enteroendocrine dysregulation
Differential Diagnosis of chronic Diarrhoe according to the Age of Onset

- **Congenital:** since birth
- **Acquired:** after a healthy period start with Diarrhea
Defects in digestion and absorption of nutrients and electrolytes
Chronic osmotic or secretory diarrhoea from defects of transporters or enzymes

Defects in enterocyte structure
Chronic secretory/osmotic diarrhoea Derives from cytoskeleton dysregulation with alterations in enterocyte structure and function

Defects in intestinal immune-related homeostasis
Chronic secretory diarrhoea derives from immune dysregulation with inflammation and mucosal damage

Defects in enterendocrine cell differentiation
Chronic osmotic diarrhoea derives from enterendocrine dysgenesis due to defects in the stem cell differentiation process
Congenital Osmotic Diarrhea

- Glucose-Galactose-Malabsorption
- Sucrase-Isomaltase-Deficiency
- Maltase-Glucoamylase Deficiency
- Adult type hypolactasia
- Congenital “Lactase-Deficiency” (very rare)
- Fructose-Malabsorption (No mutation of GLUT5)
- All have in common: diarrhea stops when n.p.o. is given and by elimination of responsible sugars or by mixture with other sugars respectively
- Diagnosis: H-2 breath test with the suspected sugar
Clinical Use of $\text{H}_2$-Breath Tests

- Glucose
- Lactose, lactulose or fructose

- Glucose fermented if SIBO is present

- Lactulose fermented in colon estimates oro-cecal transit time
- Fructose or lactose, if malabsorbed in small bowel, reach colon & get fermented

- Hydrogen Methane

Ghoshal UC J Neurogastroenterol Motil 17: 312-17, 2011
Glucose Transporter Family in Intestinal Epithelium

- SGLT 1
- GLUT 5
- GLUT 2
- Na⁺-K⁺-ATPase
- Gluc
- Fructose

Diagram shows the transport mechanisms involving Na⁺, K⁺, and Glucose.
Mutation in SGLT 1
Wright E JCI 88: 1435, 1991
• Newborn baby with watery diarrhea after the start of feeding with breast milk

• N.p.o: stop of diarrhea

• Change to carbohydrate free feeding: normal stools

• Addition of breast milk: watery stools

• Diagnosis: congenital osmotic Diarrhea

• Investigation: Glucose H2-Breath test: negative (H2-Nonproducer!) Mutation analysis: Mutation in the SGLT1 Glucose-Galactose-Malabsorption Thrives normally with fructose-containing infant formula
2 Siblings mit Glu-Gal-Malabsorption, 16 and 18 Years old
Investigation in Osmotic Diarrhea

1. Stop Feeding
2. H2-Breath test with suspected Carbohydrate
3. Elimination of CH: CH-free Formula
   - If success: molecular genetic test or Enzyme determination in intestinal mucosa
   - If diarrhea persists change to completely hydrolysed formula or AA-formula
     *Eliminate Enterokinase-Deficiency*
Congenital Secretory Diarrhea

Critical parameters: Na\(^+\), K\(^+\) and Cl\(^-\) in stool

- Cl\(^-\) > Na\(^+\) + K\(^+\) = congenital chloride diarrhea
- Na\(^+\) > Cl\(^-\) + K\(^+\) = congenital sodium diarrhea
Congenital Chloride Diarrhea

- Autosomal recessive defect of the DRA-chloride transporter (exchanges $\text{Na}^+$/HCO$_3^-$), which is located in the neighbourhood of CFTR (chromosome 7q22-q31)
- Symptoms: polyhydramnios, intrauterine diarrhea with fluid filled bowel loops. Postnatally profuse watery diarrhea with severe hypochloremia
- Therapy: orale substitution of NaCl und KCl (high doses required, usually grams)
- Prognosis: good after a period of TPN
Congenital Sodium Diarrhea


- Symptoms: polyhydramnios, intrauterine diarrhea with fluid filled bowel loops. Postnatally profuse watery diarrhea and severe hyponatremia (DD: AGS with salt loss!)

- Therapy: oral substitution of sodium citrate and glucose-electrolyte solution, TPN

- Prognosis: good (?) with persistent secretory diarrhea

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Syndromic Congenital Na\textsuperscript{+}-Diarrhoe
SPINT2 Mutation

Fetal Sonography of Adomen
Congenital mixed Secretory/Osmotic Diarrhea = Structural Defect of Enterocyte leading to Intestinal Failure

Typical symptoms: diarrhea despite n.p.o. and worsened diarrhea after feeding, metabolic acidosis

- Congenitale microvillous atrophy (myoglobin-2-deficiency, syntaxin-3 deficiency)
- Tufting enteropathy
- IPEX-Syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked)
- Anendocrinosis: lack of enteroendocrine cells

Diagnosis: Small bowel biopsy with PAS-staining, Electron Microscopy, FOXP3 mutation
Yesil, B. 2 years, Chronic diarrhea since birth
EM: Microvillus Atrophy
Congenital Microvillus Inclusion Disease (MVID)

Congenital Microvillus Inclusion Disease

Myosin Vb

MVID – Syntaxin 3 Mutation

Congenital Tufting Enteropathy
EpCAM oder SPINT2 - Mutation

Tufting Enteropathy in a 1 year old Boy from Tbilisi
IPEX-Syndrome

• Severe enteropathy
• Diabetes mellitus
• Severe Eczema
• Endocrinopathies (Thyreoiditis)
• Renal involvement (Glomerulonephritis, Tubulopathy)
• Responsible Gene: FOXP3
• Treatment: Sirolimus (0,15 mg /kg /d)
Mutant Neurogenin-3 in Congenital Malabsorptive Diarrhea

Tricho-Hepato-Enteric Syndrome

- Hair anomalies: sparse, fragile, and uncombable hair
- Hepatopathy: liver cirrhosis
- Intractable diarrhea since birth with villous atrophy
- Molecular defect: SKIV2L (40%), TTC37 (60%)

Fabre A et al. Orphanet J Rare Dis 2013, doi 1186/1750
Congenital Defect of Zinc Transporter: Acrodermatitis enteropathica

- Autosomal recessive intestinal malabsorption of zinc
- Symptoms: epidermal desquamations with erythrodermia at mouth, feet, genito-anal region, loss of hair, paronychia and chronic diarrhea
- Diagnosis: severely decreased plasma level of zinc (< 6 mmol/l)
- Therapy: oral administration of zinc (2 mg/kg/day) as zinc aspartate
Acrodermatitis Enteropathica
Acrodermatitis Enteropathica (2)
Upper GI-Series of Congenital Short bowel
2 Children 10 years old

The little boy suffers from Short bowel syndrome after operation of volvulus during the Neonatal period. Despite Bianchi-procedure severe failure to thrive. Mother not able to help with home TPN
Origine of Intestinal Failure

• Majority: Short bowel syndrome
  – Congenital atresias, gastroschisis, volvulus, NEC

• Minority: nonfunctional intestinal tract
  – Intestinal pseudoobstruction, congenital diseases of enterocyte development, autoimmune enteropathy, microvillous inclusion disease, tufting enteropathy
Natural History of „Adaptation“ in Short Bowel Syndrome

10 years

19 years
Chronic Diarrhea with Steatorrhea

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnostic Test</th>
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</thead>
<tbody>
<tr>
<td>Cystic Fibrosis:</td>
<td>Sweat test</td>
</tr>
<tr>
<td>Shwachman-Syndrome:</td>
<td>Blood count, Elastase i. stool</td>
</tr>
<tr>
<td>Lipase-Deficiency</td>
<td>Lipase in duodenal juice</td>
</tr>
<tr>
<td>Colipase-Deficiency</td>
<td>Colipase in duodenal juice</td>
</tr>
<tr>
<td>Congenitale Lymphangiectasia</td>
<td>Small intestinal biopsy</td>
</tr>
<tr>
<td>Abetalipoproteinemia</td>
<td>Beta-Lipoprotein in serum</td>
</tr>
</tbody>
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IBD in Infants: Mutations in IL-10 Receptor

Glocker EO et al NEJM 361: 2033-45, 2009

Ileostomy

Ulcers and Abscess
IBD in Infants: Mutations in IL-10 Receptor

Intramural Microabscesses

Superficial Lymphoplasmocytic Infiltration

Glocker EO et al NEJM 361: 2033-45, 2009
IL-10 Receptor Mutation in IBD

IL-10 Receptor

Strong TLR ligation (abundant TNF induction)

Pathogen killed

Abundant IL-10 needed to control inflammation

In Absence of IL-10
Substantially enhanced pro-inflammatory response
Lethal uncontrolled inflammation

Cyktor JC et al Infect Immun 2011, May
Successful Bone Marrow Transplantation in IL-10 Receptor Mutation

Before BMT

After BMT

Glocker EO et al NEJM 361: 2033-45, 2009
Protein loosing Enteropathy

Identical in all forms: Protein in stool increased (α-1-Antitrypsin or total protein)
Total protein and Immunglobulins in plasma decreased:

- Congenital Lymphangiectasia
- CDG-Syndrom Typ Ib: Mannose-Phosphate-Isomerase-Deficiency (*Isoelectric Focussing of Transferrins*)  Bloody stools!!
- Autoimmune-Enteropathy (*Anti-gut-Antibodies*)
- After Fontan-Operation
- Constrictive Pericarditis
“Key Questions“ in Congenital Diarrhea

After history and clinical examination the following questions are helpful for diagnosis:
1. Is it an osmotic or a secretory Diarrhea?
2. Structural defect of the Mucosa?
3. Additional symptoms: dysmorphism, hair anomalies, blood, mucus, fat in stool, hepatopathy?
Algorithm for Diagnostic Workup of congenital Diarrhea

1. Stop Feeding
   - Osmotic Diarrhea
     - H2- Breath Test
       - CH-free Formula
         - Molecular genetics or Enzyme activities
           - AA-Formula
     - Osmotic/Secretory Diarrhea = Structural defect
   - Secretary Diarrhea
     - Electrolytes i. Stool
       - Therapy with Electrolyte rich nutrition
         - Molecular genetics MYO5B, SPINT2 EpCAM, FOXP3
     - Intestinal biopsy
       - Microscopy, PAS-staining, EM
       - Additional tests: Zn, Abetalipoprotein, AT3, Immune status
Thank you very much for your Attention