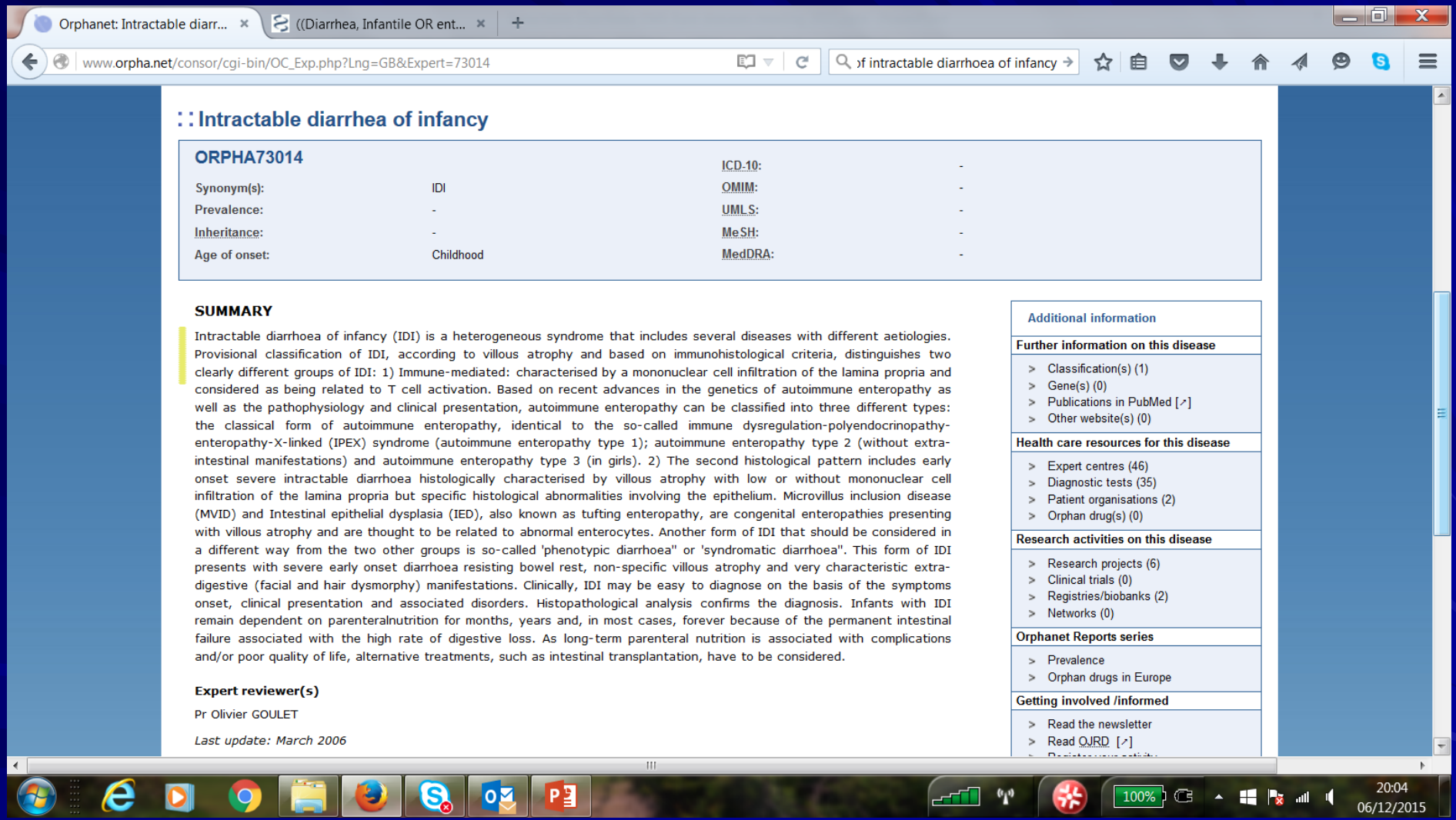
Chronic Intractable Diarrhoea of infancy

Infants with loose and frequent stools of sufficient severity and duration to require nutritional support, often parenteral nutrition

Orphanet


Orphanet: Intractable diarr...
((Diarrhea, Infantile OR ent...
www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=73014
of intractable diarrhoea of infancy
Intractable diarrhea of infancy
ORPHA73014
Synonym(s): IDI
Prevalence: -
Inheritance: -
Age of onset: Childhood
ICD-10: -
OMIM: -
UMLS: -
MeSH: -
MedDRA: -
SUMMARY
Intractable diarrhoea of infancy (IDI) is a heterogeneous syndrome that includes several diseases with different aetiologies. Provisional classification of IDI, according to villous atrophy and based on immunohistological criteria, distinguishes two clearly different groups of IDI: 1) Immune-mediated: characterised by a mononuclear cell infiltration of the lamina propria and considered as being related to T cell activation. Based on recent advances in the genetics of autoimmune enteropathy as well as the pathophysiology and clinical presentation, autoimmune enteropathy can be classified into three different types: the classical form of autoimmune enteropathy, identical to the so-called immune dysregulation-polyendocrinopathy-enteropathy-X-linked (IPEX) syndrome (autoimmune enteropathy type 1); autoimmune enteropathy type 2 (without extra-intestinal manifestations) and autoimmune enteropathy type 3 (in girls). 2) The second histological pattern includes early onset severe intractable diarrhoea histologically characterised by villous atrophy with low or without mononuclear cell infiltration of the lamina propria but specific histological abnormalities involving the epithelium. Microvillus inclusion disease (MVID) and Intestinal epithelial dysplasia (IED), also known as tufting enteropathy, are congenital enteropathies presenting with villous atrophy and are thought to be related to abnormal enterocytes. Another form of IDI that should be considered in a different way from the two other groups is so-called 'phenotypic diarrhoea" or 'syndromatic diarrhoea". This form of IDI presents with severe early onset diarrhoea resisting bowel rest, non-specific villous atrophy and very characteristic extra-digestive (facial and hair dysmorphy) manifestations. Clinically, IDI may be easy to diagnose on the basis of the symptoms onset, clinical presentation and associated disorders. Histopathological analysis confirms the diagnosis. Infants with IDI remain dependent on parenteralnutrition for months, years and, in most cases, forever because of the permanent intestinal failure associated with the high rate of digestive loss. As long-term parenteral nutrition is associated with complications and/or poor quality of life, alternative treatments, such as intestinal transplantation, have to be considered.
Expert reviewer(s)
Pr Olivier GOULET
Last update: March 2006
Additional information
Further information on this disease
> Classification(s) (1)
> Gene(s) (0)
> Publications in PubMed [↗]
> Other website(s) (0)
Health care resources for this disease
> Expert centres (46)
> Diagnostic tests (35)
> Patient organisations (2)
> Orphan drug(s) (0)
Research activities on this disease
> Research projects (6)
> Clinical trials (0)
> Registries/biobanks (2)
> Networks (0)
Orphanet Reports series
> Prevalence
> Orphan drugs in Europe
Getting involved /informed
> Read the newsletter
> Read OJRD [↗]
100%
20:04
06/12/2015

Classification:

- Normal Histology
- Abnormal histology

Normal Histology - Differential Diagnoses I

1. **CONGENITAL BRUSH BORDER ENZYME DEFICIENCIES**
   - Lactase Deficiency
   - Sucrase-isomaltase deficiency

2. **CONGENITAL TRANSPORT DEFECTS**
   - Sodium glucose co-transporter / glucose-galactose malabsorption
   - Chloride-bicarbonate exchanger / chloride losing diarrhoea
   - Sodium-hydrogen exchanger / congenital sodium diarrhoea
   - Ileal bile acid receptor defect

3. Pancreatic enzyme dysfunction/deficiency
   - Cystic fibrosis
   - **Enterokinase/Trypsinogen/lipase deficiencies**
     - **Gene PRSS7, 21q21 – Pro enterokinase (activates trypsinogen to trypsin)**
     - **PRSS1, 7q35 – trypsinogen synthesis**
     - **PNLIp – 10q26.1 (hydrolyses trigycerides to fatty acids)**

Normal Histology - Differential Diagnoses II

4. Micronutrient transport
   - Acrodermatitis enteropathica (Zinc transport defect)

5. Short bowel
   - Post operative
   - Post surgical

6. Congenital enterocyte heparan sulphate deficiency

7. Carbohydrate deficient glycosylation syndrome

CONGENITAL BRUSH BORDER ENZYME DEFICIENCIES

Congenital Lactase Deficiency

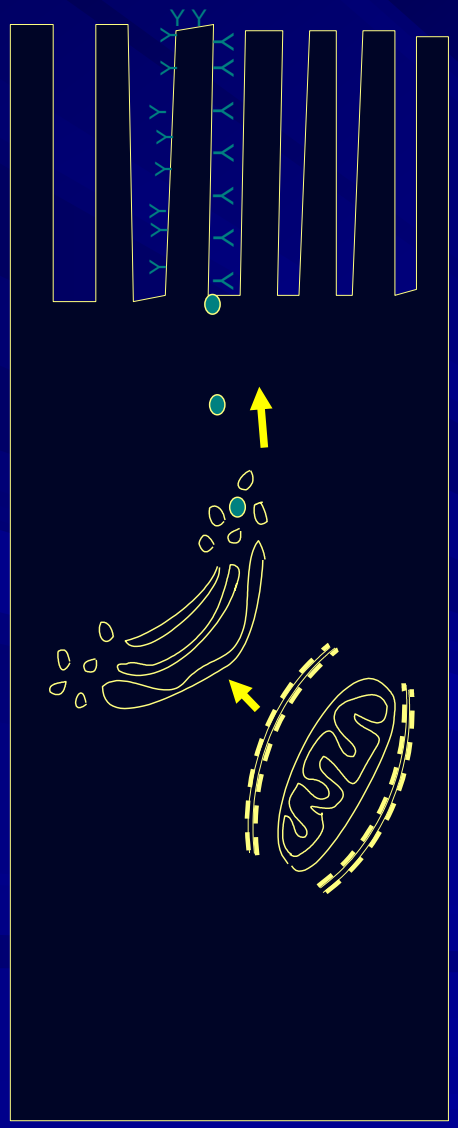
- Autosomal, recessively inherited
- Severe osmotic diarrhoea, duodenal morphology normal
- Present later with IBS like symptoms
- Lactose free diet – asymptomatic, normal growth
- Incidence of 1:60,000, enriched in Finnish population
- **LCT gene on 2q21 (Lactase phlorizin hydrolase activity)**
- **Kuokkanen et al Am J Hum Gen 2006; 78:339-344**
  - 24 families with 32 affected children
  - 5 mutations found in gene

Congenital Sucrase Isomaltase Deficiency

0.02% of Europeans, 5% of Greenlanders

Biosynthesis

3q25-q26
Isomaltase-sucrase activity



S I

Intraluminal cleavage to two active subunits

Microvillous Membrane — Direct transport to microvillous membrane

Pro-SIc

Golgi Complex — Complex glycosylation

Pro-SIh

Rough ER — Core glycosylation; Single chain poly-peptide precursor

Congenital Cl diarrhoea Holmberg 1986

SLC26A3 (7q22-q31.1) Chloride/HCO3 transporter distal ileum/colon

- 1:43,000 in Finland, plus others (c.100 cases)
- Clinically:
  - maternal polyhydramnois
  - Neonatal hydrops/ echogenic bowel loops
  - Secretory acidic diarrhoea
  - Stools [Cl] > [Na] > [K], median [Cl] 80 mmol/l
  - Mild metabolic alkalosis
- Rx:
  - Replace Cl (upto 6-8mmol/kg/d)
  - Replace Na + K
  - TPN
  - SBT
- Px: Untreated- retarded growth & development, mental & psychomotor retardation

Abnormal histology

Abnormal Histology - Differential Diagnoses

- **LIPID MALABSORPTION (Transport defect)**

  abetalipoproteinaemia, hypobetalipoproteinaemia, Anderson's (chylomicron retention disease

- Primary epithelial abnormalities
  - Microvillous Atrophy/Microvillous inclusion disease
  - Tufting enteropathy / Epithelial cell dysplasia

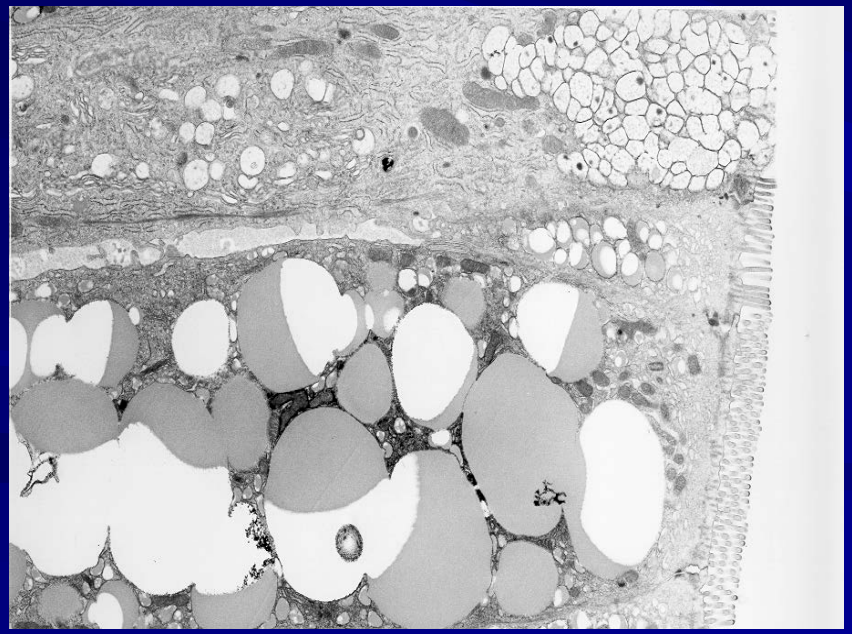
- Immunological abnormalities
  - Autoimmune enteropathy/IPEX
  - Intractable diarrhoea in severe combined immunodeficiency
  - Syndromatic intractable diarrhoea

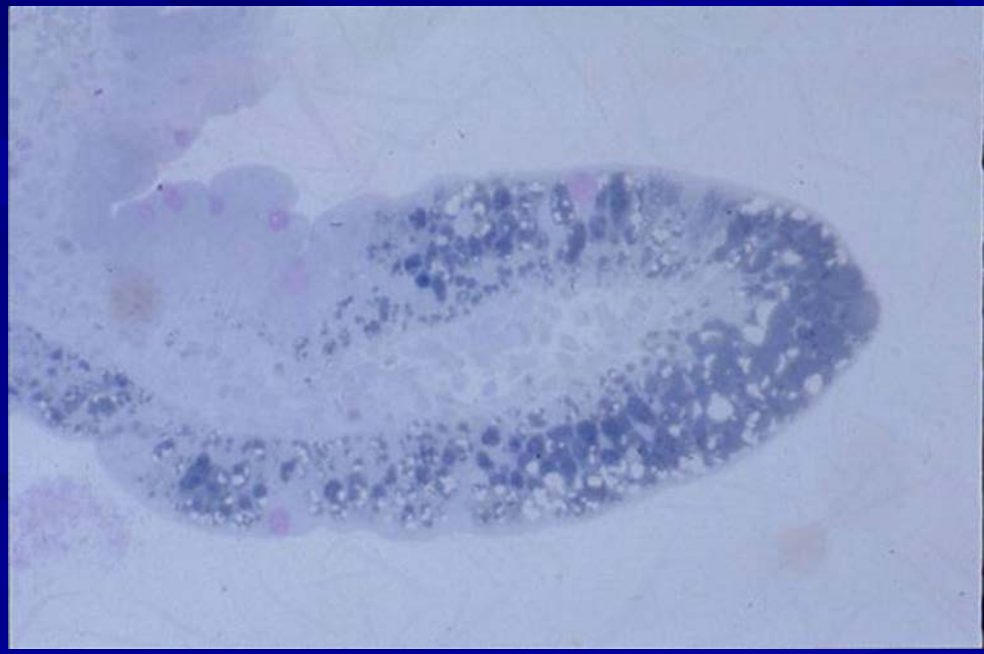
Intractable Diarrhoea - Abnormal Histology Differential Diagnosis

- Infantile inflammatory bowel disease
  - IL10RA abnormality
  - Infantile Crohn's- like disease (Roe et al 1992)
  - Chronic granulomatous disease
  - Glycogen storage disease type1b
- **Staphylococcus toxin mediated**
- **Syndromic diarrhoea**

Chylomicron Retention disorder

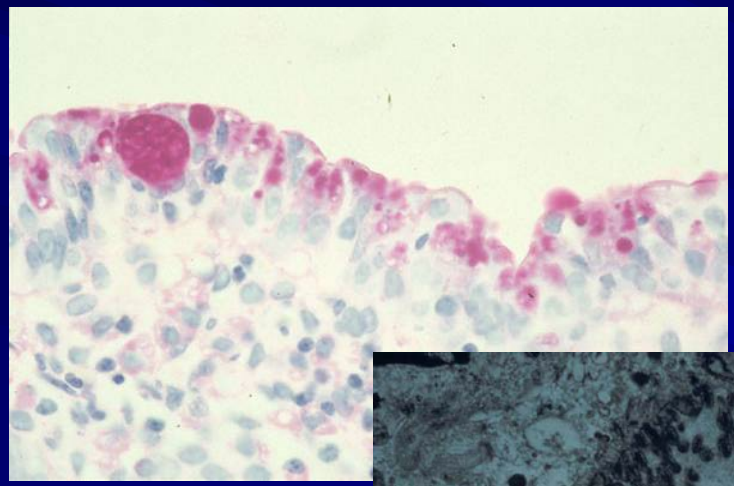
Mutations in a Sar1 GTPase of COPII vesicles are associated with lipid absorption disorders. [Journal Article] *Nature Genetics. 34(1):29-31, 2003 May.*

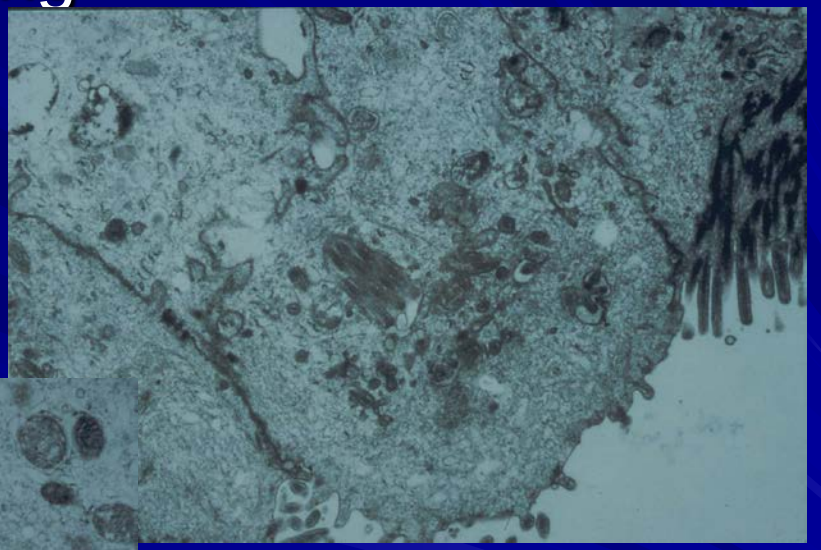


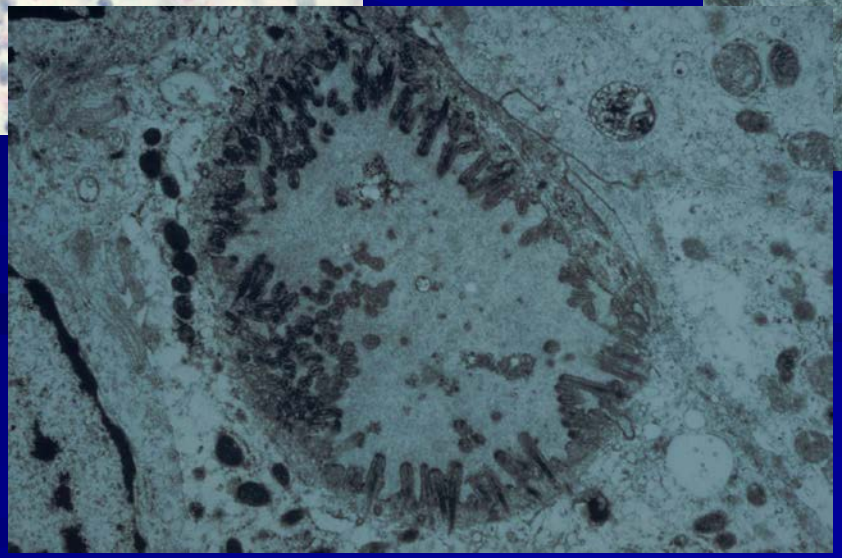


Microvillous Inclusion Disease

- Genetics MY05B (18q21)
- Intracellular protein trafficking







Protracted / Intractable Diarrhoea Summary

- Rare, but severe problems, prognosis very dependent on correct diagnosis. Must go to specialist unit.
- At least 20 clearly defined conditions, most genetic
- Most papers case reports or small series
- World-wide distribution
- Very little or no high quality incidence/prevalence data
- No intervention studies

Protracted / Intractable Diarrhoea Summary

- Fluids and PN vital in most
- Theoretical treatments:
  - Diet
  - Nutritional support
  - Anti-secretory / diarrhoeal
  - Replacement (enzyme)
  - Genetic manipulation
  - BMT
  - ?Stem cell
  - Specific therapies (targeting pathways)
- Small bowel transplant, bone marrow transplant