Malnutrition
Chronic malabsorption disorder
Prof. András Arató
Pathophysiological classification of failure to thrive

- Inadequate food intake
- Loss of ingested food
- Defective utilization
- Excess metabolic demand
Inadequate food intake

- Intrauterine malnutrition
- Poverty
- Maternal depression
- Inadequate feeding technique
- Macro- or micronutrients deficiencies
- Anorexia, refusal of foods
- Disturbance of swallowing
- Oro-motor dysfunction
- Cleft palate
Loss of ingested food

- Vomiting
- Disturbance of intraluminal digestion
- Intestinalis malabsorption
Defective utilization

• Diseases of central nervous system
• Chromosomal abnormalities (21, 18, 13 trisomies)
• Congenital infections
• Metabolic disorders (respiratory chain)
• Endocrine disorders (GH deficiency, hypothyreosis)
Excess metabolic demand

- Inflammation
- Immunodeficiency
- Infection
- Hyperthyreosis
- Hypoxia (congenital heart disease, lung diseases)
Hospital and disease related malnutrition circulus vitiosus

Disease related
- Increased loss e.x. malabsorption
- Increased demand Fever, inflammation, etc.
- Anorexia
- Stress related catabolism

Hospital related
- Problems with food supply
- Fasting because of procedures
- Drug related
- Immune dysfunction
- Altered intestinal function
- Altered healing
- Impaired muscle function

## STRONG_kids screening tool

### Screening for risk of malnutrition:
**once a week in children aged 1 month – 18 years**

| Question                                                                 | Score 
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Is there an underlying illness with risk for malnutrition <em>(see list)</em> or expected major surgery?</td>
<td>No</td>
</tr>
<tr>
<td>Is the patient in a poor nutritional status judged with subjective clinical assessment <em>(diminished subcutaneous fat and/or muscle mass and/or hollow face)</em>?</td>
<td>No</td>
</tr>
<tr>
<td>Is one of the following items present?</td>
<td>No</td>
</tr>
<tr>
<td>- Excessive diarrhoea <em>(≥5 per day)</em> and/or vomiting <em>(&gt; 3 times/day)</em></td>
<td></td>
</tr>
<tr>
<td>- Reduced food intake during the last few days</td>
<td></td>
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<tr>
<td>- Pre-existing nutritional intervention</td>
<td></td>
</tr>
<tr>
<td>- Inadequate nutritional intake due to pain</td>
<td></td>
</tr>
<tr>
<td>Is there weight loss or no weight gain <em>(infants &lt; 1 year)</em> during the last weeks-months?</td>
<td>No</td>
</tr>
</tbody>
</table>
List of underlying illnesses with risk for malnutrition

- Anorexia nervosa
- Burns
- Bronchopulmonary dysplasia (maximum age 2 years)
- Coeliac disease
- Cystic fibrosis
- Dysmaturity/prematurity (corrected age 6 months)
- Cardiac disease, chronic
- Infectious disease (AIDS)
- Inflammatory bowel disease
- Cancer
- Liver disease, chronic
- Kidney disease, chronic
- Pancreatitis
- Short bowel syndrome
- Muscle disease
- Metabolic disease
- Trauma
- Mental handicap/retardation
- Expected major surgery
- Not specified (classified by doctor)
## STRONGkids screening tool

### Risk of malnutrition and need for intervention

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk</th>
<th>Intervention and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-5 points</td>
<td>High risk</td>
<td>Consult doctor and dietician for full diagnosis and individual nutritional advice and follow-up. Consider prescribing supplements whilst awaiting confirmation of status.</td>
</tr>
<tr>
<td>1-3 points</td>
<td>Medium risk</td>
<td>Consider nutritional intervention. Check weight twice per week and evaluate the nutritional risk weekly. If necessary consult specialist/doctor for full diagnosis.</td>
</tr>
<tr>
<td>0 points</td>
<td>Low risk</td>
<td>No nutritional intervention necessary. Check weight regularly and evaluate the nutritional risk weekly (or according to hospital policy).</td>
</tr>
</tbody>
</table>
STRONG screening in Hungarian hospitalized children

- The survey was done by 30 pediatricians nationwide
- Number of screened children: 1209
- Children belonging to high risk group:
  - 184 (15%)

1st Department of Pediatrics, www.gyermekklinika.hu
Comparisons between adequately nourished and malnourished children on executive functions


VF: verbal fluency  DF: design fluency  WM: working memory
AN: adequately nourished; MN: malnourished
Intra-uterine growth delay

Caloric deprivation

Acquired hypothyroidism

Constitutional delay

Growth hormone deficiency
Structure of small intestine

- Crypt
- Vilous
- Exfoliation (apoptosis)
- Differentiation
- Maturation
- Cell division
- Cell division
Pathophysiology of diarrhoea

• **Osmotic diarrhoea**
  – Stops on fasting
  – Stool osmolality > 2x[Na⁺]+[K⁺]
    (Na<60mmol/l)
    • Ex. Lactose intolerance

• **Secretory diarrhoea**
  – Unchanged by fasting
  – Stool osmolality = 2x[Na⁺]+[K⁺]
    (Na>60mmol/l)
    • Ex. Cholera
Pathophysiology of diarrhoea

- **Reduction of absorption surface**
  - Intestinal resection, enteropathies

- **Reduced time of contact with intestinal mucosa**
  - Inflammation (Crohn’s disease)
  - Acceleration of intestinal transit (large intestinal volume)

- **Increased time of transit**
  - Bacterial overgrowth
History of disease

• Onset
• Relation to foods
• Characteristics of stools (blood, fat, mucous)
• Evolution
• Associated signs or symptoms
  – respiratory
• Family history
  – allergy, food intolerance, IBD
• Growth pattern
Evaluation of patient

- General nutrition
- Signs of chronic disease
- Abdominal distention
- Perianal lesions
Early onset diarrhoea

- Congenital microvillous atrophy
- Cytoskeleton abnormalities
- Congenital chloridorrea
- Enzyme deficiency
  - Lactase
  - Sucrase-isomaltase
Stool pH?

Reducing sugars in stools?

$H_2$ breath test?
Lactase deficiency

- Secondary
  - Transient
  - Segmental
  - Parcial
- Adult type
- Congenital
Sucrase-isomaltase deficiency

Typical story...

• Baby on infant formula (with lactose)
• Acute diarrhoea
  – Lactose free formula...
• Diarrhoea worsens...
  – Extensive hydrolisate formula (lactose free)...
• Diarrhoea continues...

could it be cow’s milk intolerance?
Diagnostic steps

- Stop feeding
- Oral rehydration solution (glucose)
- Sucrose in water  
  - (2g/kg in 10%)
- Diarrhoea stopped!
  - Osmotic!
- No diarrhoea
- Reducing sugars 3+

= Diagnosis!!
Toddlers’ diarrhoea

- “Peas and carrots syndrome”!
- Adequate growth
- No signs of chronic disease
- Investigations normal
- Self limited
Chronic Diarrhoea
common causes

- Giardiasis
- Cystic fibrosis
- Food intolerance
  - Coeliac disease
- Inflammatory bowel disease
Haematologic abnormalities?

- Coeliac disease
  - Microcytic anaemia
- Pearson syndrome
  - Sideroblastic anaemia
- Shwachman-Diamond syndrome
  - Periodic neutropenia, anaemia, thrombocytopenia
Rare causes of chronic diarrhoea in infants

- Abetalipoproteinemia
- Pearson syndrome
- Shwachman-Diamond syndrome
- Auto-immune enteropathy
- Intestinal lymphangiectasia
Investigations

- CBC
- Albumin
- Markers of inflammation
  - ESR, CRP, thrombocytosis
- Sweat test
  - Genetic testing (chromosome 7)
- Stool elastase; stool fat
- Stool calprotectin, lactoferrin, α-1-antitrypsin
- Stool microbiology
- Anti-tTG antibodies (IgA)
- pANCA, ASCA
- Anti-enterocyte antibodies; auto-antibodies
Instrumental examinations

- Breath tests after intake of different sugars
- Image forming examinations
- Plain abdominal X-ray
- Duodenal tubing (digesting enzymes, Giardia)
- Small intestinal biopsy
  - With capsule or with endoscopy
  - Analysis with light or electrone microscopy
Causes of villous atrophy

• Postenteritis syndrome
• Cow’s milk allergy
• Soya allergy
• Coeliac disease
• Giardiasis
• Immunodeficiency syndromes
• Autoimmune enteropathy
Classification of malabsorption syndrome

- Impaired intraluminal digestion
- Intestinal malabsorption
- Fermentation

In many cases, more factors elicit the malabsorption (e.g. bacterial overgrowth)
Malabsorption due to impaired intraluminal digestion

- CF
- Schwachman syndrome
- Isolated lipase or colipase deficiency
- Impaired bile acid synthesis
- Bile duct atresia
- Interrupted enterohepatic circulation
  - ileal resection
  - Crohn disease
  - Congenital malabsorption of bile acids
- Congenital trypsinogen or enterokinase deficiency
Intestinal malabsorption

- Coeliac disease
- Sensitization to food proteins (cow’s milk, soya, rice, wheat)
- Giardia infestation
- Postenteritis syndrome
- Immunodeficiency syndromes
- Acrodermatitis enteropathica
Intestinal malabsorption II.

- Bacterial overgrowth
- Crohn disease
- Short bowel syndrome
- Intestinal lymphangiectasia
- Autoimmune enteropathy
- Congenital microvillous atrophy
- Selective transport defects
Malabsorption due to fermentation

- Disaccharidase deficiencies
  - Lactose (congenital, secondary, adult)
  - Sucrose (congenital, secondary)
  - Izomaltose (primary, secondary)
- Monosaccharide malabsorptions
  - Glukose/galactose
  - Fructose (toddler’s diarrhoea)

In the primary forms the small intestine has normal structure
Pathological findings in biopsy samples

• Specific
  – Dilatated lymphatic vessels in intestinal lymphangiectasia
  – Vacules filled with lipids in abetalipoproteinaemia

• Non specific
  – Diseases with villous atrophy
Postenteritis syndrome

• Acute diarrhoea lasts more than 2 weeks
  – Small intestinal damage
  – Secondary lactose malabsorption
  – Secondary cow’s milk protein intolerance

• Treatment
  – lactose free diet
  – cow’s milk free diet
Giardia lamblia infestation

- Very frequent
- **Diagnosis:**
  - Stool analysis
  - Duodenal tubing, vegetative forms can be found only here
- **Therapy:**
  - Metronidazole
  - This treatment can be begun without diagnosis (ex juvantibus)
Classification of food allergies with gastrointestinal symptoms according to their pathogenesis

<table>
<thead>
<tr>
<th>IgE mediated</th>
<th>Mixed (IgE and non-IgE)</th>
<th>Non-IgE mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Immediate gastrointestinal hypersensitivity</td>
<td>• Allergic eosinophil oesophagitis</td>
<td>• Food allergy caused enteropathy</td>
</tr>
<tr>
<td>• Oral allergic syndrome</td>
<td>• Allergic eosinophil gastritis</td>
<td>• Food allergy caused enterocolitis</td>
</tr>
<tr>
<td></td>
<td>• Allergic eosinophil gastroenterocolitis</td>
<td>• Food allergy caused proctocolitis</td>
</tr>
</tbody>
</table>
Cow’s milk allergy

• Symptoms
  – Skin, respiratory, gastrointestinal
  – At the gastrointestinal form partial villous atrophy is characteristic

• Diagnosis
  – Symptoms cease at elimination and recur at provocation
  – Small intestinal biopsy is indicated when the differential diagnosis causes difficulties.
History, physical examination and laboratory tests

- Diagnostic elimination diet (with eHF or AAF)
  - Late reactions (e.g. atopic eczema): 1 - 2 weeks
  - GI symptoms (e.g. diarrhea, vomiting): 2 - 4 weeks

- CMP elimination & Specific IgE

- No improvement of clinical symptoms

- Improvement of the clinical symptoms
  - Spec. IgE negative
  - Spec. IgE positive

- Standardized oral challenge with CMP
  - negative
  - positive

- No diet

- Therapeutic elimination diet

- anaphylaxis or clear immediate type reaction
Treatment of cow’s milk allergy

• Cow’s milk free diet
  – Extensively hydrolized proteins (under 1500 D)
  – Hydrolisate can be prepared from cow’s milk, collagen and soya
  – Amino acid mixture
  – Soya is not indicated as in the enteral form of cow’s milk protein allergy occurrence of soya allergy is also very frequent
  – Probiotics
From the formulae containing whole protein to the aminoacid mixture

Standard formula | Extensive hydrolysate | Aminoacids mixture
1st Century A.D.: Aretaeus the Cappadocian (Greek) – Work translated by Francis Adams and published by the Sydenham Society in 1856

Wellcome Institute Library
London

From: Paveley WF. BMJ 297:1646, 1988
Cappadocia

Photo of a 15th Century map showing "Capadocia".
Arateus “The Coeliac Disease”

• He named it “koiliakos” after the Greek word “koelia” = abdomen
• If the stomach be irretentive of the food and if it pass through undigested and crude, and nothing ascends into the body, we call such persons coeliacs”.
«A comprehensive dogmatic system . . . requires the science systematized to be at a standstill, not to say dead. Knowledge is a ferment, expanding on all sides so much and so rapidly as during the past hundred years, [and] must speedily burst the old bottle of any dogmatic system.»

Medical Lectures. Chapter 14.
• 1887: Lectured and published “On the Coeliac Affection” in St. Bartholomew’s Hospital Reports:

• The disease occurs
  – in Englishmen returning from the tropics,
  – in children aged 1–5 and adults who never left England. (Gee’s Disease)
Samuel Gee about the therapy of coeliac disease

• Mention a child who „wonderfully throve when fed upon a quart of the best Dutch mussels daily, but relapsed when the season for mussels was over”

• He concludes that „if a patient be cured at all, it may be by means of diet”. 
The Lancet, August 10, 1918.

The Lumleian Lectures on Coeliac Disease.

Delivered before the Royal College of Physicians of London on March 14th, 19th, and 21st, 1918.

By G. F. Still, M.A., M.D. Cantab., F.R.C.P. Lond.,
Professor of Diseases of Children, King's College, London; Physician for Diseases of Children, King's College Hospital; Physician to the Hospital for Sick Children, Great Ormond Street.

Lecture I.

Mr. President and Fellows,—One cannot but regard it as an honour to deliver before this our College the Lumleian lectures: but one undertakes the duty with some trepidation.

I have no explanation to offer for larger figures it raises once again a point to me exceedingly interesting—namely: Why congenital hypertrophy of the colon should occur far more often in hysteria than in other conditions? Hystera should be more common in women, but it seems, if possible, in men as in women. If, indeed, coeliac disease is a functional digestive disorder, if that is the female so much more often than the male.

The age at onset is, in the main, of infancy, between the age of 3 to 7 years, but earliest in my series was 8 months. 2 other cases began as late as 4 years 11 months.

Several, however, were first seen after the age of 3. Several reached the age of 3-7 years and then reappeared. Indeed, it is by no means unusual in some cases as the disease shows. As far as I have been able to ascertain, while the child was still on breast with attacks of diarrhea, particularly severe.
Sir Frederick Still

• “Unfortunately one form of starch which seems particularly liable to aggravate the symptoms is bread. I know of no adequate substitute”

• “As far as I have been able to ascertain, in no case did the disease begin while the child was still on breast-feeding”
Willem Karel Dicke (1905-1962)

Utrecht University
Observations of Dicke

- Noticed his hospitalized coeliac toddlers, who existed on “gruel” (porridge) in the food scarce days of WWII, improved when wheat flour was not available but rice or potato flour was used.
- When Swedish planes dropped bread in The Netherlands, his patients who had improved on wheat-free diets, all relapsed.
Dicke’s PhD thesis

• "Investigation of the harmful effects of certain types of cereal on patients with coeliac disease"

• At the State University of Utrecht on 30th of May, 1950
Definition of Celiac Disease

CD is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically (mainly HLA) susceptible individuals, characterized by the presence of variable combination of gluten-dependent clinical manifestations, CD specific antibodies, HLA DQ2 and DQ8 haplotypes and enteropathy.
Definition of CD

Gluten-sensitive enteropathy in genetically susceptible individuals

The present definitions of CD are based on:

- Presence of enteropathy
- Induction of intestinal lesions (and symptoms) by gluten
- Genetic susceptibility
- Specific serologic markers
Healthy subjects

Latent coeliac disease

Silent coeliac disease

Manifest coeliac disease

Morphology of jejunum

Genetic inclination

DR3-DQ2
DR5/7-DQ2
DR4-DQ8

Villous atrophy

Normal mucosa

Coeliac iceberg
Typical endoscopic picture of normal (a) and coeliac mucosa (b)
Normal (a) and coeliac disease (b) small intestinal mucosa
Positive EMA test on monkey oesophagus section
Intestinal deposits of IgA anti-TG2 antibodies

TG 2

IgA

TG2 + IgA
Pathogenetic factors in coeliac disease

• Genetic background
• Gliadin
• Transzglutaminase
Coding of characteristic heterodimer in cis and trans position

Sollid LM. Nature Rev. 2002, 2, 647-655

1st Department of Pediatrics, www.gyermekklinika.hu
Gliadin

• Trigger factor of coeliac disease
• Trigger factors of other autoimmune disease are not known
Transglutamininase enzyme

• It is ubiquitous in the connective tissues and makes crossbonds between the polypeptid chains

• Transglutamininase is the substrate of antiendomysium, antireticulin and antijejunal antibodies

• In coeliac disease the transglutamininase is the autoantigen
Enzymatic actions of transglutaminase enzyme

Sollid LM. Nature Rev. 2002, 2, 647-655
Binding to the A HLA II molecules

Van De Wal Y. Gut 2000, 46, 734-737
The effect of transglutaminase to the epitop structure of gliadin

Van De Wal Y. Gut 2000, 46, 734-737
Coeliac disease as a gluten-sensitive enteropathy (Interlaken 1969)

**Diagnosis based upon:**

1. Structurally abnormal jejunal mucosa when taking a diet containing gluten
2. Clear improvement of villous structure when taking a gluten-free diet
3. Deterioration of the mucosa during challenge
Revised ESPGHAN criteria for diagnosis of coeliac disease (1990)

**Compulsory**

1. Histological findings compatible with CD (hyperplastic villous atrophy)
2. Unequivocal clinical and serological response to GFD

**Supportive**

1. History and clinical presentation compatible with CD; in subject < 2 years old r/o other clinical conditions mimicking CD
2. CD-associated serology
Child / Adolescent with Symptoms suggestive of CD

TG2 IgA & total IgA

Positive serology

Negative serology

Not CD

Consider further diagnostic work up in case of:
- IgA deficiency
- Age: < 2 years
- History: - low gluten intake
- drug pretreatment
- severe symptoms
- associated diseases

Transfer to Ped. GI before GFD

Ped. GI: discussion with family the 2 diagnostic pathways and their consequences considering patient's history and TG2 concentration

EMA & HLA DQ8/DQ2
ff TG2 >10 x ULN and no OEGD wanted

EMA pos
HLA pos

EMA pos
HLA neg

EMA neg
HLA neg

EMA neg
HLA pos

Marsh 0 -1

Unclear case
Consider:
false positive serology
false negative biopsy
or potential CD
Extended evaluation of
HLA/serology/biopsies

CD+

Consider false neg. HLA test
Consider false pos. initial serology

GFD & F/u

Marsh 2 or 3

CD+

GFD & F/u

Or specific IgG base
Asymptomatic person at risk for CD
explain implication of positive test result(s) and get consent for testing

HLA DQ2 or DQ8 (+/- serology)

HLA positive DQ2 and/or DQ8

HLA negative DQ2 and DQ8

No CD, no risks for CD

Consider retesting in intervals or if symptomatic

Serology TG2 & total IgA*

High titer (> 5 x ULN)

Low titer (< 5 x ULN)

TG2 Negative

Not CD

OEGD & Biopsies from Bulbus & 4 x pars descendens, proper histological work up

EMA positive

EMA negative

Consider:
False negative results, exclude IgA deficiency and history of low gluten intake or drugs

Marsh 2 or 3

Marsh 0 or 1

CD+

Unclear case

F/u on normal diet Consider: false pos serology, false neg biopsy or potential CD

GFD & F/u

Consider:
Transient or false positive TG2 F/u on normal diet with further serological testing

* Or specific IgG based tests
Prevalence rate of coeliac disease in IDDM

Austria: 3% (Schober, 2000)
Sweden: 6% (Carlsson, 1999)
Spain: 6,45% (Vitoria, 1998)
Canada: 5,1% (Fraser-Reynolds, 1998)
Italy: 7% (DeVitis, 1996)
Finland: 2,4% (Saukkonen, 1996)
United Kingdom: 2% (Page, 1994)
Possible new treatment modalities in the future

- Peptidase supplementation (generate new target sequences for brush border enzymes)
- Transglutaminase inhibition (unwanted side effects)
- Binding MHC II binding sites
- Silencing of gluten reactive T cells (Treatment with anti-CD3 during gluten challenge)
Possible new treatment modalities in the future

- Cytokine therapy (IL-10, anti-IL15, anti-IFN gamma)
- Selective adhesion molecule inhibition (Natalizumab)
- Inhibition of NKG2D (Prevents killing epithelial cells by NK cells)
Shan et al. Science 2002, 297, 2275
Gastrointestinal symptoms in CF

- Neonates: Meconium ileus
  - Prolonged jaundice
- Infants and toddlers
  - Steatorrhea
  - Slowed weight gain
  - Polyphagia
Gastrointestinal symptoms in CF

- Childhood
  - Meconium ileus equivalent
  - Portal hypertension
  - Hypersplenia
  - Stricture of colon strictura (when prepared containing enzymes in high concentration are used)
CF Newborn Screening Result:
- Positive IRT/DNA or IRT/IRT

Notification of parents and PCP

CF Center Diagnostic Evaluation:
- Sweat Chloride Test

- ≥ 60 mmol/L
  - 2 CF mutations
  - 0-1 CF mutation
  - no DNA data

- 30-59 mmol/L
  - 0-1 CF mutation
  - no DNA data

- ≤ 29 mmol/L
  - no DNA data

Outcomes:
- Diagnosis of CF
- Possible CF
- CF very unlikely

CF Center Follow-up:
- DNA analysis if IRT/IRT
- Clinical Assessments
- Begin therapy aimed to stay healthy
- Sweat test siblings

DNA analysis
- Using CFTR multiamutation method
- Ancillary tests

Repeat sweat chloride test

1-2 months

2-6 months

* If the baby is at least 2kg and more than 36 weeks gestation at birth, perform bilateral sweat sampling/analysis with either Gibson-Cooke or Macroduct® method; repeat as soon as possible if sweat quantity is less than 75 mg or 15 μL, respectively.

† CF mutation refers to a CFTR mutant allele known to cause CF disease.

‡ The disease is very unlikely; however, if there are 2 CF mutations in trans, CF may be diagnosed.

§ After a repeat sweat test, further evaluation depends on the results as implied above.
Causes of false positive sweat test

- Adrenal insufficiency
- Nephrogenic diabetes insipidus
- Hypothyreosis
- Malnutrition, malabsorption
- Anorexia nervosa
- Fucosidosis
- Glycogen storage diseases
- Familiar hypoparathyreosis
Standpoints patients’ care in CF

• Diet
  – High energy intake (150% of normal)
  – Increased protein intake
  – Near normal fat intake
  – Replace of fat soluble vitamins

• Enzimpreparates
  – Mode of intake
  – Dose