CASE 4

Short case number: 3_16_4
Category: Children and Young People
Discipline: Paediatrics_Medicine
Setting: Hospital outpatients.
Topic: Chronic diarrhoea and malabsorption in children.

Case

You are an intern in a paediatrics rotation, 9 month old Samantha Longley presents with her mother. They have been referred by their GP. Samantha has been losing weight over the last 2 months and is more unsettled and seems to be in pain after meals. Her mother also informs you that Samantha's bowel motions are more frequent and more liquid than before.

She was born at term following an uneventful pregnancy and delivery.
At birth: weight 3.0 Kg; length 51 cm; head circumference 34.5 cm.

She had been growing normally along the 50th centile up until 6 months of age, when her weight gain slowed;
She currently weighs 7.0 Kg, length 70 cm, head circumference 44.5 cm.

Questions

1. You are concerned that Samantha may have a malabsorption problem – outline the key features of your history and examination.
2. Outline the diagnostic approach to suspected malabsorption.
3. Summarise the normal physiology of fat, carbohydrate and protein digestion and absorption.
4. Summarise in a table the key clinical features of nutrient malabsorption.
5. Describe the key features of steatorrhoea, watery diarrhoea and bloody diarrhoea.
6. You are concerned that Samantha may have coeliac disease, briefly summarise the key clinical features of coeliac disease and outline the investigation process to confirm the diagnosis of coeliac disease.
7. Malabsorption is also a clinical feature of Cystic Fibrosis. Briefly, outline the pathophysiology of malabsorption in Cystic Fibrosis.

Suggested reading:

Duff, S, & O'Loughlin, E. (2012). Chronic diarrhoea and malabsorption. In South, M & Isaacs, D. (Eds) Practical Paediatrics (pp 724 – 734). Edinburgh, Churchill Livingston.

ANSWERS

1. You are concerned that Samantha may have a malabsorption problem – outline the key features of your history and examination

Clinical assessment
HISTORY

Diarrhoea is the most common presentation and may be accompanied by loss of appetite, decreased physical activity, lethargy and growth failure. Children with coeliac disease may have decreased appetite, and are often cranky and irritable. In contrast, children with pancreatic insufficiency often develop a voracious appetite. In children with failure to thrive, such as Samantha, a detailed dietary history is required. Occasionally, parents manipulate the child's diet in an attempt to control the diarrhoea, which can lead to significant dietary insufficiency with attendant weight loss. Assessment of the age of introduction of various foods into the diet may give insight to the underlying diagnosis. Onset of symptoms 3-6 months after the introduction of wheat products suggests the possibility of coeliac disease. Onset shortly after introduction of cow's milk suggests cow's milk protein intolerance. History of overseas travel is important, as some unusual infections, such as amoebic dysentery, can cause chronic bloody diarrhoea.

The nature of the loose stool is important to ascertain, as it provides important clues to the pathophysiology and thus aetiology. Diarrhoea can be thought of in terms of fatty stools (steatorrhoea), watery diarrhoea (osmotic because of carbohydrate malabsorption or secretory) and bloody diarrhoea.

Assessment of general health is important, as many gastrointestinal disorders exhibit extraintestinal manifestations. Cystic fibrosis, Shwachman syndrome and immunodeficiency disorders are associated with infections, particularly sinopulmonary infections. Delayed pubertal development can accompany many chronic disorders but is particularly prevalent in Crohn disease

Family history may be of note. Cystic fibrosis, primary disaccharidase deficiencies and abetalipoproteinaemia are recessively inherited. Coeliac disease and inflammatory bowel disease are more frequently observed in first-degree relatives.

EXAMINATION: Physical examination includes assessment of growth, nutritional status and pubertal development. Plotting percentile charts is mandatory. A child who is growing normally is unlikely to be suffering from serious gastrointestinal disease. Plotting longitudinal measurements, if available, is very important as it may give clues to the onset of disease and could indicate the diagnosis. Other physical signs of malabsorption and specific nutritional deficiencies include: loss of muscle bulk and subcutaneous fat; peripheral oedema (hypoproteinaemia); bruising (vitamin K deficiency); glossitis and angular stomatitis (iron deficiency); finger clubbing (cystic fibrosis, Crohn disease, coeliac disease); skin rashes in coeliac disease (dermatitis herpetiformis) and inflammatory bowel disease (erythema nodosum, pyoderma gangrenosum); and specific skin disorders associated with zinc, vitamin A and essential fatty acid deficiencies . Rickets (vitamin D deficiency) is very uncommon in sunny

climates, even in conditions with severe steatorrhoea. It is important to examine carefully as there are many extraintestinal manifestations of gastrointestinal disease and malnutrition.

2. Outline the diagnostic approach to suspected malabsorption.

Initial clinical assessment and stool examination will suggest the diagnosis in most children.

Stool microscopy and measurement of stool-reducing substances can be performed in the clinician's office and are readily available 'bedside' tests. If the diagnosis is not immediately obvious, the clinician will be in a position to investigate a limited differential list with simple and well directed diagnostic tests.

In patients with steatorrhoea the following will be useful but are not necessarily indicated for each patient:

- full blood count and differential white cell count
- serum triglycerides/cholesterol
- sweat test
- small bowel biopsy
- X-ray of long bones.

In patients with carbohydrate maldigestion/malabsorption the following might be indicated:

- breath hydrogen testing: challenge with the carbohydrate of interest (e.g. lactose)
- small bowel biopsy/mucosal disaccharidase activities
- occasionally with monosaccharide malabsorption
- inpatient dietary manipulation with close observation of stool output.

In patients with bloody diarrhoea (if stool cultures negative for pathogens) consider:

- gastroscopy and colonoscopy
- biopsy of small bowel and colon
- sometimes radiology looking for inflammatory bowel disease in jejunum/ileum.

Sometimes highly specialized investigations will be required to establish the diagnosis of some disorders:

- measurement of micronutrients such as iron, zinc and calcium for suspected deficiency
- Schilling test is required for the workup of vitamin B_{12} deficiency. Abnormally low urinary excretion of the ingested radioactive vitamin B_{12} indicates vitamin B_{12} malabsorption
- Schilling test can be used to assess patients with bile salt malabsorption due to ileal resection
- specialized breath tests are used in the workup of bacterial overgrowth syndrome
- immunoglobulins and B- and T-cell subset determination for detection of immunodeficiency disorders.

Practical points

- Diagnosis is not by exclusion
- A thorough history, physical examination and stool examination will suggest the diagnosis in most disorders
- simple well-directed investigations usually confirm the clinical diagnosis
- there is no such thing as a 'malabsorption workup'

3. Summarise the normal physiology of fat, carbohydrate and protein digestion and absorption.

Fat

Ingested fat in the form of triglycerides, cholesterol and phospholipids is, to a large extent, digested in the lumen of the small intestine and absorbed in the jejunum. This requires bile salts, which form micelles and solubilize the fat; pancreatic enzymes, such as lipase and colipase, which digest the fat; and an intact intestinal mucosa, which is required for absorption of the products of digestion. Following digestion in the micelles, breakdown products diffuse across the enterocyte apical membrane and are reconstituted in the cell into chylomicrons. These are small packets of triglyceride, phospholipid and cholesterol which associate with carrier proteins, such as beta lipoprotein, essential for cellular trafficking of the chylomicrons. After the chylomicrons are reconstituted they exit the mucosa into the lymphatic system and subsequently pass into the systemic circulation. Some small chain triglycerides can bypass this system and enter the portal venous system directly.

Protein

Protein digestion begins in the stomach by the action of pepsin and acid. However, most protein hydrolysis occurs in the lumen of the jejunum by action of pancreatic proteases. These are secreted as inactive precursors. Chymotrypsin is converted to trypsin by the action of the small intestinal enzyme enterokinase. Activated trypsin further activates chymotrypsin and other proteases, such as car-boxypeptidase. The products of protein hydrolysis are amino acids and oligopeptides. The latter are further hydrolysed to mono-, di- and tripeptides by brush border hydrolyases and are absorbed by specific membrane transporters. Di- and tripeptides undergo hydrolysis to amino acids in the cytoplasm of the enterocyte. Isolated protein maldigestion/malabsorption is extremely rare. It usually occurs in association with malabsorption of other macronutrients

Carbohydrate

Dietary carbohydrates are primarily starch (polysaccharides, amylose and amylopectin), disaccharides (sucrose, in table sugar; lactose, in milk) and some monosaccharides such as fructose.

Starch polymers are large molecules composed of long chains of glucose. These chains are broken down by the action of salivary and pancreatic amylase, which release a disaccharide (amylose), trisaccharide (maltotriose) and a series of branched oligosaccharides (alpha limit dextrins). These molecules are further digested by the brush border enzymes, sucrase-isomaltase and glucoamylase, to the monosaccharide glucose.

The disaccharides sucrose and lactose are metabolized by disaccharidases on the intestinal brush border. Sucrase breaks sucrose down to glucose and fructose and lactase breaks down lactose into glucose and galactose. Glucose and galactose are absorbed by the enterocyte sodium-glucose cotransporter (SGLT), which absorbs the monosaccharides in an energy dependent fashion. Fructose is absorbed by facilitated diffusion (non-energy-dependent) by the transporter termed GLUT-5.

4. **Summarise in a table the key clinical features of nutrient malabsorption.**

Table 200-1. Some symptoms and signs of nutrient deficiencies

Protein		Growth failure
		Muscle wasting
		Hypoproteinaemic oedema
Fat		Weight loss
		Muscle wasting
		Manifestation of deficiency of vitamins A, D, E, K
Carbohydrate		Weight loss
Salt/water		Electrolyte disturbances
		Growth failure (chronic salt deficiency)
		Dehydration (acute loss)
Vitamins	A	Night blindness
		Skin rash
		Dry eyes (xerophthalmia)
	D	Rickets
		Hypocalcaemia
	K	Bruising (coagulation defects)
	E	Anaemia
		Peripheral neuropathy
	B_{12}	Megaloblastic anaemia
		Irritability
		Hypotonia
		Peripheral neuropathy
	Folate	Megaloblastic anaemia
		Irritability
Minerals	Iron	Microcytic anaemia
		Delayed development
	Calcium	Rickets
		Irritability
		Seizures
	Zinc	Diarrhoea
		Skin rash (mouth, perineum, fingers and toes)
		Poor growth

5. **Describe the key features steatorrhoea, watery diarrhoea and bloody diarrhoea.**
   steatorrhoea: fatty stools fat globules seen on microscopy, classically stools float in toilet bowl

   watery diarrhoea: very fluid and high volume may be osmotic (because of carbohydrate malabsorption) or secretory

   bloody diarrhoea. Either visible blood or microscopic. May contain mucous if inflammatory cause.

6. **You are concerned that Samantha may have coeliac disease, briefly summarise the key clinical features of coeliac disease and outline the investigation process to confirm the diagnosis of coeliac disease.**

   KEY FEATURES

   Coeliac disease (gluten enteropathy):

   Coeliac disease is a disorder characterized by intestinal injury induced by the cereal protein gluten. Gluten is a glycoprotein found in wheat, barley and rye and, to a lesser extent, oats. In susceptible individuals, the ingestion of gluten induces a cell-mediated injury of the intestinal mucosa resulting in severe villous atrophy, crypt hyperplasia and infiltration of the epithelium with lymphocytes (intraepithelial lymphocytes). In Western countries, the incidence of coeliac disease in the general population may be as high as 1 in 70, although not all affected individuals develop the classical manifestations of coeliac disease.

   Modes of presentation include:
   'Classical' coeliac disease
   between 9 and 18 months of age
   anorexia, weight loss, abdominal distension and wasting
   chronic diarrhoea with or without:
   iron deficiency anaemia
   hypoproteinaemic oedema
   fat-soluble vitamin deficiency

   The older child with:
   growth failure
   chronic diarrhoea
   iron deficiency

   NOTE: diarrhoea may be steatorrhoeic or watery depending on severity

   APPROACH TO DIAGNOSIS
   Positive antibody screening (now the commonest form of assessment leading to diagnosis).
   Examples of antibodies used to screen when there is suspicion of coeliac disease include:
   antigliadin
   anti endomysial
   antitissue transglutaminase antibodies.

Antiendomysial and antitissue transglutaminase antibodies have sensitivity and specificity of greater than 95%. However, it is important to note that these are screening tests only.

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small bowel biopsy is mandatory for the diagnosis

small bowel biopsy should be performed while the patient is on an unrestricted diet

there is no place for an empirical trial of a gluten-free diet

definitive diagnosis is important, as treatment is a lifelong gluten-free diet.

A second biopsy can be undertaken to establish that the intestine has returned to normal on a restricted diet. If there is doubt about the diagnosis, a subsequent gluten challenge with repeat biopsy can be undertaken.

7. Malabsorption is also a clinical feature of Cystic Fibrosis. Briefly, outline the pathophysiology of malabsorption in Cystic Fibrosis

Cystic fibrosis:

- is the commonest cause of pancreatic malabsorption in the Caucasian population
- has an incidence in the population of approximately 1 per 2000
- is an inborn error in epithelial chloride secretion (cystic fibrosis transmembrane conductance regulator (CFTR)).

Organs affected include:

- gastrointestinal tract and liver
- sinopulmonary tract
- **pancreas** → Lipase (aids the bile salts in fat absorption)
- exocrine portion of the sweat glands
- vas deferens
- sweat duct (CFTR absorbs rather than secretes chloride in this organ).

Because of the fluid and salt transport defects, patients with cystic fibrosis produce more viscous secretions in lung, gut, pancreas and vas deferens, leading to:

- chronic suppurative lung disease
- nasal polyps
- **pancreatic insufficiency**
- intussusception
- meconium ileus and distal intestinal obstruction syndrome
- infertility
- elevated sweat sodium and chloride, which can lead to heat prostration in warmer climates.

Malabsorption in cystic fibrosis frequently results in malnutrition and there may be symptoms and signs of specific nutrient deficits such as hypoalbuminaemic oedema, night blindness due to vitamin A deficiency or skin rash due to essential fatty acid deficiency. Median life expectancy is 30 years, with death usually from respiratory failure or haemorrhage from portal hypertension and oesophageal varices.

Many mutations have been identified in the CFTR. Depending on what part of the channel the mutation affects, the phenotype can vary from mild to severe disease. Individuals with milder mutations have milder lung disease and do not usually have malabsorption, as pancreatic function is normal.