Medical and Surgical Conditions for the Treatment of Malabsorption

Discussion Leader: Wolfgang Fischbach (Aschaffenburg)

Participants: Oliver Al-Taie (Gütersloh) Christoph Dietrich (Stolberg)
Jörg Felber (Jena) Kerstin Schütte (Magdeburg)
Michael Schumann (Berlin)

Question 1: In daily clinical usage the terms maldigestion, malabsorption, and malassimilation are not always clearly separated. What are the exact definitions as a basis for understanding as well as regarding reasonable differential diagnostics?

Dietrich: Malassimilation is the umbrella term for a deficit of nutrients and includes maldigestion (failure of enzymatic intraluminal extraction of chyme) and malabsorption (failure of taking up the extracted nutrients by the intestinal epithelium).

Question 2: You see a patient for the first time. In your opinion, which symptoms and clinical signs are potentially indicating malabsorption? In this situation, which basic laboratory findings do you deem necessary in order to confirm your suspicion of malabsorption?

Al-Taie: Patients suffering from malabsorption can present with a broad spectrum of often non-specific symptoms such as bloating, flatulence, and diarrhea or fatty stools. In addition, weight loss, fatigue, ataxia, tetany, skeletal pain, and amenorrhea can also be caused by malabsorption.

In cases of mild malabsorption, no specific signs can be detected on examination. However, cachexia, hypoproteinemic edema, paleness, nail and hair dystrophy and ecchymosis, disturbances of deep sensibility, and osteoporotic fractures can indicate severe global or specific malabsorption.

Basic laboratory tests to confirm malabsorption include different blood tests such as complete blood count, iron, ferritin, C-reactive protein, ALT, AST, albumin, creatinine,

cholesterol, calcium and potassium, and international normalized ratio (INR). Depending on the suspected underlying disease, extended laboratory examinations comprise serum 25-hydroxyvitamin D, vitamin B₁₂, folic acid, tissue transglutaminase antibodies, serum electrophoresis, gastrin, vasoactive intestinal polypeptide (VIP), fecal elastase, and fecal calprotectin.

Dietrich: Malabsorption is marked by unspecific symptoms such as diarrhea, underweight, paleness, and wasting of muscles, in severe cases also by the presence of ascites. Determination of albumin, total protein, prothrombin time, cholesterol, electrolytes, and ferritin may contribute to a confirmation of this clinical impression.

Schütte: The spectrum of symptoms seen in global malabsorption is broad. Weight loss despite adequate food intake, diarrhea with voluminous and foul-smelling stools, and edema secondary to hypoalbuminemia are the classic clinical signs. While some patients may even be asymptomatic, the majority present with rather mild gastrointestinal symptoms like abdominal distension and flatulence. Malabsorption of specific nutrients results in more specific symptoms, e.g. vitamin B₁₂ deficiency resulting in polyneuropathy or pernicious anemia.

A diagnosis of malabsorption cannot be established on the basis of blood tests alone. A diligent medical history frequently leads to the suspicion of malabsorption followed by a further work-up. Laboratory tests including assessments of differential blood count and of concentrations of protein, albumin, folate, vitamin B₁₂, ferritin, total iron-binding capacity, coagulation status, calcium, vitamin D, and alkaline phosphatase (AP) are a good start. Further diagnostic tests should

be chosen dependent on the individual patient and his signs and symptoms with tests for fat malabsorption (e.g. fecal fat determination) and carbohydrate malabsorption (e.g. D-xylose test and specific breath tests (amongst others lactose, fructose, sorbitol)) in addition to ultrasound with the assessment of the small bowel, esophagogastroduodenoscopy with duodenal biopsies, and ileocolonoscopy with biopsies being important parts of the diagnostic cascade.

Schumann: I feel that zinc is a good additional marker for measuring small intestinal absorption. If its level is found to be reduced, it is also worthwhile to substitute zinc, since a number of complications the patient experiences in daily life might improve with a normalization of zinc levels (i.e. dermatitis, glossitis, hair loss, nail dystrophy, recurrent infectious complications). Similarly, magnesium might be helpful [1].

Question 3: Disturbances of biliary secretion may cause malabsorption. For clinical practice, which hepatobiliary disorders have to be evaluated in differential diagnosis? Which diagnostic procedures do you recommend? What are the therapeutic options?

Dietrich: Cholestasis, regardless of its origin (intrahepatic or posthepatic), leads to a lack of micelles in the small intestine [2]. Since the presence of micelles is a prerequisite for absorption of lipophilic compounds in the intestinal lumen, this condition leads to malabsorption of these compounds, especially of the fat-soluble vitamins A, D, E, and K. In general, the presence of any liver disease can be diagnosed by the simple determination of the classic liver enzymes GOT (AST), GPT (ALT), gamma-glutamyl transferase (γ -GT), and AP, and bilirubin [3]. In rare cases of cirrhosis, these values are normal despite the presence of a liver disease and require further investigations (e.g. ultrasound, serum protein electrophoresis).

If cholestasis is present, it must be characterized as intrahepatic (cellular) or posthepatic (obstructive). While in obstructive cholestasis due to stones or tumors endoscopic retrograde cholangiopancreatography (ERCP) is warranted, treatment of ursodeoxycholic acid can be helpful in intrahepatic cholestasis without cirrhosis, depending on the diagnosis (primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune cholangitis (AIC), or other diseases)). In the short term, the lack of vitamin K is most important because it rapidly leads to impaired coagulation. To differentiate between malabsorption and reduced liver function as a cause for clotting disturbances, intravenous administration of vitamin K followed by the determination of prothrombin time on the next day (Koller's test) is a useful test [4].

Question 4: Untreated celiac disease (CD) is a comparably common cause of malabsorption. If in a patient with CD responding primarily to a gluten-free diet (GFD) signs of malabsorption reoccur, refractory CD (RCD) has to be considered. What is the diagnostic approach after having excluded dietary errors?

Dietrich: A new gastroscopy with duodenal biopsies should prove persistent duodenal atrophy and exclude lymphoma. Duodenal atrophy can also be pretended by for example collagenous sprue [5], so that differential diagnoses have to be carefully excluded again.

Felber: Until the 20th century, CD was considered a relatively rare condition that usually presented in childhood with symptoms of intestinal malabsorption, i.e. abdominal distension steatorrhea, weight loss, and/or failure to thrive. Nowadays, CD is much more common in the Western World (prevalence 1:300 in Germany), and patients with symptoms of malabsorption constitute only the tip of the iceberg. Very often adult CD patients present with 'non-classical' symptoms in their fourth or fifth decade in life. These patients with asymptomatic or oligosymptomatic CD often present with irritable bowel syndrome-type symptoms, abdominal discomfort, altered bowel habits, and anemia (most commonly as iron deficiency anemia). Nevertheless, the withdrawal of gluten from the diet leads also in these patients with 'non-classical' CD to a normalization of the intestinal mucosa and the disappearance of symptoms.

If symptoms reoccur, non-compliance to a GFD must be excluded vigorously. If known or unknown diet failures are excluded, microscopic colitis, including collagenous and lymphocytic colitis, irritable bowel syndrome, bacterial overgrowth, lactose intolerance, and most importantly RCD, enteropathy-associated T cell lymphoma (EATL), and ulcerative jejunitis (UJ) must be suspected.

With a cumulative incidence of 1.5% of CD patients, RCD belongs to the family of rare or orphan diseases. If RCD is suspected, a sequence of tests is required to rule out or confirm the diagnosis. If RCD is confirmed, it is important to distinguish between type I and type II RCD as prognosis and treatment differ greatly. Apart from blood tests (ferritin, complete blood count, lactate dehydrogenase (LDH), beta-2-microglobulin, albumin), distal duodenal biopsies have to be obtained and histological (presence of villous atrophy; at least Marsh III), immunohistological (CD8, T cell receptor- β), and molecular pathological (analysis of T cell receptor clonality) tests have to be performed. Cross-sectional imaging of the abdomen is mandatory to rule out lymphadenopathy, thickening of the small bowel wall, or atrophy of the spleen. In the case of significant findings, a small bowel enteroscopy is required to confirm the presence of ulcerations and to take biopsies for the confirmation of RCD, EATL, or UJ. Type II RCD is defined by the

presence of >20% aberrant intraepithelial lymphocytes (IEL; CD3- and CD8-negative) in FACS (fluorescence-activated cell sorting) analysis and coexistence of T cell receptor clonality. No FACS analysis is required if >50% of the IELs are CD3- and CD8-negative in immunohistological studies.

Schütte: Small intestinal villous atrophy should be confirmed by endoscopy. Other causes of villous atrophy (amongst others autoimmune enteropathy, tropical sprue, Crohn's disease, combined variable immunodeficiency, and eosinophilic enteritis) should be evaluated in differential diagnosis, and EATL needs to be ruled out. Biopsies should be taken and analyzed for abnormal intestinal lymphocytes, including immunohistochemistry and quantification of CD3- and CD8-positive cells.

Schumann: At least 7% of CD patients do not – either primarily or secondarily – respond to a GFD. After dietary errors have been excluded (most of the cases! Done best by a professional nutritionist with experience in GFD), diagnostic tests have to be applied to exclude an additional diagnosis that might be responsible for the malabsorption syndrome (in a reasonable context of the patient's history, Crohn's disease, Whipple's disease, giardiasis, intestinal tuberculosis, AIDS enteropathy, eosinophilic enteritis, autoimmune enteropathy, and radiation-associated enteritis should be considered). If no additional diagnosis is found, RCD must be taken into account and multiple (six) duodenal biopsies are collected during an esophagogastroduodenoscopy, which should show Marsh III enteropathy (i.e. villous atrophy and crypt hyperplasia) to establish RCD diagnosis. Further work-up on the histology specimen is done by the pathologist for RCD subtyping (i.e., if type I or type II is present), including a CD8/CD3 immunohistochemistry (percentage of CD8-negative intraepithelial lymphocytes) and a molecular pathology analysis (e.g. a Genescan analysis of the variable region of the T cell receptor to look for T cell monoclonality in the small intestinal sample). RCD type II, which is the subtype that frequently turns into an EATL, has to be considered if the CD8 portion of T cells is <50% and a monoclonality is found in the Molpath analysis. Furthermore, additional imaging is needed. An abdominal magnetic resonance imaging (MRI) with a specific focus on the small intestine (either done as a magnetic resonance enteroclysis or MRI of the small intestine) can be done to identify small intestinal wall abnormalities or irregularities of small intestinal folding and will also identify enlarged abdominal lymph nodes. Capsule endoscopy might identify UJ, which is frequently a substrate of RCD type II, or – if the disease has progressed – EATL. If alterations are found in the jejunum that might be compatible with lymphoma, a single-balloon enteroscopy can be performed to collect biopsies. As the diagnostic work-up with the histology samples as well as the imaging work-up is best performed in centers that offer specific expertise on RCD, the guidelines have recommended to consider transferring an RCD patient to a center with experience in this entity [6–8].

Question 5: A patient with short bowel syndrome requires total parenteral nutrition. What is the ideal management of parenteral nutrition? What does the patient need and what is an adequate follow-up?

Dietrich: We use so-called 'mix-bags' with amino acids and 40% glucose for daily treatment given via central venous line. Lipids and lipophilic vitamins can be given every other day or three times per week. Additional micronutrients are added on clinical grounds. Recommendations for laboratory monitoring vary; we use a panel of blood count, electrolytes, vitamins etc. in intervals depending on the stability of the patient.

Question 6: Do intestinal infections need to be considered as a potential source of malabsorption?

Dietrich: To my knowledge (and that of established textbooks), bacterial overgrowth, tropical sprue, Whipple's disease, infections with *Giardia lamblia*, and cryptosporidiosis can lead to malabsorption (though seldom in a severe form).

Felber: Yes, indeed; gastrointestinal infections, such as chronic *G. lamblia* infection or the rare Whipple's disease caused by *Tropheryma whipplei*, are reasons for severe malabsorption. Whipple's disease is characterized by arthralgia, weight loss, diarrhea, and abdominal pain. Patients may present with neurological symptoms (e.g. cognitive dysfunction, supranuclear ophthalmoplegia, nystagmus, myoclonus) and cardiological complaints (e.g. dyspnoe, pericarditis, sterile endocarditis). Arthralgia may precede the diagnosis by a number of years. Other causes are intestinal infections with *Cryptosporidium parvum*, *Isospora belli*, *Cyclospora cayetanensis*, and the microsporidia.

References

- 1 Saper RB, Rash R: Zinc: an essential micronutrient. *Am Fam Physician* 2009;79: 768–772.
- 2 Hofman AF: Bile acids: trying to understand their chemistry and biology with the hope of helping patients. *Hepatology* 2009;49:1403–1418.
- 3 Chopra S, Griffin PH: Laboratory tests and diagnostic procedures in evaluation of liver disease. *Am J Med* 1985;79:221–230.
- 4 Pereira SP, Rowbotham D, Fitt S, Shearer MJ, Wendon J, Williams R: Pharmacokinetics and efficacy of oral versus intravenous mixed-micellar phyloquinone (vitamin K1) in severe acute liver disease. *J Hepatol* 2005;42:365–370.
- 5 Soendergaard C, Riis LB, Nielsen OH: Collagenous sprue: a coeliac disease look-alike with different treatment strategy. *BMJ Case Rep* 2014;DOI: 10.1136/bcr-2014-203721.
- 6 Daum S, Ipezyński R, Schumann M, Wahnschaffe U, Zeitz M, Ullrich R: High rates of complications and substantial mortality in both types of refractory sprue. *Eur J Gastroenterol Hepatol* 2009;21:66–70.
- 7 Schumann M, Bojarski C, Moos V, Daum S: Refractory celiac disease new diagnostic approaches and current treatment. *Int J Celiac Dis* 2014;2:33–37.
- 8 Van Weyenberg SJ, Meijerink MR, Jacobs MA, van Kuijk C, Mulder CJ, van Waesberghe JH: MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system. *Radiology* 2011;259:151–161.

Participants

PD Dr. Oliver Al-Taie
Medizinische Klinik
Sankt Elisabeth Hospital Gütersloh
Stadtring Kattenstroth 130, 33332 Gütersloh, Germany
oliver.al-taie@sankt-elisabeth-hospital.de

PD Dr. Christoph Dietrich
Klinik für Innere Medizin
Bethlehem Gesundheitszentrum Stolberg gGmbH
Akademisches Lehrkrankenhaus der Rheinisch-Westfälischen
Technischen Hochschule Aachen
Steinfeldstraße 5, 52222 Stolberg, Germany
dietrich@bethlehem.de

Dr. med. Jörg Felber
Klinik für Innere Medizin IV (Gastroenterologie, Hepatologie,
Infektiologie)
Universitätsklinikum Jena
Bachstraße 18, 07743 Jena, Germany
joerg.felber@med.uni-jena.de

Dr. med. Kerstin Schütte
Klinik für Gastroenterologie, Hepatologie und Infektiologie
Universitätsklinikum Magdeburg A.ö.R.
Leipziger Straße 44, 39120 Magdeburg, Germany
kerstin.schuette@med.ovgu.de

Dr. med. Michael Schumann
Medizinische Klinik für Gastroenterologie, Infektiologie und
Rheumatologie
Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin
Hindenburgdamm 30, 12200 Berlin, Germany
michael.schumann@charite.de