Ministry of Healthcare of Ukraine

Poltava State Medical University

Approved
at the meeting of Internal Medicine №1
Department "____"_____
Protocol № ____ from _____
The Head of the Department
Associate Professor Maslova H.S.
_____

Methodical guidelines

for students' self-studying to prepare

for practical (seminar) classes and on the lessons

Academic discipline	Internal medicine
Module №	1
Topic of the lesson	Chronic diseases of the small intestine: celiac diseases and other enteropathies.
Course	IV
Faculty	of foreign students training

1. Relevance of the topic: Gluten enteropathy is a chronic immune-mediated intestinal disease caused by genetically determined gluten intolerance, diffuse atrophy of mucous membrane, that leads to generalized malabsorption. About 22% of patients diagnosed with IBS or with microscopic (lymphocytic) colitis have celiac disease. It is sometimes difficult to make diagnosis of celiac disease, especially when it represents with its symptoms in adulthood. Another difficult task is to distinguish celiac disease from other enteropathies.

2. Certain aims:

– To analyze symptoms from lower GI tract and make the preliminary diagnosis.

– To explain pathogenesis of celiac disease and other enteropathies generally and in individual patients.

– To propose further management tactics for those with suspected celiac disease and other enteropathies.

– To classify celiac disease and other enteropathies and FD.

– To interpret data of CBC, EGDS, colonoscopy, hydrogen breath tests and other tests essential to make a diagnosis of enteropathy.

– To draw schemes, charts of patient's follow-up.

– To analyze data of survey, physical examination, additional methods of investigations to confirm the clinical diagnosis of patients with suspected celiac disease and other enteropathies.

– To make the full diagnosis according to the current classifications and prescribe treatment for patients with celiac disease and other enteropathies.

3. Basic knowledge, abilities, skills required to study the topic (interdisciplinary integration).

Names of previous disciplines	Obtained skills
1. Anatomy 2. Histology 3. Anatomy	To describe the structure of the gastrointestinal tract, blood supply and innervation in health and disease; to

4. Physiology 5. Pathology 6. Radiology 7. Propaedeutic internal medicine 8. Pharmacology	establish the preliminary diagnosis, to use additional methods of examination and interpret their data to make final diagnosis; to manage the patient with celiac disease and other enteropathies; to classify celiac disease and other enteropathies, and drugs for their treatment; to identify markers of gastrointestinal tract function and to know their normal values; to draw a scheme of patient's follow-up; to compare celiac disease and other enteropathies with other diseases with the same symptoms; to demonstrate practical skills during physical examination of the patient, analyzing the clinical and laboratory results.

4. Tasks for self-studying to prepare for the lesson and on the lesson.

4.1. List of main terms, parameters, characteristics that should be learnt by student during preparation for the classes:

Term	Definition
Enteropathy	an intestinal disease caused by wide range of factors, characterized by wall changes leading to the development of such "enteric" symptoms as diarrhea, bloating, pain, etc.
Celiac disease (gluten enteropathy)	chronic progressive immune-mediated intestinal inflammatory

	disease that is characterized by genetically determined gluten intolerance, diffuse atrophy of mucous membrane, and leads to generalized malabsorption.
EMA, anti-tTG	antiendomysial and anti-tissue transglutaminase antibodies that are associated with celiac disease.
Autoantibodies	an antibody produced by the body and active against own body's tissue. Typical for autoimmune diseases.

4.2. Theoretical questions for the lessons:

1. What is enteropathy?
2. What is celiac disease?
3. How enteropathies should be classified?
4. What are the risk factors for celiac disease?
5. Explain the pathophysiological mechanisms of celiac disease and other enteropathies.
6. Name the diagnostic criteria of celiac disease and other enteropathies.
7. What are the endoscopic characteristics of celiac disease and its stages?
8. Specify the principles and features of celiac disease and other enteropathies pharmacotherapy according to modern recommendations.
9. What lifestyle modifications should be recommended for patients with celiac disease and other enteropathies?

4.3. Practical work (tasks), performed on the lesson:

1. Interpret changes in general blood test in case of celiac disease and other enteropathies.

2. Interpret data of biochemical blood tests in case of celiac disease and other enteropathies.

3. Interpret data of diagnostic tests to confirm celiac disease.

4. Perform survey and physical examination of the patient and make preliminary diagnosis.

5. Manage the patient with suspected celiac disease or other enteropathies, prescribe relevant laboratory and instrumental investigations and further treatment.

Topic content:

Enteropathy is common name for diseases, characterized by pathologic (inflammatory, hemorrhagic, erosive, ulcerative or atrophic) changes of small intestine. Despite of wide range of modern diagnostic tests, it is still hard to distinguish different forms of enteropathies.

Clinical features usually include:

– chronic diarrhea;

– symptoms of malabsorption;

– autoimmune signs;

– abdominal pain (less frequent).

There are different types of enteropathies: enteropathy-associated T-cell lymphoma, immunodysregulation polyendocrinopathy and enteropathy, X-linked (see FOXP3), protein-losing enteropathy, radiation enteropathy, tropical enteropathy, HIV enteropathy, celiac disease, eosinophilic enteropathy, environmental enteropathy, etc.

The main test to make a diagnosis is upper endoscopy with biopsy and further histological assessment.

The therapy is often symptomatic. Elimination diets are often provided.

Celiac disease

Synonyms: Gluten-sensitive enteropathy, Gluten enteropathy, Non-tropical sprue.

Definition. Gluten enteropathy is a chronic progressive immune-mediated intestinal inflammatory disease that is characterized by genetically determined

gluten intolerance, diffuse atrophy of mucous membrane, and leads to generalized malabsorption.

Classification. Classic form (active form with gastrointestinal symptoms), non-classic (when gastroenterological symptoms are minimal or absent, but there are extra intestinal symptoms) and asymptomatic.

Epidemiology. Most common in the Irish, British, and other northern European populations. Screening studies for the antiendomysial (EMA) and anti–tissue transglutaminase (anti-tTG) antibodies that are associated with celiac disease suggest a prevalence in white populations of about 1%. About 20% of patients diagnosed with irritable bowel syndrome or with microscopic (lymphocytic) colitis have celiac disease.

Etiology. Genetic disease, associated with HLA-DQ2 and HLA-DQ8. Autosomal-dominated. Disease manifests only after peroral gliadine consumption. High-risk groups for celiac disease include first-degree relatives and individuals with type 1 diabetes mellitus, autoimmune thyroid disease, primary biliary cirrhosis, Turner's syndrome, or Down syndrome.

Pathogenesis. Gluten is a protein of gramineous plants (cereals) such as wheat, barley, rye. Gliadin is alcohol-soluble component of gluten, which can be produced from gluten by pathologic proteolysis and trigger intestinal inflammation in susceptible individuals. A 33-mer peptide that is a natural digestion product of α2-gliadin may be important in the pathogenesis of celiac disease. This peptide resists terminal digestion by intestinal brush-border proteases and contains three previously identified antigenic epitopes. It also reacts with tissue transglutaminase and stimulates human leukocyte antigen (HLA)-DQ2-restricted intestinal T-cell clones from individuals with celiac disease.

One group of scientists considers that celiac disease is an immune mediated injury to enterocytes accompanied by serum antibodies to gliadin.

tTG (the autoantigen recognized by EMA) may enhance intestinal inflammation by deamidation of select glutamine residues in gliadin to negatively charged glutamic acid. In the deamidated form, most gliadin peptides have a higher

binding affinity for DQ2 and are more potent stimulants of glutensensitized T cells. Villous atrophy may be caused by inflammation that is triggered by γ-interferon released from DQ2- or DQ8-restricted CD4 T cells in the lamina propria. Alternatively, intraepithelial lymphocytes may directly kill intestinal epithelial cells under the influence of IL-15 released from stressed enterocytes.

The other theory is genetically determined fermentative deficiency that leads to inability to ferment gluten to non-toxic fractions.

Clinical features. Celiac disease usually manifests early in life, at about 2 years of age (after wheat has been introduced into the diet), or later in the second to fourth decades of life, but it can occur at any age. It can be characterized by absent gastrointestinal symptoms and a wide spectrum of non-intestinal manifestations that can involve any organ of the body, and very frequently may be completely asymptomatic.

Classical symptoms are:

- watery diarrhea (is caused by many mechanisms, including a decreased surface area for water and electrolyte absorption, the osmotic effect of unabsorbed luminal nutrients, an increased surface area for chloride secretion (crypt hyperplasia), and the stimulation of intestinal fluid secretion by inflammatory mediators and unabsorbed fatty acids),
- abdominal distention,
- flatulence,
- fatigue,
- weight loss, growth retardation,
- malabsorption: iron, mineral and vitamin deficiency.

Adults with celiac disease often present with anemia or osteoporosis without diarrhea or other gastrointestinal symptoms. These individuals most likely have proximal disease that impairs iron, folate, and calcium absorption but an adequate surface area in the remaining intestine for absorption of other nutrients.

Other extraintestinal manifestations of celiac disease include rash (dermatitis herpetiformis), neurologic disorders (peripheral neuropathy, ataxia, epilepsy),

psychiatric disorders (depression, paranoia), reproductive disorders (infertility, spontaneous abortion), short stature, dental enamel hypoplasia, chronic hepatitis, or cardiomyopathy.

Diagnosis. The diagnosis of celiac disease is made by characteristic changes found on a small intestinal biopsy specimen and improvement when a gluten-free diet is instituted.

An upper endoscopy with biopsy of the duodenum (beyond the duodenal bulb) or jejunum is performed to obtain multiple samples (four to eight) from the duodenum. It is the "gold standard" of celiac disease diagnosis. Mucosal flattening may be observed endoscopically as scalloped or reduced duodenal folds. Characteristic features found on intestinal biopsy include blunted or absent villi, crypt hyperplasia, increased intraepithelial lymphocytes, and infiltration of the lamina propria with plasma cells and lymphocytes. In some individuals, the only abnormal biopsy finding is increased intraepithelial lymphocytes. A hypoplastic mucosa indicates irreversible (end-stage) intestinal disease.

Serologic markers for celiac disease are useful in supporting the diagnosis or in screening, and in monitoring the response to a gluten free diet.

- EMA (anti-endomysial antibodies) immunoglobulin A (IgA) antibodies, detected by indirect immunofluorescence, are highly sensitive (90%) and specific (90 to 100%) for active celiac disease in skilled laboratory testing.
- The newer antideamidated gliadin (a biotinylated synthetic γ-gliadin peptide with glutamic acid substituted for glutamine) IgA and IgG antibody immunofluorometric assay has a sensitivity and specificity that approaches that of EMA.
- The anti-tTG (anti-transglutaminase antibodies) IgA antibody test, when obtained with a serum IgA level, is a cost-effective strategy for screening high-risk groups.
- NB! Patients with mild disease may have negative antibody studies. Anti-tTG, gliadin peptide, and EMA IgA antibodies tests are also negative in individuals with

selective IgA deficiency. In these patients, anti-tTG or gliadin peptide IgG antibodies may be helpful in diagnosis.

HLA genotyping is useful to exclude the diagnosis of celiac disease in persons who lack the DQ2 or DQ8 gene.

• Bone densitometry should be performed on all individuals with celiac disease because up to 70% have osteopenia or osteoporosis. Patients with diarrhea and weight loss should be screened for vitamin and mineral deficiencies. Stool fat test may be ordered, to evaluate malabsorption.

Common complications. Iron deficiency, vitamin B12 and folate deficiency, osteoporosis, cancer, malnutrition, lactose intolerance, intestinal ulcers.

Differential diagnosis. Other causes of malabsorption are: immune conditions, hypersensitivity/allergy/eosinophilic gastroenteritis, infection, Whipple's dis., tropical sprue, bacterial overgrowth, nutritional deficiencies, amyloidosis, lymphoma, lipid storage, short bowel. Diarrhea is common for infectious and non-infectious enteritis, IBS, lactase deficiency, diabetic enteropathy, different colitis.

Treatment. The only available treatment for celiac disease is a strict lifelong gluten-free diet in which the diseased person does not ingest any gluten. Wheat, rye, and barley grains should be excluded from the diet. Rice and corn grains are tolerated. Oats (if not contaminated by wheat grain) are tolerated by most.

Owing to secondary lactase deficiency, a lactose-free diet should be recommended until symptoms improve.

Deficiencies of vitamins and minerals should be replenished. Patients with vitamin D or calcium deficiency should receive supplements, with the dose monitored by 25-OH vitamin D levels and a 24-hour urine test for calcium.

Cobalamin deficiency is more common and usually corrects itself on a gluten-free diet. Symptomatic individuals require supplementation of vitamin B12.

Materials for self-control:

A. Tests and situational tasks for self-control:

1. The etiology of celiac disease is:

A) bacteria

B) NSAIDs

C) immune

D) chemical damage

E) environmental factors

2. The only available treatment for celiac disease is:

A) a strict lifelong gluten-free diet

B) corticosteroids

C) probiotics

D) antibiotics

3. A 2 y.o. boy was admitted to the hospital with weight loss, unstable discharges, anorexia, following the semolina's introduction (since 5 months). The child is adymanic, flabby, with pale dry skin, subcutaneous layer is emaciated. Distended and tensed abdomen, tympanitis on percussion of the upper part of the abdomen, splashing sounds, feces are foamy, light, foul. On coprocytogram: a lot of neutral fat. What is the cause of the disease?

A) Celiac disease

B) Mucoviscidosis (cystic fibrosis)

C) Intestinal dysbacteriosis

D) Chronic enteritis

E) Disaccharidase insufficiency

4. A 43 y.o. male complains of stomach pain, which relieves after defecation, and is accompanied by abdominal winds, rumbling, the feeling of incomplete evacuation or urgent need for bowel movement, constipation or diarrhea in alternation. These symptoms have lasted for over 3 months. No changes in laboratory tests. What is the most likely diagnosis?

A) Irritable bowel syndrome

B) Spastic colitis

C) Colitis with hypertonic type dyskinesia

D) Chronic enterocolitis, exacerbation phase

E) Atonic colitis

B. Situational tasks for self-control:

5. Teenager, 14 years old, has complaints on diarrhea, weakness, weight loss. The condition worsened after taking of plenty of flour products. Such phenomena are observed from babyhood. Objectively: general state is satisfactory, body weight is reduced, physical development is delayed. The reason of the disease is:

A) Lactase deficiency

B) Invasion with intestinal worms

C) Chronic pancreatitis, syndrome of maldigestion

D) Dysbacteriosis of intestine

E) Gluten enteropathy

6. A 45-year-old male patient presented to hospital with 2-year history of excessive hair loss, flatulence, abdominal pain, occasional diarrhea without blood or mucous. O/E: the patient is malnourished, the skin is thin and pale, scanty hair, angular stomatitis. Laboratory findings, he was found to be anaemic (Hb lOg/dl MCV 65), serum iron, TIBC and folate levels were all low. What is your preliminary diagnosis? What instrumental investigations do you need? What changes do you expect to find if you suspect celiac disease?

Answers: 1-C, 2-A, 3-A, 4-A, 5-E, 6 – enteropathy; endoscopy of GIT; loss of folds, villous atrophy.

Recommended literature

I. Main:

1. Internal Medicine: in 2 books. Book 1. Diseases of the Cardiovascular and Respiratory Systems: textbook / N.M. Seredyuk, I.P. Vakaliuk, R.I. Yatsyshyn et al. Київ, Медицина., 2019. - 664 + 48 кольор. вкл.).

2. Internal medicine: Part 1 (cardiology, rheumatology, haematology): textbook for English-speaking students of higher medical schools / edited by Professor M.A. Stanislavchuk and Professor V.A. Serkova. - Vinnytsia: Nova Knyha, 2019. - 392 p.
3. Медицина за Девідсоном: принципи і практика / Навчальний посібник: пер. 23-го англ. вид.: у3 т. Т.3 С. Ралстона, Я. Пенмана, М. Стрекена, Р. Гобсона; К.: ВСВ «Медицина», 2021. – 642 с.
4. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)/
5. Побічнадіяліків – SideEffectsofMedications: навчальнийпосібнику 2 т. / зазаг.ред. В.М. Бобирьова, М.М. Потяженка. – Вінниця:
6. Cardiovascular diseases. Classification, standards of diagnosis and treatment / Edited by Academician Kovalenko V.M., Prof. Lutaia M.I., Prof. Sirenko Yu.M., Prof. Sychova O.S. – Kyiv. – 2020.
7. Perederii V.H., Tkach S.M. Principles of internal medicine. – Vol.2 / Textbook for students of higher educational institutions. – Vinnytsia: Nova knyha. – 2018.
8. Internal diseases. The textbook based on the principles of evidentiary medicine, 2018.

II. Additional literature:

1. Recommendations of the Association of Cardiologists of Ukraine for the diagnosis and treatment of chronic heart failure / Voronkov L.H. – moderator, working group of the Ukrainian Association of Heart Failure Specialists. – 2017.
2. Respiratory diseases / Ghanei M. - In Tech, 2012. - 242 p.
3. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.

4. Principles and practice of interventional pulmonology / Ernst A., Herth F. - Springer, 2012. - 757 p.
5. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
6. Petrov Y. The chief symptoms and syndromes in patients with cardiovascular pathology : The practical handbook fur medical students / Ye. Petrov, Yu. Goldenberg, N. Chekalina; UMSA. - Poltava : TexcepBic, 2010. - 143 .
7. Gastroenterology and Hepatology Board Review: Pearls of Wisdom, Third Edition (Pearls of Wisdom Medicine) by John K. DiBaise (May 11, 2012)
8. Clinical Pulmonology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Oct 30, 2011) - Kindle eBook
9. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
10. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
11. Hematology: Clinical Principles and Applications, 4e by Bernadette F. Rodak MS MLS (Feb 18, 2017)
12. Rheumatology, 2-Volume Set: EXPERT CONSULT - ENHANCED ONLINE FEATURES AND PRINT, 5e by Marc C. Hochberg MD MPH, Alan J. Silman MD, Josef S. Smolen MD and Michael E. Weinblatt MD (Oct 19, 2019)
13. Endocrine Pathology: Differential Diagnosis and Molecular Advances by Ricardo V. Lloyd (Nov 5, 2018)
14. Clinical Endocrinology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2017) - Kindle eBook
15. Williams Textbook of Endocrinology: Expert Consult-Online and Print, 12e by Shlomo Melmed, Kenneth S. Polonsky MD, P. Reed MD Larsen and Henry M. Kronenberg MD (May 27, 2016)
16. Electrocardiography, 3e with Student CD (Booth, Electrocardiography for Health Care Personnel) by Kathryn A. Booth (Jan 27, 2017)

17. Echocardiography Review Guide: Companion to the Textbook of Clinical Echocardiography: Expert Consult: Online and Print, 2e (Expert Consult Title: Online + Print) by Catherine M. Otto (Mar 7, 2017).