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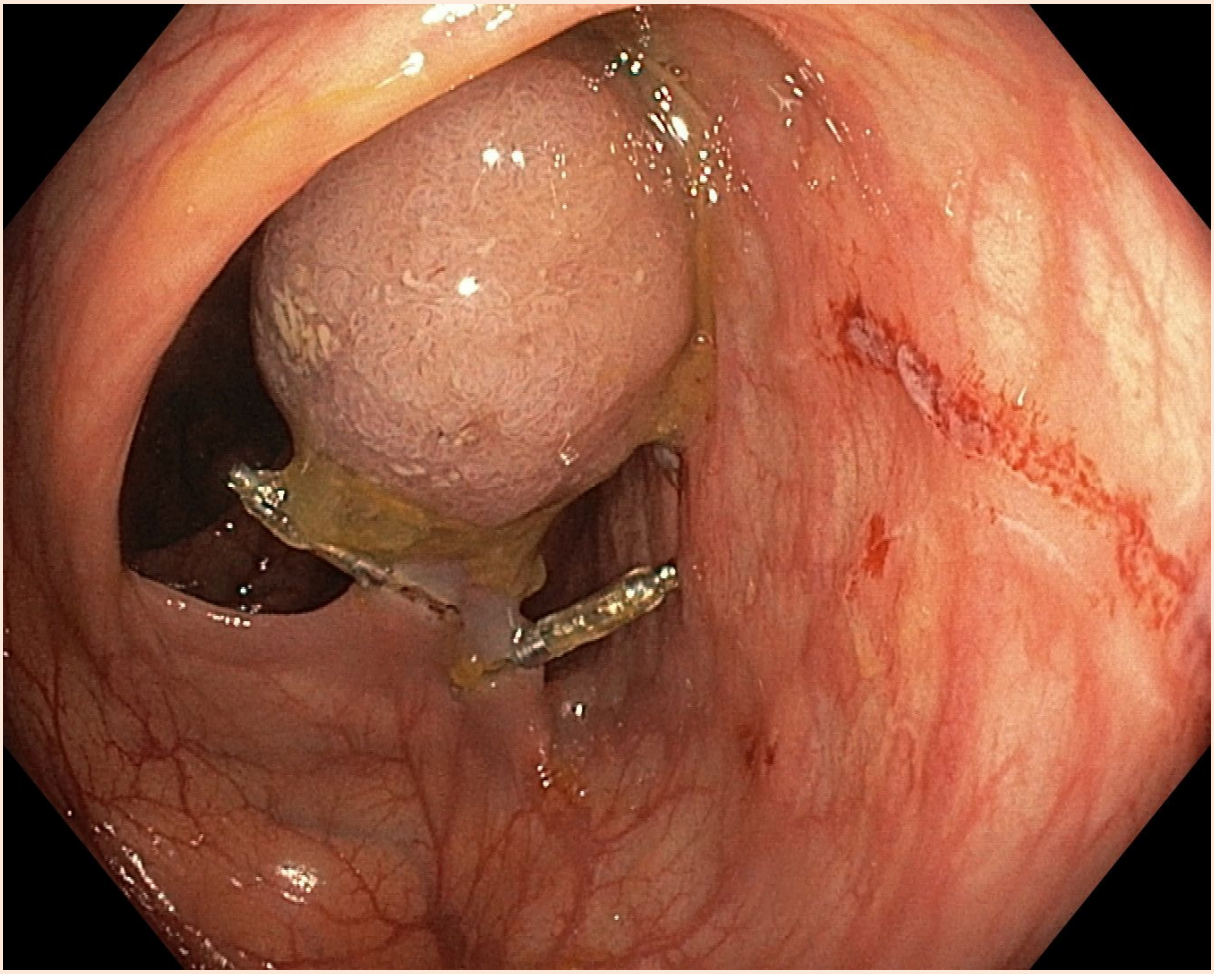
TEXTBOOK
OF
GASTROENTEROLOGY
AND
HEPATOLOGY



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A. GASTROENTEROLOGY

1. GASTRO-ESOFAGEAL REFLUX DISEASE

Definition. Gastro-esophageal reflux disease (GERD) includes the cluster of symptoms caused by the reflux of the gastric contents into the esophagus.

Gastro-esophageal reflux (GER) represents the passage of the gastric content into the esophagus, a physiological phenomenon that becomes pathological when the antireflux mechanisms are overcome.

Reflux esophagitis (RE) - Esophageal injury induced by GER, that are not encountered in all the cases of pathological GER.

GERD is a clinical entity relatively frequently found in clinical practice, with a multifaceted symptomatic picture.

Prevalence: ER affects ~ 4% of the general population and increases with age. It has an increasing trend.

Etiopathogenesis

Two main causes are considered to damage the anti-reflux mechanisms:

A. Physiological causes

1. Decrease in the lower esophageal sphincter (LES) pressure. In normal conditions this pressure is 20 - 25 mmHg and dicreases only at the moment of swallowing. GER occurs either when LES temporarily relaxes without swallowing, or when the baseline LES pressure drops below 6 mmHg, allowing the passage of the gastric content into the esophagus.

LES pressure may be reduced by drugs (anticholinergics, aminophilin, nitrites, benzodiazepines, calcium channel blockers), food (chocholate, fats, onion, citrus fruit, tomato juice, menthol flavors), coffee (due to xanthinic derivatives), smoking and alcohol (that also increase acid secretion).

2. Decreased gastric motility and delayed gastric emptying.

3. Impaired esophageal clearance of the refluxed gastric content. The clearance together with the swallowed saliva have the role to buffer the refluxed acid.

B. Mechanical causes

1. Hiatal hernia. It reduces the LES tonus and thus favors reflux.

2. Increase of intra-abdominal pressure, leading to the widening of the diaphragmatic hiatus, which explains GER in pregnant women and patients suffering from obesity, giant abdominal tumors or ascites.

3. Enlargement of the His angle. This angle between the esophagus and the stomach is usually sharp, playing the role of a safety valve at the stomach entrance. In obese patients it widens and loses its physiological role.

4. Relaxation of the diaphragmatic sling; this is formed of the crural diaphragm and is the muscle canal through which the esophagus passes from the thorax into the abdomen. It slackens when the intra-abdominal pressure or the thoracic volume (emphysema) increase.

5. Sclerodermia. Esophageal motility disturbances are due to fibrotic and atrophic processes of the smooth muscles, the so-called "glass esophagus".

Development and severity of reflux esophagitis depend on 3 factors:

- increased reflux frequency
- increased reflux duration
- aggressive effect of the gastric content on the esophageal mucosa.

Clinical picture

Typically is represented by ***acid regurgitation*** and ***pyrosis,*** which have a continuous or discontinuous character. Symptoms may be occasional or persistent.

Retrosternal pain or dysphagia are relatively rare. The presence of these two symptoms should prompt for a more severe diagnosis. More rarely, in atypical forms, symptoms may mimic angina-like cardiac disturbances or asthma attacks.

Pyrosis - is the feeling of retrosternal burn going up to the throat. It is accentuated by manoeuvres that increase abdominal pressure (bending forward, weight lifting, lying down immediately after meals), being sometimes accompanied by ***acid regrugitation.***

If LES incompetence is severe, even food content may be regurgitated.

Retrosternal pain - it often raises problems of differential diagnosis with heart conditions. It may occur in isolation, not accompanying pyrosis.

Odynophagia - (painful swallowing) occurs in case of spastic LES contraction.

Dysphagia - Difficult swallowing.

Respiratory symptoms (suffocation, nocturnal dyspnea, asthma attacks)

ENTsymptoms - (laryngitis, pharyngeal numbness, dysphonia) are caused by the regurgitation of the refluxed acid and its aspiration.

Paraclinical examinations

The examinations required to assess GERD will include: eso-gastroscopy, pH-metry and esophageal manometry. Which of these tests will be performed and when? Trying to be less invasive, but at the same time not miss severe injury, it is difficult to decide on the diagnostic methods.

Upper gastro-intestinal endoscopy.

In the presence of annoying esophageal symptoms (especially pain and dysphagia), ***eso-gastroscopy*** will be performed. It will prove an existing esophageal injury (esophagitis, stenosis), or it will rule them out. It will also diagnose associated or symptom-inducing gastro-duodenal injuries. The presence of hiatal hernia may also be proved. Endoscopy also allows to take bioptic samples (evidence of Barrett's epithelium for instance).

The most typical consequence of GER is reflux esophagitis, which is the injury (denudation) of esophageal mucosa due to acid or alkaline reflux.

The severity of endoscopic lesions is assessed using the **Los Angeles classification**.

According to this classification esophagitis is of several grades (A-D):

A) One or more substance loss areas smaller than 5 mm in size.

B) At least one area larger than 5 mm of substance loss, but non-confluent.

C) At least one area of extended substance loss between 3 or 4 mucosal folds, but non-circumferential.

D) Circumferential substance loss.

Esophageal pH-metry of 24-hour duration (usually in outpatient conditions) is very useful to assess the reflux duration, time spent of the lower esophagus at a pH under 4 (acid). It also helps correlate clinical symptoms with acid pH, or atypical symptoms (presternal pain, asthma bouts) with reflux. The drawbacks are related to the cost of the equipment, its low availability and patients compliance.

Esophageal manometry usually associated with pH-metry, allows the diagnosis of esophageal motility disturbances and their correlation with clinical symptoms.

Barium meal test (controversial for this condition), it may demonstrate esophageal motility disturbances (achalasia, diffuse esophageal spasm), a possible esophageal stenosis, hiatal hernia (in Trendelenburg's position). The evidence of esophagitis injury is not possible, therefore it is an examination with limited value.

Diagnosis

Positive diagnosis

The positive diagnosis is clinical, but needs confirmation by paraclinical tests. There are two distinct situations: the differentiation between gastro-esophageal reflux as a cause of discomfort and reflux esophagitis as a consequence of reflux. In most patients with occasional esophageal reflux, the examinations will not show injury. In case of persistent (permanent) reflux, morphological lesions will be present.

Differential diagnosis

A. With digestive diseases:

- gastroduodenal ulcer is typically manifested by epigastric pain; heartburn indicates the association with acid reflux;
- the differentiation between acid and alkaline reflux (especially post-cholecystectomy), when the morning or quasi-permanent bitter taste occurs;
- esophageal diverticulum, achalasia, esophageal ulcer, esophageal cancer.

In case of dysphagia, especially in elderly patients (but not necessarily), or odinophagia (intense pain at swallowing), we should consider an esophageal neoplasm and diagnostic upper GI endoscopy is mandatory (Note: barium meal test may lead to misdiagnosis)

B. With non-digestive diseases:

- retrosternal or chest pain will be differentiated from heart conditions (ECG or exercise test is necessary; in doubt, perform coronarography);
- asthma attacks may be sometimes triggered by acid reflux, therefore pH-metry correlated with these attacks may be useful for the therapy; this is mainly important in children.

Evolution, complications

Evolution is of long term, with ups and downs generally depending on the eating habits and life style.

Complications that may occur in GERD are:

- *reflux esophagitis*, to various grades, up to
- *esophageal ulcer*

and

- *esophageal stenosis* (exceptionally rare situations in our setting, where grades A and B esophagitis prevail)
- *Barrett's epithelium* (endo-brachy-esophagus) is a columnar metaplasia of the normal Malpighi esophageal mucosa, a consequence of the reflux disease healing after acid exposure, and is a premalignant condition. Endoscopically, Barrett's mucosa appears red, as opposed to the normal pink esophageal mucosa. It may be circular, or in the shape of extensions or islets.

There are two forms of Barrett's esophagus:

a) long – more than 3 cm above the esogastric junction;

b) short – situated in the first 2-3 cm above the esogastric junction.

The positive diagnosis is histopathological – intestinal type metaplasia.

In 2004 a new classification of Barrett's epithelium was established – **the Prague classification**. According to this classification there are two parameters assessed: circumferential Barrett and maximal Barrett (**c and m**, expressed in centimeters).

The crucial problem of Barrett's esophagus is its malignant potential, which is 30 – 125 times higher than in the general population; on average one of 125 individuals with Barrett's esophagus develops esophageal cancer.

The management targeting the early detection of malignancy depends on the histopathological findings:

- intestinal metaplasia without dysplasia – conservative therapy with endoscopic follow-up and biopsy every 2 years;
- low grade dysplasia – conservative therapy and annual follow-up and biopsy;
- high grade dysplasia – surgical or endoscopic therapy (endoscopic mucosectomy or radioablation). Medical treatment may be an alternative with biopsies every 3-6 months.

- *upper digestive hemorrhage* (hematemesis and/or melena) is a rare complication. It usually occurs as melena, as bleeding is mild to moderate, caused by ulcer or severe esophagitis.

Treatment

A. General care and diet

Most cases are resolved by sustained diet measures, such as:

- avoiding large meals, and food that lower the LES pressure: coffee, chocolate, fizzy drinks, menthol, fats, alcohol, or food that increase acid secretion: orange juice, fizzy drinks, white wine, acid foods;
- avoiding smoking: it is believed that smoking increases acid secretion and lowers LES pressure;
- avoiding lying down with a full stomach or bending right after meal;
- obese subjects should lose weight (abdominal pressure);
- avoiding drugs that lower the LES pressure: nifedipin, nitrates, euphillin or caffeine.

B. Drug therapy

Includes 3 types of drugs:

1. Antisecretory treatment - These drugs decrease gastric acid secretion:

Proton pump inhibitors - they are the most powerful antisecretory agents. A wide range is available nowadays: omeprazole (Losec, Omeran, Ultop, Antra,

Omez) 2x20 mg/day, pantoprazole (Controloc) 40 mg/day, lanzoprazole (Lanzop, Lanzap) 30 mg/day, rabeprazole 20mg/day. Esomeprazole (Nexium, Emanera) 40mg/day is the 2nd generation of PPI.

In case of reflux esophagitis the treatment duration will be 4 – 8 weeks (according to severity). Antisecretory therapy may be used on demand in case of intermittent acid reflux.

2. Prokinetic drugs

- the classical metoclopramide administered 3 x 1 tb (10 mg) 30 minutes before meals. The effect is an increased LES tonus and also it increases esophageal and gastric emptying.

- Domperidon (Motilium) also has an effect on the LES and gastric kinetics. It does not induce extrapyramidal symptoms. It is preferred to metoclopramide due to reduced side effects.

3. Antacids

Drugs with direct neutralizing effects: Maalox, Novalox, Rennie, Dicarbocalm, Gaviscon, which contain magnesium and aluminium salts; patients take them for rapid relief of symptoms. Their effect is only symptomatic and temporary, they do not heal the esophageal injuries.

The therapeutic strategy in case of acid reflux is to start with antisecretory medication, preferably PPI. In case of failure a prokinetic is introduced (Domperidon). If patients have biliary reflux, therapy will be only prokinetic.

C. Endoscopical treatment

- *Esophageal stenosis* - The treatment of choice for peptic stenosis is endoscopic dilation with Savary probes or balloons.

- *Upper GI hemorrhage* - Severe forms benefit from endoscopic hemostasis with adrenalin injection, photocoagulation with Argon Beamer or hemoclips application.

- *Barrett's esophagus* - The areas of cyllindric epithelium with various degrees of dysplasia may be destroyed by radiofrequency ablation, dynamic phototherapy or endoscopic mucosectomy.

- *Endoscopic fundoplication* - It is a new, non-invasive method that consists of creating a sharp His angle by folding the gastric surface of the LES. Currently there are several endoscopic devices for endoscopic fundoplication.

D. Surgery

The rare cases with severe esophagitis refractory to treatment may have indication for surgical treatment (exceptionally rare in our country). The surgical procedure consists of Nissen's fundoplication (making a gastric sheath around the distal esophagus); nowadays it is performed laparoscopically.

2. ESOPHAGEAL MOTILITY DISTURBANCES

They are relatively rare, sometimes difficult to diagnose. Two important entities will be described: achalasia and diffuse esophageal spasm.

ACHALASIA

Definition: The main diagnostic elements are LES hypertonicity, the absence of the LES relaxation at swallowing and the absence of peristalsis in the lower two thirds of the esophagus. Practically the LES does not relax during swallowing.

Etiopathogenesis is insufficiently known; genetic (predisposition) factors are incriminated, environmental factors (neurotrophic virus), emotion and stress as triggering factors.

Autoptic studies have showed an impairment of the nervous control of motility and esophageal muscles. The hypothesis of a neurotoxin-secreting virus implication is supported by the presence of secondary achalasia in Chagas disease (Tripanosoma Cruzi infestation), in which the parasite causes neurotoxic injuries leading to mega-esophagus.

The clinical picture is dominated by *dysphagia* and, possibly *odinophagia*. Usualy dysphagia is paradoxical, with difficulty in swallowing liquid food, but good tolerance of solid food.

Hiccups occur late, due to marked esophageal distension.

The *regurgitation* of food and saliva is frequent, occurring several hours after ingestion, but it decreases with the dilation of the esophagus. At night the regurgitation may induce cough and dyspnea. In the final stages the patient assumes a typical position (Valsalva), by which s/he increases the chest pressure and eases the passage of the bolus into the stomach.

Diagnosis

The clinical diagnosis will be confirmed by endoscopy, radiology and manometry.

Endoscopy will show a marked dilation of the esophagus, containing food remnants and abundant saliva, generally without mucosal injury. The pressure of the endoscope will push the bolus easily into the stomach (differentiating the condition from organic stenosis). The most important endoscopic element is to establish the absence of neoplasia.

Esophageal barium examination is useful and valuable; it shows a dilated esophagus, symmetrically narrowing in its lower segment, "radish" aspect. Following the swallowing process will prove the absence of esophageal peristaltic waves, lack of sphincter relaxation and hypertonic LES at rest.

Differential diagnosis should be done firstly with esophageal cancer, then with organic esophageal stenosis, diffuse esophageal spasm, hyper-peristaltic esophagus (nutcracker esophagus), and post-caustic esophageal stenosis.

Treatment

It is often difficult and includes three alternatives:

A) Drug therapy - Drugs that lower the LES pressure: nitrates, nitrites, calcium blockers (nifedipin, diltiazem, verapamil). One or two drugs are administered; they may be effective in the early stages.

B) Endoscopy - LES dilation procedures using balloons under fluoroscopic guidance. Another endoscopic procedure is the injection of inactivated botulin anatoxin BoTox into the LES (achieves temporary muscular paralysis).

Another treatment technique developed by the Japanese endoscopists, at the border between interventional endoscopy and surgery, is represented by POEM (Per-Oral Endoscopic Myotomy), recently implemented also in our country. This technique is based on the sectioning of the esophageal circular muscle fibers at the level of the lower esophagus, at the cardia level and 2-3 cm subcardial, using special cutting devices (Hook knife, IT knife, triangle knife), the mucosal defect produced being subsequently covered with metal clips. .

C) Surgery - Surgery is resorted to when everything else failed; it consists of Heller LES cardiomyotomy (longitudinal sectioning of the circular fibers). It may entail esophageal reflux.

DIFFUSE ESOPHAGEAL SPASM AND NUTCRACKER ESOPHAGUS (PERISTALTIC ESOPHAGUS)

Clinically manifested by dysphagia and retrosternal pain.

The diagnosis is established by x-ray and manometry.

The treatment consists in the administration of nitrates, nitrites, anticholinergic drugs, and less of calcium blockers. Sedative medication may be useful. In case of no therapeutic response esophageal dilation can be performed using balloon or bougies.

3. ESOPHAGEAL CANCER

Esophageal cancer represents ~ 15% of digestive cancers. Histologically most of cases are epidermoid carcinomas. It is more frequently found in men (male/female ratio = 3/1), and the mean age of onset is ~60-65 years.

Among **predisposing factors** we mention:

- smoking
- alcohol consumption
- alimentary factors: protein deficit, reduced vitamin A, B and C supply, excess of nitrozamines, zinc and molibden deficiency
- other factors: consumption of very hot drinks (tea), exposure to ionizing radiations, infectious agents (Papilloma virus), genetic factors.

There are also a number of **other conditions predisposing** to esophageal neoplasm:

- Barrett's esophagus
- ENT cancers
- mega-esophagus
- esophageal diverticuli
- post-caustic stenoses
- peptic stenoses

Morphopathology

Several aspects are described:

- the most frequent location is in the lower one third of the esophagus (over 50% of cases) and only 20% in the upper third;
- macroscopically, the most common form is ulcero-vegetative
- microscopically – 90% of the cases present an epidermoid carcinoma.

Rarer forms are: adenocarcinoma, or, very rarely, sarcoma, lymphoma, melanoma

Clinically, a number of symptoms are described, unfortunately occurring at stages that are past the possibility of surgical intervention: dysphagia, regurgitation, chest pain, body weight loss, dysphonia.

The diagnosis is mainly *endoscopical*, with biopsy sampling. *Radiology* (barium meal) is useful in case of esophageal stenosis preventing the endoscope passage. *Endoscopic ultrasound* (EUS) is necessary and useful for preoperative staging, and so is *contrast enhanced computer tomography* (CE-CT).

Evolution of esophageal cancer is rapid, prognosis is poor, with only 5% survival rate at 5 years.

The complications worsen the prognosis: aspiration pneumonia, eso-bronchial fistulae, perforations, hemorrhage, severe denutrition.

The treatment includes several options:

1. ***Surgery*** – the method of choice, consisting of esophagectomy. It can be associated with:

2. ***Radiotherapy*** – palliative

3. ***Chemotherapy*** – may be performed with Bleomycin, Cisplatin, 5-fluorouracil. Both radio- and chemotherapy may sometimes lead to spectacular results.

4. ***Endoscopical treatment***:

- endoscopic mucosal resection, mucosectomy, indicated in early esophageal cancer. This technique is performed using a polypectomy loop after injecting saline and adrenaline into the submucosa, in order to elevate the mucosa for better tumor resection.

- *endoscopic stenting* is a palliative method that improves the quality of life and treats dysphagia (in advanced cases). Nowadays sheathed extensible stents, made of shape-memory alloys, are used (to prevent tumoral invasion). The endoscopic dilation of the tumour is often necessary before the application of the stent. Stenting (which makes dysphagia subside and the patient is able to eat) is followed by radio- and chemotherapy.

4. GASTRITIS

Definition

Gastritis is an acute or chronic gastric disease characterized by inflammatory injuries caused by various factors; they may be asymptomatic or with unspecific clinical expression.

On the other hand, *gastric diseases* are injuries of the gastric mucosa, mainly epithelial and /or vascular (stasis or ischemia), with absent or minimal inflammation.

Classification

Gastrites are classified according to several criteria:

1. Clinical-evolutive classification

A. *Acute gastritis*- They evolve toward healing or chronic disease. Most of them are self-limiting and heal spontaneously.

B. *Chronic gastritis* - Long-term inflammations, they may heal or progress despite treatment.

2. Endoscopic classification

A. *Endoscopic forms* of gastritis

- Exudative erythematous
- Erosive macula
- Erosive papula
- Atrophic
- Hypertrophic
- Hemorrhagic

B. *Classification according to location-extension*

- Antral – B type – caused by H. pylori infection
- Fundic – A type – autoimmune (may induce Biermer's anemia)
- Pangastritis

3. Histological classification

A. *Acute gastritis* - Characterized by the presence of many neutrophils in the epithelium, lamina propria, or aggregated in the glandular lumena (cryptic abscesses)

B. *Chronic gastritis* is defined by the presence of immunocompetent lymphocytes and plasmocytes. It develops over several decades into atrophic gastritis. The degrees of activity depend on the presence of neutrophils and the

deep infiltration. Mild activity is characterized by the presence of neutrophils only in the lamina propria. In moderate activity neutrophils are extremely dense in the gastric foveolas. Severe activity is when neutrophils are present intraepithelially. Chronic gastritis is inactive when neutrophils are absent.

C. *Atrophic gastritis* represents the ultimate stage of chronic gastritis development and is characterized by the disappearance of the oxyntic glands and the distortion of the reticulin mesh. The inflammatory infiltrate invades the whole wall thickness. Histopathology must prove the presence or absence of intestinal metaplasia.

The most synthetic classification of gastrites is the Sydney system, which claims to be an all-embracing classification of gastrites. The system includes an endoscopic section with three subsections: topography, type of lesions and endoscopic category, and a histological section that includes, in its turn, etiology, topography and the forms of gastritis.

Though it does not include clinical data and risk factors inventory, the Sydney system allows to establish a complex diagnosis based on endoscopic, histological and etiological data.

The grading of histological injuries of gastritis according the Sydney classification refers to the following 6 histological features, each of them graded as mild, moderate or severe:

- acute inflammation – neutrophils
- chronic inflammation – lympho-plasmocytes
- activity – polymorphonuclear infiltration
- atrophy – loss of specialized glands
- intestinal metaplasia
- present or absent Helicobacter pylori

4. ***Etiological clasification***

A. Infectious:

- bacteria
- H. pylori (prevalent), Helicobacter Heilmanni, alpha-hemolytic streptococcus, staphylococcus etc.
- viruses: cytomegalovirus, herpes virus
- fungi: candida
- parasites: strongyloides, toxoplasma

B. Autoimmune - Atrophic gastritis with Biermer's anemia

C. Drug-induced: NSAIDs (non-steroidal antiinflammatory drugs)

D. Specific: Crohn's disease, eosinophillic gastritis, lymphocytic gastritis

H. PYLORI-POSITIVE CHRONIC GASTRITIS

It is type B gastritis, defined by the inflammation of gastric mucosa, mainly antral, induced by Helicobacter pylori (HP).

Antral gastritis is associated with HP in 70% to 95% of cases.

H. pylori is a spiral Gram negative bacteria, located in the stomach under the mucus layer.

Pathogenetic mechanism: Gastric injury is produced in relation to the bacterial characteristic features and the enzyme profile, the final effect being the host immune response (local and systemic) to the various bacterial proteic structures. The antibodies to the HP secreted proteins, with a protective role, seem to be involved in the pathogenesis of gastritis.

The **macroscopic** aspect is of diffuse or patchy congestion, mainly antral, with acute or chronic erosions. In 25% of the cases nodular gastritis occurs.

Microscopically a polymorphonuclear infiltration is seen, with injury to the gastric crypts, aggregates with lymphoid follicles and decrease of the mucus in the epithelial cells.

The clinical picture may include chronic active gastritis (rich in polymorphonuclear infiltration) and an inactive chronic gastritis (mononuclear cells dominate).

Clinical symptoms are unspecific and overimposed on non-ulcerous dyspepsia. Heartburn, nausea and vomiting are described. Symptoms disappear after the eradication therapy.

The diagnosis of B type gastritis is endoscopic, which shows antral alterations, histological on antral biopsy samples, and with evidence of the HP by various methods.

The **evolution** is toward atrophic chronic gastritis, which may shift to intestinal metaplasia, dysplasia and eventually gastric cancer or non-Hodgkin lymphoma.

The treatment consists on the eradication of the HP infection (see chapter on ulcer therapy).

5. GASTRIC AND DUODENAL ULCER

Definition

Gastric ulcer (GU) and duodenal ulcer (DU) are circumscribed, unique or multiple, disruptions in the integrity of the gastric or duodenal wall, accompanied by a fibrotic reaction starting from the mucosa and possibly penetrating down to the serosa.

Gastro-duodenal ulcer was until recently a disease with chronic, cyclic evolution, in which the peptic factor was incriminated. The concepts have changed drastically lately, transforming ulcer from a disease marked by acid secretion ("no acid, no ulcer") in a diseases caused by infectious agents (Helicobacter pylori). In literature it is also called peptic ulcer or ulcerous disease.

In 1938 Warren and Marshall drew for the first time the attention to germs discovered in the stomach and possibly involved in the pathogenesis og GU and DU. Because of the resemblance to campylobacter they were called Campylobacter pylori, and later became Helicobacter pylori (HP). Subsequent studies proved the involvement of HP in the pathogenesis of chronic gastritis, GU and DU, MALT gastric lymphoma and gastric cancer. In 2005 Warren and Marshall received the Nobel prize for the discovery of HP and its role in gastric pathology.

Epidemiology of peptic ulcer

The clinical prevalence (total number of cases, old and new) is 5-10% of the general population. The real prevalence, based on necrotic studies, is 20-30% in men and 10-20% in women. The current tendency is to decrease, especially due to the infection eradication.

Etiopathology of gastro-duodenal ulcer

It is known that about 10% of the adult population suffer or suffered from gastro-duodenal ulcer. The main cause is the Helicobacter pylori – the bacteria that infects over 2 billion people worldwide. The infection is acquired by fecal-oral route, or oral-oral, very early in poorly developed countries (at the age of 30 about 70% of people are HP infected), and later in the developed countries (only 15-20% infected at this age). The general rate of infection also depends on the living conditions (30-40% of the developed countries adults and over 80% of developing countries are positive).

The infection once acquired remains for the rest of life unless special eradication therapy is initiated.

The acute HP infection manifests as a self-limiting acute gastro-duodenitis. A chronic gastritis will persist however, involved in the genesis of ulcer. In case of antral gastritis (inflammation), it will lead to increased gastrin secretion and implicitly acid hypersecretion. In response to the acid excess which reaches the duodenum, gastric metaplasia occurs in the duodenum, a mandatory phase of duodenal ulcerogenesis. In case of gastric body gastritis, it will lower the mucosal resistance to aggressive factors, generating gastric ulcer. The prevalence of HP in duodenal ulcer is up to 70-80% (considering that the remaining 20-30% are generated by NSAIDs or, more rarely, a Zollinger-Ellison syndrome) and about 50-70% in gastric ulcer.

Pathophysiology of gastric and duodenal ulcer

Though the role of HP is paramount, it may not completely explain the many differences between the two ulcer types, such as HP-negative ulcers (20-30% of the DU and 30-50% of GU). Therefore the classical theory of the imbalance between aggressive factors (high) and defense factors (low) on the gastric and duodenal mucosa, all of them under the influence of environmental and genetic conditions, still holds.

In the following we shall analyze these three factors:

A. Aggressive factors

These factors have an increased role in the genesis of peptic ulcer. There are 3 important aggressive factors:

a) Helicobacter pylori infection

HP is a Gram-negative spiral and flagellated microbe. The most probable transmission mechanism is fecal-oral, the source of infection in developing countries being water. Its location in the stomach is at the interface between the apical membrane and the mucus layer, being well adapted to the gastric acid environment. Its pathogenic factors are the enzymes and cytotoxins it secretes:

- urease (splits the urea with ammonium elimination, which creates an alkaline pH),
- phospholipase and protease (digest mucus and the apical and duodenal mucosa),
- vacuolizing cytotoxin.

Ulcerogenesis induced by HP is by direct action on the gastroduodenal mucosa and indirectly by increase of the acid secretion. The direct mechanism is determined by the inflammatory process initiated by the HP toxins, which triggers an acute gastritis that subsequently becomes chronic.

HP does not grow on the duodenal mucosa, only on the gastric metaplastic areas in the duodenum; they develop in defense reaction of the duodenal mucosa to the increased acid secretion. The indirect HP mechanism is achieved by the

urease secretion and creation of an alkaline environment around the gastrin-secreting cells, thus the gastrin secretion and therefore acid secretion being stimulated.

b) Hydrochloric-peptic hypersecretion

Neither GU nor DU can develop without acid secretion, its role being more important in DU. The most important causes of HCl secretion are: increase of the parietal HCl-secreting cells count by genetic mechanism or hypergastrinemia, vagal hypertonia, hypersensitivity of parietal cells to vagal stimuli, gastric motility disturbances (higher in DU, with constant bombardment of the duodenum with acid), lower in GU, with gastric stasis).

Besides the HCl secretion increase, pepsin, a proteolytic enzyme, also is increased.

c) Bile acids: they are aggressive and ulcerogenic by a mechanism of cleansing of lipids in the mucosal cells.

B. Defense factors

They are decreased in ulcerous disease, especially in GU. They may be distributed, topographically, into three groups:

a) Pre-epithelial, represented by:

- surface mucus, with protection function of the gastric and duodenal mucosa, forming the "sturdy" layer of viscous mucus that opposes the retrodiffusion of H ions and lubricates the mucosa;
- dicarbon (HCO3-) ions secretion, which makes a neutral 7 pH gradient in the epithelium against the acid gastric lumen.

b) Epithelial, represented by the integrity of the apical membrane of the gastroduodenal mucosa, with great resistance, tight intercellular junctions and a high regeneration capacity.

c) Post-epithelial, of vascular nature, capillaries having a nutrition role, supplying bicarbonate ions and taking away H+ ions.

C. Environmental and individual factors

Ulcerogenic environmental factors are:

a) smoking: certain, intervening by decrease of the pancreatic alkaline secretion and annihilation of the acid secretion inhibition mechanisms

b) drugs such as: **aspirin and NSAIDS**, which act directly by penetrating the apical membrane, releasing H+ and indirectly by inhibiting cyclo-oxigenase and blocking the E2, F2 and I2 prostaglandins (PG) synthesis. High doses (over 1g hydrocortisone/day) **corticosteroids** by be ulcerogenic especially in oral administration, by affecting the mucus and PG synthesis.

c) other factors often incriminated, though without convincing statistical reports, are: stress, chronic alcohol consumption and various diets.

Individual factors are genetic; there are studies that clearly show familial aggregation (increased prevalence in twins or first degree relations); the existence of genetic markers (blood group 0 and especially the type not secreting blood group antigen in the saliva).

Diagnosis of gastric and duodenal ulcer

Clinical diagnosis

It is based on classical symptomatology of the time patterns. *The pain* characteristic related to meals (painful hunger in DU), pains occurring mainly in spring and autumn, are typical signs suggesting ulcer. In the last time ulcers are more frequently discovered by endoscopy in the absence of typical, revealing symptoms. Any painful epigastric dyspepsia should make us think of an ulcer. Other times the onset may be dramatic, by *upper digestive bleeding (hematemesis or melena), or ulcer perforation.* Pain is the cardinal symptom of ulcer, its description including several features: location, rhythm (occurs with various foods), time pattern (typically in spring and autumn and at certain times during the day), radiation, changes in the pain character.

Other symptoms of ulcer are *vomiting, appetite alterations, dyspeptic signs (burping, meteorism, early fulfillment).*

Paraclinical diagnosis is established by evidencing ulcer and HP infection.

Digestive endoscopy

The diagnosis of gastric and duodenal ulcer is endoscopic (gastro-duodenoscopy). Endoscopy has a high diagnostic sensitivity, assesses ulcer accurately by evidencing its activity and possible bleeding, arrested or current. It also allows biopsy, in GU, which assesses the benign or malignant nature of the injury. The assessment of healing is also done by endoscopy, which evidences scarring.

The endoscopic diagnosis of GU must establish the benign/malignant character by biopsy. The biopsy of GU is mandatory.

X-ray examination

It is a complementary diagnostic method, especially when stenosis and impaired gastric emptying are suspected (pyloric stenosis). This method is old and obsolete and was replaced by endoscopy for the diagnosis of peptic ulcers.

Currently gastric ulcer cannot be diagnosed solely by barium meal, without endoscopic and biopsy tests. There are also superficial ulcers which escape x-ray exam. Perhaps a double contrast barium passage (with air insufflation) might be helpful, but it cannot equal endoscopy.

Assessment of Helicobacter pylori status

- causing agent of most gastro-duodenal ulcers its evidence is mandatory in the ulcer assessment strategy, as it orients therapy. HP may be determined by direct or indirect methods:

Direct methods - ***require endoscopy*** and gastric biopsy, in which HP is evidenced by staining, urease test (change of pH indicator color in the presence of urease-producing HP), or culture (special media in microaerophillic environment).

Indirect methods - ***do not require endoscopy*** and are as follow:

- *determination of HP antibodies in the serum or whole blood* (micro-drop with lower sensitivity, or anti-HP antibodies in the saliva (easy test);

- *respiratory tests (using the non-radioactive carbon 13 isotope, or the radioactive carbon 14)*, which marks the urea; HP urease in the stomach will split the urea and the carbon dioxide will be exhaled and dosed)

- *determination of HP antigen in the feces* (fecal HP antigen)

The most sensitive indirect methods of HP diagnosis are the respiratory ones (gold standard, but relatively expensive) and fecal HP antigen (a little less expensive).

All these tests have a sensitivity over 90% and a good specificity, which allows to establish the HP etiology of ulcer and antibacterial therapy.

The serum test is enough for a first assessment, but checking eradication requires breath or fecal test.

Differential diagnosis

Based on clinical symptoms the differential diagnosis is with other upper digestive complaints, such as gastric neoplasm, lymphoma (endoscopy with biopsy), biliary lithiasis (ultrasound), chronic pancreatitis or ulcer-like dyspepsia. Endoscopic differentiation should be with an ulcerated neoplasm, which makes biopsy mandatory both at the time of diagnosis and follow-up.

Evolution

Unlike 20-30 years ago the evolution GDU is much improved. With the advent of very potent antisecretory drugs (H+/K+ ATPase pump inhibitors), the ulcer evolution is good, complications are reduced, while cases requiring surgery are rare. Moreover anti-HP therapy has reduced recurrence to a minimum.

Complications

Possible complications of ulcer are:

- upper digestive hemorrhage (hematemesis and/or melena) – the most frequent complication (~15%)
- ulcer perforation with acute abdomen. The penetration is covered by neighboring organs
- pyloric stenosis (relatively rare with modern therapies)
- ulcer malignancy shift (possible for GU, never DU). The risk of GU malignancy is low

Prognosis

It improved in the last decades, especially in the last two, when effective HP eradication therapy reduced recurrence rates under 10% per year, as compared to 70% before HP eradication. Mortality of ulcerous disease is high in patients over 75-80 years with upper GIH.

Treatment of ulcer disease

The last decade brough a number of changes in therapy

1. Diet, which was drastic before, became more permissive due to potent antisecretory agents. Only smoking is proved to delay endoscopic healing of the ulcerative lesion. Diet and coffee banning did not prove to speed healing. However, acid or spicy foods are to be avoided.

In patients with active ulcer aspirin, NSAIDS and corticosteroids are forbidden.

2. Drug therapy

It consists of:

A) Antisecretory agents - H2 receptor blockers: ranitidine 300 mg/day, nizadine (Axid) 300 mg/day or famotidine (Quamatel, Famodar) 40 mg/day. This was largely replaced by H+/K+ ATPase (IPP) pump inhibitors: omeprazol (Losec, Omeran, Omez, Antra, Ultop) 40 mg/day, pantoprazol (Controloc) 40 mg/day, lanzoprazol (Lanzol, Lanzap) 30 mg/day, rabeprazol (Pariet) 20mg/day,

esomeprazol (Nexium) 40mg/day. IPP therapy is effective, improving painful symptoms quickly, therefore it represents the choice therapy of active ulcers.

The duration of antisecretory therapy will be 6-8 weeks, which is the time necessary for an ulcer to heal

B) Gastric mucosa protectors

In GU gastric protective agents may be associated – sulfacrate 4 g/day X 4 times.

C) *HP infection eradication.*

If antisecretory therapy cures the pain (with frequent recurrences in the next interval), when HP is eradicated the risk of ulcer recurrence decreases dramatically (under 10%/year). Therefore the key of ulcer therapy seems to be HP eradication.

Drug regiments for the HP infection

The indications of HP eradication are included in the Maastricht European Consensus (1997), revised last time in 2016 (Maastricht V), which indicate the patient categories to be treated (definite or optional indication). Thus, current or past GDU represent a firm indication for anti-HP therapy.

Though sensitive to many antibiotics in vitro, clinical experience has documented the necessity of drug combinations. The regimens include proton pump inhibitors (esomeprazol, omeprazol, lanzoprazol, pantoprazol) associated with two antibiotics. Triple or quadruple regiments are both used (eradication rate 70-90%)

a) Triple therapy contains:

OAM = omeprazol (2x20 mg/day) + amoxicilin (2x1000mg/day) + metronidazole (3x500mg/day);

or

OAC = omeprazol + amoxiciline (2000mg/day) + clarythromycin (macrolide in a dose 2x500 mg/day).

b) Quadruple therapy is composed of omeprazol (2x20 mg)+ subcitric bismuth (De-Nol) (2x2 tb/day)+ tetracycline(3x500 mg/day) + metronidazole (3x500 mg/day).

c) ***Quinolone based therapy:*** consists of PPI (2x40 mg / day) + levofloxacin 2x500 mg + amoxicillin (2x1000 mg / day) for 10 days.

In practice, the sequence of these schemes is changing, given the emergence of studies showing changes in HP resistance to various antibiotics.

At present, it is recommended to start treatment with quadruple therapy for 14 days (or possibly with triple therapy based on levofloxacin).

Some authors only treat HP-positive ulcer for 7 days. The latest European and American guidelines suggest that the minimum duration should be 10 or even 14 days. It is preferable that this therapy is followed by proton pump inhibitors for one month.

The therapeutic regimens with metronidazole are effective depending the resistance to it in this area (in developing countries in which metronidazole was widely used resistance is high). In Romania, the OAC regimen is preferable, but currently we are seeing an increase in resistance, including to Clarithromycin.

According to the latest Maasticht consensus, in areas of resistance increased to Clarithromycin and Metronidazole, quadruple therapy, or regimen including Levofloxacin may be used as first line.

If rescue therapy is not successful either, you can switch to "sequential therapy", which is based on 10 days of PPI + 2 antibiotics, in two sequences of 5 days. It is estimated that up to 99% of patients treated with one or more regimens will be eradicated from HP.

Verification of the eradication of HP infection can be done by endoscopy with biopsy (in which the HP can be highlighted directly) or easier by indirect tests (ideal is the respiratory test or stool HP antigen). Verification of eradication of HP infection is done at least 30 days after the end of antibiotic therapy and free of PPI (fecal test or respiratory test), respectively.

Absolute indications of HP infection eradication according to Maastricht consensus are:

- acute or latent ulcer, including complicated ulcer
- MALT lymphoma with a low degree of malignancy
- atrophic chronic gastritis
- after gastric cancer resection
- first degree relatives of patients with gastric cancer
- at the patient's request (following the practitioner's recommendation)

3. Endoscopic therapy

Addresses the complications of ulcer:

- **Endoscopic hemostasis** of bleeding ulcers is the choice therapy of UGI. It may be performed by ***adrenalin injection 1/10,000*** followed by ***bipolar thermo-coagulation*** or ***hemoclips placement***. It is non-invasive, extremely efficient and free of complications, sparing the patient the surgical shock.

Hemostasis by adrenalin injection 1/10,000 arrests the bleeding by the vasoconstriction and mechanical compression. Hemostasis by hemoclips is the endoscopic placement of clips on the visible vessels and on the bleeding sites; the bleeding arrest is spectacular.

-Endoscopic dilation of pyloric stenosis is performed by balloons, thus avoiding traumatic surgery.

- **Mucosectomy** of the gastric ulcerations with dysplasia or even gastric cancer *in situ*: a method that is developing, devised by Japanese endoscopists, which makes possible the excision of premalignant and malignant lesions *in situ*. It avoids traumatic surgery, but it requires accurate staging by echoendoscopy.

4. Surgical therapy

The surgical option for ulcer has decreased markedly in the last years. The surgical indications are extremely selective and concern the forms of GU refractory to drug therapy for at least 2 months, penetrating forms, life threatening hemorrhage or ulcers with evidence of malignancy. DU has even less surgical indications: hemorrhage that cannot be arrested by endoscopy or pyloric stenosis impossible to dilate otherwise. Perforation and penetration are of course absolute indications.

6. FUNCTIONAL DYSPEPSIA

Definition

Functional dyspepsia represents a functional disease (no organic basis) characterized by symptoms in the upper abdomen, manifested as epigastric pain, feeling of fullness, bloating, general discomfort.

About 70-80% of the patients have symptoms in the upper abdomen, though the modern investigation methods cannot evidence organic injury (ulcer, neoplasm, biliary lithiasis, pancreatitis etc.). These patients are considered to suffer from functional dyspepsia. The other 20-30% have organic dyspepsia (evidence of organic injury).

Etiopathogenesis of functional dyspepsia

There is a number of aspects not elucidated as yet. Thus, in the patients with quasi-ulcerous symptoms the HP or hypersecretion maybe incriminated; in those with bloating, gastric emptying disturbances may be the cause, or even subjective perception (the patients feels s/he has too much gas in the bowels).

Classification of functional dyspepsia

It is based on the dominant symptom as follows:

- *ulcer-like dyspepsia* - in case of ulcer-like dyspepsia epigastric pain. heartburn and often hunger pain dominate, though endoscopy does not evidence ulcer.

- *dysmotility dyspepsia* - In dysmotility dyspepsia the patient complains of fullness, "epigastric weight, bloating, burping.

- *essential dyspepsia* - Essential dyspepsia is a mixture of symptoms combining the two above.

Another classification of functional dyspepsia is made in:

- *Postprandial distress syndrome (PDS),* in which the symptoms appear predominantly postprandial, as discomfort. The main mechanism of occurrence would be gastric dysmotility.
- *Epigastric pain syndrome,* with ulcer-type symptoms. The main mechanism of action would be visceral hypersensitivity.

Diagnosis

Clinical diagnosis consists of more or less noisy symptoms, but without body weight loss, bleeding or anemia (which indicate organic condition). The type of symptoms will point to the type of dyspepsia.

Paraclinical diagnosis consists of tests that will rule out organic injury. We start with an abdominal ultrasound (US) to evidence the absence of gallstones, normal pancreas and liver. Upper GI endoscopy will evidence normal esophagus stomach and duodenum. Colonoscopy will not evidence colic alterations. Old tests like barium enema do not allow to establish the diagnosis of functional dyspepsia, as there are many superficial ulcers not evidenced by barium.

Differential diagnosis is with all the upper abdominal diseases (reflux esophagitis, esophageal neoplasm, achalasia, GDU, gastric cancer, gastric lymphoma, acute or chronic pancreatitis, biliary lithiasis etc.)

We should also differentiate with other functional diseases in the lower abdomen, like irritable bowel (characterized by distension, transit disturbances, feeling of incomplete defecation, lower abdomen discomfort). Some authors include functional dyspepsia and irritable bowel in the same concept of "irritable digestive tract".

Evolution is favorable, with better or worse periods, usually related to feeding, stress etc. Prognosis is good.

Treatment of functional dyspepsia

It addresses the symptoms and is administered when they appear.

Ulcer-like dyspepsia is treated by antisecretory drugs of the H2 histamine blockers (ranitidine 300 mg/day, famotidine 20-40 mg/day), associated with PPI (omeprazole 20-40 mg/day).

It is under scrutiny whether HP should be eradicated when found by direct or indirect tests. In about half of the patients in which the triple regimen eradicates HP the symptoms subside, but some of them still persist.

Dysmotility-like dyspepsia (very frequently found in practice) is treated by prokinetic drugs. They may be from the old class, like metoclopramide (1 tb. 30 min. before meals). Domperidon is preferred as it does not cause drowsiness or extrapyramidal manifestations. Digestive ferments (Digestal, Mezym forte, Festal, Creon, etc.) or intestinal gas absorbants like dimeticon (Sab-simplex).

Essential functional dyspepsia therapy will address the dominating symptoms (pain, distension, fullness).

In all the forms of dyspepsia stress plays a role in triggering symptoms, which requires a mild sedative or even psychotherapy (the finding that there is no organic injury often has a great positive psychological effect on the patient).

7. GASTRIC CANCER

Gastric cancer (GC) is an important health issue in Romania, due to its still high frequency. Worldwide gastric neoplasm is one of the important mortality cause by cancer.

Epidemiology

Its frequency varies largely according to geographical area, being directly related to diet (very high frequency in Japan). In Europe it is more frequent in northern regions, also related to diet (preserved foods). It is 2-3 times more frequent in men than women, and increasing with age (average diagnosis age is 60 years). It is rare under the age of 45. Its frequency has started to drop in the last decade with the HP eradication.

Etiopathogenesis

The relationship with the HP infection has become more consolidated. WHO considers HP as a 1st degree oncogene. The HP eradication led to the decrease of gastric cancer incidence (more markedly in the developed countries).

Risk factors include:

- *nutrition habits*: high content of nitrozamines in foods preserved by salt and smoke; on the other hand, fruit and vegetables containing vitamins A and C protect the stomach
- *genetic factor*: disease may run in the family
- *low social economic level*, by food or HP infection
- *Helicobacter pylori infection*: it is more and more obvious that HP plays a role in the etiology of GC, as documented by WHO (rank I oncogene). HP induces chronic atrophic gastritis with intestinal metaplasia, potentially leading to dysplasia and neoplasia.

Predisposing gastric diseases include:

- *chronic atrophic gastritis*, especially intestinal metaplasia, often HP related; dysplastic injury may also occur, evolving from mild to severe dysplasia (considered a true intra-epithelial cancer)
- *gastric adenomatous polyps*: represent a premalignant state, mainly the large ones (over 1 cm, while those over 2 cm may shift to malignancy).

Endoscopic polypectomy is therefore indicated. Gastric hyperplastic polyps do not represent a premalignant state

- *previous gastric resection* (for ulcer) generally more than 15 years after operation. Usually an inflammatory stomitis and gastritic injury of the gastric stump are found. Hence the necessity of endoscopic follow-up of the resected stomach for more than 15 years after operation.

- *Menetrière's giant folds gastritis* entails 15% of malignancy shift, though it is rare

- *gastric ulcer* presents a low malignancy risk, it is often a question of endoscopic confusion, some neoplasms having epithelization periods (ulcerated cancer). Multiple biopsies should be collected at every endoscopy and also ulcer healing should be checked endoscopically (biopsy from the scar). To keep in mind the possibility of scarring of ulcerated cancers under drug treatment.

The clinical picture of gastric cancer

It may take several forms, depending on the stage. The most frequent symptoms are *epigastric pain*, *altered appetite* (even its loss or giving up eating meat), progressive *body weight loss, iron deficiency anemia*. Heartburn may mimic ulcer, pain occurring after meals, relieved by gastric pain killers. Weight loss may be very severe, down to neoplastic cachexia. More rarely *hemorrhage* is present (hematemesis or melena). In the advanced stages an *epigastric mass* may be palpable.

Often gastric cancer is discovered through an *anemic syndrome*, mild or moderate, with or without dyspeptic symptoms.

Paraneoplastic phenomena may also occur: migratory phlebitis, achantosis nigricans etc.

Early gastric cancer is usually asymptomatic or with mild dyspeptic signs. Its diagnosis is often incidental, on the occasion of an endoscopic examination for epigastric symptoms.

Morphopathological features of gastric cancer

Histologically, gastric cancer is an *adenocarcinoma*, with a variable degree of differentiation. The less differentiated, the more aggressive. There are early neoplasms with a histological aspect of **"signet ring"**, which are particularly aggressive.

Macroscopic aspect:

The neoplasm may have a *protruding budding aspect, an ulcerated and an infiltrative aspect*. The bleeding protruding budding form is typical of malignancy. The ulcerated one has irregular margins, infiltrated and hard, and

should be differentiated endoscopically from GU (multiple biopsies). The infiltrative type (plastic linitis) generates a diffuse wide infiltration of the gastric wall, making it rigid; should be differentiated from gastric lymphoma.

The parietal extension is usually early, with invasion of the neighbouring organs (pancreatic body, transversal colon). Lymph extension is also rapid, involving the gastric lymph drain then further on. Metastases are mainly to the liver and lungs. Carcinomatous peritonitis may also occur.

TNM staging (tumor, lymph node, metastasis) will allow to establish the prognosis and therapeutic management:

- tumor

T1 invasion of mucosa and submucosa
T2 invasion of the muscularis propria
T3 invasion of the serosa
T4 invasion of neighbouring organs

- **lymph nodes**

N0 absence of nodular invasion
N1 invasion of neighboring nodes (up to 3 cm from tumor)
N2 invasion of distance lymph nodes

- **metastases**

M0 absence of metastases
M1 metastases at a distance

Diagnosis of gastric cancer

Commonly it starts from a dyspeptic syndrome, epigastric pain, weight loss, unclear anemic syndrome. Family clustering or premalignant lesions may draw the attention.

Physical exam

Usually poor, though in advanced stages epigastric mass and/or subclavicular adenopathies may be palpated (Virchow's sign)

Paraclinical tests

- *biology* will show moderate or severe iron deficiency anemia. However, there are gastric cancers without anemia (plastic linitis).

- *gastroscopy* is the diagnostic method of choice. It visualizes the injury, its features (brittleness, bleeding) and multiple biopsies will provide the pathological diagnosis. Endoscopically the advanced gastric cancer may be: protruding, ulcerated or infiltrating (mixed types may occur)

Early gastric cancer (invading only the mucosa and submucosa) is classified by endoscopy (Japanese classification) as follows:

-type I - protruding
-type II- superficial: II a sup. elevated
II b sup. flat
II c sup. depressed
-type III- excavated.

The diagnosis of *early gastric cancer* is rare in Europe, where the disease is discovered incidentally. In Japan, where the disease is frequent and endoscopic screening is performed in the population over 40 years, the diagnosis is relatively frequent. The operative prognosis depends on the stage of the disease. In case of early gastric cancer 5 year survival is noted in 95% of cases.

- *gastric barium enema:* It is an obsolete method, used in advanced cancers or plastic linitis. X-ray cannot detect the early stages and does not allow biopsy sample collections. Endoscopy is always the preferred first method.

- *transabdominal US* may show liver metastases or perigastric lymph nodes. Sometimes a routine US may evidence a kidney-like (target lesion) epigastric mass that may suggest a gastric neoplasm (endoscopic check out is mandatory).

- *endoscopic ultrasound* makes possible tumor staging (T) by assessing gastric wall extension (layers) and loco-regional lymph nodes.

Prognosis

The prognosis depends on the TNM stage, histological type (poor or good differentiation), patient's age. Survival is good only for early stages (95% at 5 years). Radical surgery of gastric cancer is possible only in 1/3 of cases, with a 5-year survival rate of 25%.

Treatment

A. Surgical

The choice for radical treatment in gastric cancer is surgery. Gastrectomy with lymphadenectomy is performed. Usually gastrectomy is total or subtotal (eso-jejunostomy), depending on the tumor location and extension.

B. Endoscopic

Endoscopic mucosectomy may be performed in early cancers "in situ" (involving only the mucosa).

It consists of the injection of saline solution under the neoplastic lesion and its transformation into a sessile polyp which may be excised. The resected piece will be submitted to pathology tests to check procedure's radicality.

Cancers beyond operability may benefit from endoscopic argon Beamer hemostasis or application of endoscopic stents in stenosing neoplasms (palliative).

C. Chemotherapy

a) Pre- and postoperative

Recent studies have suggested that preoperative induction chemotherapy followed by radio-chemotherapy triggers an important histological response leading to increased survival rate.

The most used therapeutic regimens (approved by the National Comprehensive Cancer Network NCCN) for localized inoperable gastric cancers as chemo-radiotherapy option include 5-FU/leucovorin or one of the following regimens: based on 5-FU, cisplatin and irinotecan. The chemo-radiotherapy options include 5-FU/leucovorin sau 5-FU/cisplatin.

b) Palliative chemotherapy

Advanced gastric cancer cannot be cured, but chemotherapy may have a palliative effect in symptomatic patients. The chemotherapeutic regimen *combines chemotherapy based on cisplatin or 5-FU*. Several agents and their combinations proved to be efficient.

In general the **prognosis** of gastric cancer remains reserved. This is why protocols for early detection are sought for, along with endoscopic removal of precancerous lesions (gastric polyps), regular follow-up of after gastric resection (after 15 years).

A delicate issue is the HP infection, rank I carcinogen according to WHO. Eradication of HP in certain patients (Maastricht consensus) is envisaged, including descendants of GC patients or previous gastric resections. The high prevalence of HP in the population would lead to high costs that the health system could not afford. The development of an anti-HP vaccine in the future would probably solve many a problem related to gastric cancer.

8. INFLAMMATORY BOWEL DISEASE

Definition

The common feature of inflammatory bowel diseases is bowel inflammation; they are represented by **Crohn's disease** and **ulcerative colitis** (or ulcero-hemorrhagic colitis)

Epidemiology

These digestive diseases are relatively widespread in the developed countries of the northern hemisphere, with a marked north-south gradient (much more frequent in the Scandinavian countries than in the Iberic peninsula), but also a west-east one (due to development and civilization). Therefore in Romania, even though ulcerative colitis is encountered, its severe forms are rare. Regarding Crohn's disease, it is also quite rare, though in the last year, due to the western habits (nutrition mainly), its frequency is growing. The question arises whether these diseases did not exist or rather they were not diagnosed in our country. The first assumption seems true, because they have a long-term evolution leading to surgical complications if left untreated (especially Crohn's disease). Though the clinical picture of the two conditions may bear similarities, there are many differences, therefore we shall deal with them separately.

I. ULCERATIVE COLITIS

Definition

It is an inflammatory bowel disease, characterized by recurrent flares of diarrhea with mucus and blood alternating with silent periods. It is also called: hemorrhagic rectocolitis or ulcerative colitis.

Clinical picture

The clinical picture includes digestive and non-digestive manifestations.

Digestive manifestations include episodes of diarrhea containing blood, mucus and pus. Abdominal pain, tenesmus and abdominal cramps also occur. Palpation of the abdomen is painful in the hypogastrium and on the colic

trajectory. During the diarrheic bouts there are 3-10 stools/day (rarely more), while in the severe bouts blood, mucus and pus are also passed. Outside the acute bouts stool may be normal, or 2-3 stools per day, usually blood free.

Extra-digestive manifestations are: anemia secondary to blood loss, fever or subfebrile episodes, weight loss, asthenia. Sometimes arthritis, erythema nodosum, uveitis may occur (relatively rare). Other associated conditions occurring with UC may be: sclerosing cholangitis (to be considered in a patient with cholestatic syndrome), secondary amyloidosis, ankylosing spondylitis.

Pathophysiology

Several factors are incriminated in the pathophysiology of IBD, such as: environmental, immune and genetic factors

a) Environmental factors – intestinal microbiota

For a long time, pathogenic agents have been sought that could explain the disease onset. They were viral or bacterial agents (like mycobacterium). At present it is considered that the normal intestinal bacterial population itself may trigger the disease by the loss of the normal immune tolerance of intestinal mucosa. It is known that normally the bowel develops a tolerance to microbial antigens in the intestinal flora. Its loss will lead to the onset of the disease.

b) Immune factors: local immunity deficiency at the mucosal level.

The normal mucosal immune system has the remarkable capacity to recognize the immunogens which it tolerates and the ones it rejects. This is achieved by a fine balance between the pro-inflammatory and anti-inflammatory mechanisms. Intestinal epithelial cells have the capacity of producing cytokines by macrophages activation. The proinflammatory cytokines are TNF alpha (tumor necrotizing factor), IL1, IL6, IL8 (interleukines) etc. Lymphocytes also participate in the immune mechanism.

c) Genetic factors: it is certain nowadays that genetic background is involved in the pathogenesis of IBD. There is a familial clustering for IBD, 10-20% of the patients having a relative suffering from the same condition; it is more frequent in the white population, 3-4 times more frequent in the Jewish population.

To sum up etiopathogenesis, IBD occurs under the action of environmental factors (which act as triggers) on a genetic background. The nature of the environmental factors is not clear yet, but it seems that the normal intestinal flora may be incriminated, in conditions of the loss of mucosal immune tolerance to the normal bacterial population.

Paraclinical examinations

Laboratory tests

The paraclinical examinations contributing to the diagnosis of UC are: biological tests and investigations evidencing morphological changes. The changes occurring during flares are: iron-deficiency anemia, hypochromia and low sideremia, hypoalbuminemia by loss, inflammatory syndrome (increase of ESR, sometimes leukocytosis, and C reactive protein). Fecal test is useful only to exclude an infection, such as bacteria dysentery.

Endoscopic examination is mandatory, because the colonic aspect establishes diagnosis easily. *Typical for UC are ulcerations in the rectum (rectocolitis) and the continuous character of injuries*. With a simple **rectoscopy** the diagnosis may be suggested macroscopically and then confirmed by biopsy analysis. Endoscopy evidences the typical bout aspect of the mucosa that oozes blood. Mucosa is frail, with superficial ulcerations, diffuse erythema, having lost its typical vascular pattern, and covered by mucus and pus. In the chronic forms the aspect of inflammatory pseudopolyp may be seen. During *remission* the aspect is different, mucosa is less frail, bleeding may still occur when touched by the endoscope. The mucosa has a faded or absent vascular pattern, while pseudopolyps may be present.

To assess the ***extension*** of ulcerative colitis, total **colonoscopy** is required. When faced with a flare of UC explorations begins with diagnostic rectoscopy, followed by total colonoscopy when symptoms subside, in order to assess the disease extension.

Biopsy from the colonic mucosa is mandatory for the diagnosis, evidencing an inflammatory infiltrate with polymorphonuclear cells in the mucosa (not all the layers), crypt abscesses, ulcerations. It also allows the evaluation of injury severity.

X-ray examination as a classical diagnostic method, rarely used at present, will evidence changes mainly in the chronic forms, in which the colonic alterations are more marked. Irigography will evidence a granular aspect of the mucosa, pseudopolyps, loss of normal colic haustra and a tubular aspect of the colon in the chronic forms.

Transabdominal ultrasound may be useful for the assessment of the affected colic wall thickness and colonic extension, in the acute phase (when colonoscopy may cause perforations).

We will evaluate the colonic wall which is thickened over 5 mm (usually 7-10 mm) in the areas affected by the disease, thus we can assess the colonic extension. The transabdominal US examinations requires and experienced specialist.

The positive diagnosis is based on the presence of diarrhea with blood, mucus and pus, then on the endoscopic findings (rigid or flexible rectosigmoidoscopy or coloscopy), followed by bioptic sample pathology confirmation.

Clinical forms

- *Fulminant form*;

- *Intermittent chronic form* (acute episodes alternating with complete or almost complete remission)

- *Continuous chronic form* (rarer, but increasing in frequency)

- *An isolated flare*, with definitive healing after treatment, without recurrence.

Assessment of severity is based on the number of stools and the intensity of clinical signs (Truelove's classification). Thus, there are mild, moderate and severe forms:

- *the mild form* is with up to 4 stools/day, with just a little blood and mucus, general state is good, no fever of denutrition, very mild anemia;

- *moderate form*: 4-6 stools/day, anemia, slight fever;

- *severe form*: more than 6 stools a day, fever over 38 C, anemia and hypoalbuminemia, large amounts of blood in the stool, altered state.

According to the ***UC location*** there are several forms:

- *proctitis or proctosigmoiditis* (rectal or rectosigmoid location)

- *left colitis* (up to the splenic angle)

- *pancolitis* (the whole colon is affected)

Differential diagnosis can be performed with the following diseases:

- colonic cancer, especially left, associated with rectal bleeding. It is the first disease to consider in an elderly patient, endoscopy will establish the diagnosis.

- bacterial dysentery or other infections: Salmonela, Shigella, Campylobacter jejuni, Clostridium difficile (pseudomembranous colitis), which may resemble clinically and even endoscopically; fecal test will evidence the germ.

- ischemic colitis – endoscopic diagnosis (segmental diagnosis, usually on the descending colon) and biopsy.

- radiation colitis – history of abdominal radiotherapy

- collagenic colitis or lymphocytic colitis – chronic diarrhea, watery diarrhea (no blood passage), with normal endoscopic aspect (also called *microscopic colitis)*; biopsy will evidence the presence of a submucosal collagen strip or lymphocytic infiltrate.

- Crohn's disease, which is presented further on; it is characterized by discontinued injuries (continuous in UC), endoscopy evidences deep ulcerations, sometimes linear, histological lesions involve the entire wall (only the mucosa in UC), and are granulomatous lesions. Crohn's disease may affect any portion of the digestive tract, more often the terminal ileum and colon.

- Indeterminate colitis - an inflammatory bowel disease in which we can not specify from the beginning whether it is Crohn's disease or ulcerative colitis.

- In the latter years, an increasing problem is the ***acute colitis*** caused by ***Clostridium difficile (pseudomembranous colitis)***. It can occur either in patients with inflammatory bowel disease (in whom it aggravates prognosis), but also in other patients at risk (hospitalized patients with severe comorbidities). The main clinical sign is worsening or reappearance of diarrhea in connection with recent or current hospitalization. The favoring factors are: multiple, severe comorbidities, recent or current antibiotics and/or proton pump inhibitors treatment. Diagnosis is made based on the stool exam in which ***Clostridium difficile toxin*** is searched for. The first-line treatment in Metronidazole and if it fails, Vancomicine per os (orally) for 7-10 days. In patients with severe comorbidities ***Clostridium difficile*** infection can be lethal. In cases with relapse, there is an indication for a fecal transplant, which would reduce the risk of recurrence.

Evolution

The evolution is with acute episodes varying in length, usually weeks or months, followed by remissions.

There are several criteria for assessing the severity of the disease, in current practice the most commonly used being the Truelove and Witts score.

Truelove and Witts severity classification

	MILD FORM	**MODERATE FORM**	**SEVERE FORM**
Stools with blood/day	<4	>4 but <6	≥6
Heart rate	<90 bpm	≤90 bpm	>90 bpm
Temperature	<37.5˚C	≤37.8˚C	>37.8˚C
Hemoglobin	>11.5g%	≥10.5g%	<10.5g%
ESR	<20mm/h	≤30mm/h	>30mm/h
CRP	Normal	≤30mg/l	>30mg/l

Complications

Possible complications are:

- toxic megacolon – rare in our geographical area; it is extremely severe, with fever, stools without feces, leukocytosis, acute abdomen (perforation with peritonitis), severe dehydration;
- intestinal stenosis (rare);
- massive hemorrhage and severe anemia;
- colon cancer (high risk at an evolution longer than 10 years, especially of pancolic forms);
- severe extra-digestive manifestations.

Treatment

A. Diet: Diet during acute phases is of digestive sparing, avoidance of milk and dairy products, raw fruit and vegetables, concentrated sweets. In severe cases parenteral nutrition may be administered for a few days.

B. Drug therapy depends on the severity.

In severe cases we start parenteral nutrition, to rebalance fluid and electrolytes, corticotherapy, usually iv: 250–500 mg hydrocortisone hemisuccinate/day (then oral Prednisone, max. 1 mg/kg body weight/day, doses are lowered by about 5-10 mg/week; in septic-toxic forms antibiotics are added, mainly anaerobic (Metronidazole). Prednisone is administered in 40-60 mg/day (according to gender, body weight, intensity of symptoms), lowering doses weekly to reach a maintenance dose of 10 mg. Treatment is continued with Salazopyrin 4-6 g/day, or better with 5-aminoslycilic acid (Mesalazine) 3-4 g/day (Salofalk, Pentasa, Asacol) – this is the active ingredient of Salazopyrin, and adverse reactions (especially digestive) are minimized.

In severe forms, which after 3-5 days of treatment do not respond to previous measures, there are two therapeutic options: immunosuppressive or anti-TNF treatment, which can act quickly and save the patient from possible surgery. These are represented by cyclosporine iv. 2-4 mg / kg / day, respectively Infliximab (Remicade) at a dose of 5 mg kg / body at 0, 2 and 6 weeks.

The moderate UC forms (4-6 stools or more a day) benefit from Salazopyrin 4-6 g/day or 5-aminoslycilic acid (Mesalazine) 3-4 g/day (Salofalk, Pentasa, Asacol).

In the distal forms (rectosigmoid): local therapy with suppositories, foam or micro-enemas with 5-aminoslycilic acid (Salofalk suppositories 3x1/day or micro-enema), or topical corticoid (Budesonid).

Mild forms: Mesalazine (5-ASA) 2-3 g/day, or salazopyrin 3-4 g/day.

UC attack treatment will be followed by maintenance treatment (after reduction or disappearance of symptoms, with lower doses, on a period of up to 6 months, with the aim of preventing or delaying relapses).

In the chronic continuous forms treatment is indefinite.

The attack therapy with steroids in UC will be followed by a maintenance treatment with immunosuppressive agents – Azathioprine (Imuran 2-3 mg/kg body weight, i.e. 100-150 mg/day).

In cortico-resistant or in cortico-depended forms a new treatment with i.v (*Infliximab*) or subcutaneous (*Adalimumab*) anti-TNF agents can be administered.

Infliximab is given 5 mg/kg body weight at 0, 2 and 6 weeks, as an induction dose, followed by maintenance treatment, 5 mg/kg body weight at 8 weeks. Adalimumab is given with two doses of 160 mg induction at 0 and 2 weeks, then 40 mg or 80 mg at 2 weeks.

In addition to these two biological medications currently available in Romania, covered by CNAS, there are three new products approved by EMEA and FDA:

- *Golimumab* - monoclonal antibody, inhibitor of tumor necrosis factor alpha (TNFalpha).
- *Vedolizumab* - anti-integrin antibody, is administered iv, for induction 300 mg at 0, 2 and 6 weeks, then maintained at intervals of 8 weeks.
- *Tofaticinib* - an oral Janus kinase inhibitor, used for the treatment of induction and maintenance of remission in RUH.

In chronic intermittent forms the acute phase is treated by higher doses, lowered during remission: salazopyrine about 2-3 mg/day, or mesalazine 1.5-2 g/day.

Endoscopic follow-up may be performed along with the clinical one for monitoring therapy, establish dosage and duration.

Endoscopic biopsy samples may better assess the antiinflammatory effect of therapy and decide whether doses should be lowered.

Fecal calprotectin can be used to assess remission (decreasing levels if the treatment is efficient).

We must keep in mind that remission is clinical, endoscopic and histological. Along with clinical remission (reduced stools, no more bleeding and mucus, no rectal tenesmus), endoscopic remission should also be documented (mucosa restores to normal, maybe just with a little granulation or faded vascular pattern). Each endoscopy should collect biopsy samples to assess the arrest of the inflammatory process (biopsy is important for the management).

C. Surgical therapy is rare (very rare in our country): it for cases of toxic megacolon, perforation or bleeding uncontrollable otherwise. Total colectomy or procto-colectomy are performed.

The development of colorectal cancer may occur after 10 years of the disease, in case of pancolitis (the whole colon is affected), and with severe epithelial dysplasia. This is why the endoscopic follow-up of long-term UC is mandatory.

II. CROHN'S DISEASE

Definition

Crohn's disease (CD) is also a chronic inflammatory disease of the digestive tract, which needs to be detailed in order to understand it accurately. Thus, to contradict a classical concept of terminal ileitis, it should be said that CD involves the terminal ileum only in about 30% of cases, while in about 50% there is an ileo-colonic involvement, and sometimes only the colon is affected. In fact, any segment of the GI tract may be affected (including the esophagus, stomach, duodenum or appendix, though rarely).

Etiopathogenesis

It is not clearly known, and several theories exist regarding the cause of CD. Bacteria have been mentioned (mycobacterium, pseudomonas), viruses, food allergy, environmental factors, smoking and industrial agents; genetic factors (familial or ethnic) may also lead to the onset and persistence of CD. Thus, the genetic predisposition to CD is high, with increased risk, in the Jewish population. The role of immune factors (humoral and cellular), stress, in triggering bouts, is known.

Clinical picture

It may sometimes be vague or absent, or other times suggestive. What is important is to take the disease into consideration and look for its signs.

Typical clinical signs include:

a) digestive

- diarrhea (without blood)
- abdominal pain
- malabsorption
- perianal injury (perianal fistulae, often damaging, typical of the disease)

b) extra-digestive

- fever or subfebrility
- asthenia
- weight loss

- erythema nodosum
- uveitis etc.

The clinical context suggestive for this disease includes: chronic diarrhea (even if only 2-4 stools/day), states of fever, asthenia, perianal injury (damaging fistulae). Clinical examination may show an abdomen diffusely painful at palpation, sometimes a mass is palpated in the right iliac fossa. It should be mentioned that every time an abdominal mass is palpated, it should be investigated, as it may be a neoplasm.

Diagnosis

The diagnosis of CD is not always easy and it often comes as a surprise during an operation performed for a complication, such as digestive fistula.

The diagnostic means are not always easily available (total colonoscopy with ileoscopy), which explains the proportion of missed diagnoses.

The diagnosis is based first on ***endoscopy with biopsy***. This will reveal *aphtous lesions, deep linear ulcerations, cobblestone aspect of the mucosa given by the ulcerations dividing the inflamed mucosa*, with areas of inflammatory stenosis. These lesions may occur in the terminal ileum, colon, but also stomach or duodenum. Total *colonoscopy* will be performed, with assessment of the terminal ilem, and also *gastro-duodenoscopy* is needed.

Biopsy is mandatory, as it will evidence *the granulomatous type transparietal inflammation* (different from the UC aspect). The presence of deep ulcerations, fibrosis, fissures is a rule.

X-ray examination is less accurate, useful if endoscopy is not available. Irigography with ileal reflux may be used or enteroenema (administration of barium through the duodenal catheter) in order to evidence injuries in the terminal ileum, or even barium meal with follow-up at 1, 2, 3 and 4 hours. *The cobblestone aspect in the terminal ileum, stenotic areas and superjacent dilation*, fistulae will be revealed.

Capsule endoscopy represents the new diagnostic technique for the assessment of the small bowel. The capsule the size of a medicine capsule is swallowed by the patient and send images from the GI tract by a cordless system. The cost of a one-time use capsule is about 500 euros, but the images are of high quality. It is not indicated in case of suspected stenosis as it may be trapped. The endocapsule may evidence small injuries from small bowel areas that cannot be explored otherwise.

Transabdominal ultrasound will evidence the thickening of the intestinal wall in the inflammation area and thus assess its extension. Areas of stenosis and dilation may be seen, possible complications like perforation, fistulae. It requires an experienced examiner.

EnteroCT or enteroMRI represent modern techniques that show the jejuno-ileal injuries.

The biological picture during flares will show the inflammation with increased ESR, leukocyte count, fibrinogen, C reactive protein. Anemia and hypoalbuminemia may occur. A biological test for the suspicious cases is the ***fecal calprotectin***. If fecal calprotectin is positive there is a high probability for an inflammatory bowel disease and total colonoscopy with ileoscopy should be performed. Normal fecal calprotectin levels are up to 50 mg%.

Staging of Crohn's disease

It is performed according to a number of parameters, which form the Best or CDAI - Crohn Disease Activity Index. These parameters are: no. of stools/day, abdominal pain, general state, extradigestive symptoms (fever, arthitis), use of antidiarrheic drugs, palpation of abdominal mass, anemia and weight loss. Based on the CDAI the severity of a flare may be assessed. CDAI values higher than 400 are suggestive for a severe attack, while CDAI lower than 150 is indicative for remission.

The Montreal classification of CD
A L B (Age Location, Behavior)
A (Age at diagnosis):
- A1< 16 years
- A2 17-40 years
- A3 > 40 years

L (Location)
- L1 terminal ileum
- L2 colon
- L3 both ileum and colon
- L4 the upper GI tract

B (Behavior)
- B1 non-stenosing, non-penetrating
- B2 stenosing
- B3 penetrating, fistulating
- P – perianal manifestations

Differential diagnosis should be performed with:
- UC
- ischemic colitis, radiation colitis
- celiac disease, microscopic colitis
- acute appendicitis

Evolution

The evolution is characterized by recurrence. As a rule, more than 50% of the cases have a relapse after initial resection. Some studies have reported a frequency of recurrence inversely related with the time between diagnosis and first resection.

Complications are a rule for CD:

- stenosis
- internal fistulae (entero-enteral, entero-colonic, entero-vezical, entero-vaginal) and/or external fistulae (entero-cutaneous)
- perforation
- abscesses
- sepsis (rare).

Treatment

In the ***acute phase*** (induction) *prednisone* (or prednisolone) is administered (possible i.v Cortisone hemisuccinate) approximately 50-60 mg/day, for 3-4 weeks, after which the dose is tapered by 10 mg/week, to reach about 10-15 mg/day after 6-10 weeks. We continue with 10 mg/day for 6 months if we see clinical remission. The attack treatment with Prednisone is consolidated by *Azathioprine* (Imuran) 2-3 mg/kg/day for a long period. In colonic location it may be associated with mesalazine 1.5-2 g/day. *Metronidazole* 500-1000 mg/day can be useful especially for colonic location with ano-rectal fistulae, but for no more than one month.

Chronic treatment (maintain remission) of CD is with Imuran (*azatioprine*) 2-3 mg/kg/day) for a long time. Imuran is initiated at the same time with corticotherapy, as azatioprine starts taking effect after 6-8 weeks.

The introduction of a new corticoid with local action (*Budesonid*) and minimal systemic effect has brought an improvement in therapy. It is given mainly in ileal or ileo-colonic forms. The attack dose is 9 mg /day, maintenance 3 mg/day (3 mg tablets, Budenofalk or Entocort), the attack dose being used only for 2 months at most.

Practically during the acute phase we start with an oral corticoid (Prednisone or Budesonide), while maintenance is performed with Imuran (100-150 mg/day) for 1-2 years.

In the severe forms of CD, with fistulae, antiTNF medication is indicated with *Remicade* (*infliximab*). It is administered in perfusion at 2 weeks (3 times), with spectacular results in some cases. Maintenance therapy with i.v. perfusions of Remicade every 2 months is recommended for a long period. *Adalimumab*, another antiTNF drug, is a therapeutic alternative that has the advantage that it is

administered subcutaneously. It can be given to patients who no longer respond to Remicade. Other anti-TNF agents became available in the last years, as well as other therapeutic classes (anti-integrin agents). These are represented by *Vedolizumab* - anti-integrin antibody, which is administered iv, and *Uztekinumab* - monoclonal antibody directed against interleukins 12 and 23.

Diarrhea is controlled by imodium or codeine.

Surgical therapy addresses mainly complications, such as segmental stenosis, perforations or forms that do not respond to drug therapy. The operations are segment resections with anastomosis, or, more rarely, colectomy with ileorectal anastomosis or panproctocolectomy with ileostomy (severe and invalidating recurrent forms).

Sometimes endoscopic methods for stenoses are applied (balloon dilation).

After segmental resections the long-term therapy with mesalazine or imuran may prevent recurrence or cure acute bouts.

At present there are two therapeutic strategies:

- **step-up** – consists of initiating corticotherapy, and in case of failure anti-TNF (infliximab or adalimumab) is used. Infliximab is given in i.v. perfusion, while adalimumab subcutaneously. We start with attack doses and continue with maintenance doses

- **step-down** – consists of a start with antiTNF, maintenance with Imuran.

On the other hand, improtant clinical studies have shown that the association anti-TNF and Imuran is superior to monotherapy. The advantage of anti-TNF is represented by mucosal healing, which is a new therapeutic standard in Crohn's disease, but anti-TNF therapy is extremely expensive, thousands of euros per year.

Before initiating anti-TNF therapy, previous exposure to tuberculous bacillus should be checked, as there is a risk of reactivation of this condition.

In approximately 5-10% of cases, differential diagnosis between UC and CD is difficult ***("indeterminate colitis")***, since clinical and endoscopic features of both entities are present.

9. COLORECTAL CANCER

Colorectal cancer (CC) represents a public health issue, given that in many European countries it is at the top of neoplastic diseases.

Even if lung neoplasms predominate in men and the gynecological one in women, in the two genders together colorectal cancer is the first cause of malignancy.

Epidemiology

In France colorectal cancer is on the first place (15% of all cancers), in Romania it is the first of digestive cancers. Its frequency varies according to the geographical area, being very frequent in Europe and the USA, less in South America and Africa. The differences are mainly due to eating habits and also partially due to genetic factors.

The incidence of CC is about 30-40/100,000 population in western Europe, in Romania ~ 10/100,000 population (reporting may be flawed).

Regarding the gender ration: B/F = ~1.5-2/1.

The special problem of CC is that it may be somehow prevented, as the adenoma-carcinoma filiation has been documented, therefore an active endoscopic detection of polyps will prevent it. The role of the genetic factor is also known (Lynch syndrome).

Etiopathogenesis

Several factors are involved in the appearance of CC: nutrition, the involvement of bile acids (under controversy), the role predisposing conditions.

a) Nutrition is involved in the etiopathogenesis of CC (based on epidemiological studies), protective factors being considered: greengrocery, diet rich in fibers, calcium, vitamins. Negative factors: animal fats and proteins, red meat, alcohol, excess calories.

b) The role of bile acids: Experimental studies indicate their implication. Certain epidemiological-clinical studies have showed a relation between cholecystectomy and increased CC frequency (especially the right colon). These studies await confirmation.

c) Predisposing conditions for colorectal cancer are:

- colorectal polyps
- familial adenomatous polyposis

- inflammatory bowel diseases (long-term ulcerative colitis, Crohn's disease)
- family history
- Lynch syndrome

Colorectal polyps represent a frequent condition in gastroenterological practice, about 10% of people over 50 years and up to 30% of those over 70 having colonic polyps. They may be adenomatous (adenomas) or hyperplastic.

Adenomatous polyps (true polyps) are of several histological types: tubular, tubular-villous and villous. The highest malignancy potential is held by the villous polyps, the lowest by the tubular ones. Hyperplastic polyps (inflammatory) do not have a malignancy potential. The shift of polyps to malignancy seems to depend on genetic factors (family), metabolic (co-carcinogenic effect of bile acids) and nutrition (negative effect of the lack of greeneries and fibers). Polyps entail a malignancy risk proportional with their size (especially over 2 cm diameter), number, and dysplasia. Starting from these premises, colonoscopy is necessary to discover polyps and endoscopic polypectomy will remove them, thus ensuring a good CC prophylaxis.

Familial adenomatous polyposis is a genetic condition, characterized by the presence of more than 100 polyps in the rectum and colon, occurring before the age of 30 years. The genetic transmission is autosomal dominant, while the evolution to cancer is the rule. This require active investigation of the familial transmission and early total colectomy, before malignancy occurs.

Inflammatory bowel diseases with long term evolution, have an increased risk of CC, which is about 10% after 25 years of UC (risk becomes important after 10 years). The risk is lower with long-term Crohn's disease.

Family predisposition – there is a high risk for the descendants of a family with CC (increased 2-3 times for first degree relatives)

Lynch syndrome or hereditary non-polypid colon cancer (without a polyp phase and important hereditary component) is characterized by the presence in several family members, onset at a young age, association with other neoplasias (ovary or endometrium). The Amsterdam criteria for the Lynch syndrome diagnosis are: at least 3 family members with diagnosis (pathology) of CC, of which one is a first degree relative, from one generation transmission is to the two next successive generations, at least one is diagnosed before the age of 50.

The elements suggesting a Lynch syndrome are the discovery of a CC at a young age and familial clustering. In this syndrome the neoplasm is often located to the right colon and may be synchronous or metachronous.

Morphopathology

More than half of rectocolonic cancers are located in the rectosigmoid. 20% are located in the ascending colon.

Histologically CC are *adenocarcinomas*, that may be macroscopically *vegetating, ulcero-vegetating or stenosing*.

The staging of CC is performed either using the *TNM classification* (tumor-lymph node-metastasis), or the *Duke's classification*:

- stage A – tumor located in the mucosa
- stage B1 – tumor invades the muscularis propria
- stage B2 – tumor in the whole colic wall (no nodes affected)
- stage C – tumor invades local and regional ganglia
- stage D – metastases at a distance

Postoperative survival rates depend on the Dukes stage at diagnosis, being 90% at 5 years for stage A and about 50% for stage C.

Clinical picture

The clinical picture of CC is relatively suggestive in its advanced forms. Typical signs include: rectal bleeding, transit disturbances, subocclusive syndrome, anemia.

Rectorrhagia is an important sign occurring especially in neoplasms with left location (rare in ceco-ascending neoplasma). According to the CC location, blood may be red, crimson, mixed with feces, envelop feces; it may be just stool emission or stool with mucus. Very important in practice is the patient's and physician's attitude. Thus, rectorrhagia in an adult or elderly patient will always include the suspicion of malignancy and only after excluding serious causes will hemorrhoids or anal fissure be considered. Adopting this strategy there are better chances in diagnosing a neoplasm in due time and not delay diagnosis.

*Transit disturbances m*ay suggest a colon neoplasm. Refractory exacerbated constipation may suggest left colon neoplasm, while diarrhea may be associated with right colon injury. Not all transit disturbances suggest CC, but together with other signs, especially in elderly patients, they may ring a bell.

Subocclusive syndrome, with intermittent or incomplete arrest of the fecal-gaseous transit, may raise the suspicion of CC.

Anemic syndrome may be a sign of colon cancer. Anemia is due to iron deficiency (hypochromic, microcytic) and is mild to moderate. It may not be preceded by rectal bleeding, as occult bleeding (microscopic amounts) is frequent. Faced with an anemic syndrome without apparent blood loss, the physician should consider microscopic amounts lost through the colon, therefore neoplasm.

CC is often asymptomatic, mainly in its early stages. There is no satisfaction for a physician discovering an abdominal tumoral mass (advanced

neoplasm) or a metastatic liver tumor, as at this stage the patient is beyond treatment. Unfortunately many cases of CC are diagnosed on the occasion of a surgical operation performed for bowel obstruction.

Diagnosis

The diagnosis of colorectal neoplasm may be established by the following methods: rigid rectoscopy (rectal neoplasm), flexible rectosigmoidoscopy (rectosigmoid neoplasm), colonoscopy, CT – colonography (virtual colonoscopy), irigography with double contrast, Fecal occult blood test (FOBT), as a screening test (or fecal immune blood test for occult bleeding in the stool – FIT).

*Rigid rectoscopy r*equires a rigid metallic rectoscope and visualizes about 10-25 cm of the rectosigmoid. The device is not expensive, the technique is easy to perform and establishes the rectal cancer diagnosis. Associated with anal digital examination and anuscopy (for the diagnosis of the anal canal and rectal ampulla), it may assess accurately the end segment of the GI tract.

Flexible rectosigmoidoscopy uses the flexible sigmoidoscope. It assesses accurately the left colon (up to the splenic angle), the site of 70-80% of CC. The technique is relatively easy, the patient's preparation requires only enemas (2 enemas with Enemax), while the patient's discomfort is mild (performed in outpatient conditions).

Colonoscopy is the ideal examination method, as it may visualize any injuries in the colon and collects biopsy samples. It also includes therapeutic techniques, such as endoscopic polypectomy (secondary prophylaxis of CC). Colonoscopy is a laborious procedure, relatively expensive and relatively painful. It requires special preparation (purgation with 4 liter or Fortrans or 2 liters of Moviprep on the previous day). It is the only method that can show vascular injuries in the colon (colonic angiodysplasia), unexplained anemia, and also perform endoscopic hemostasis. It is the gold standard technique for the diagnosis of colonic pathology.

Irigography visualize the colon by retrograde opacification with barium. The double contrast technique (using air insufflations) is useful. It does not allow biopsy samples collection or therapeutic methods (polypectomy). It used to be the most widely used method for colon assessment, but it is inferior to colonoscopy, which is currently replacing it.

Lately, the use of *CT* (virtual colonoscopy or CT colonography) allows the virtual reconstruction of the colon starting from an abdominal CT, which then may diagnose neoplastic lesions or polyps. The technique is under development; its main drawback is that it does not allow collection of biopsies or polypectomy.

Endoscopic ultrasound (transrectal ultrasonography) assesses the extension of the neoplasm in the mucosal layers and is used for rectal neoplasms.

Fecal occult blood tests (Hemocult tests) are used for detecting occult bleeding in the stools. It is a population based screening targeting asymptomatic individuals and meant to discover suspicious cases to be further submitted to endoscopy. The Hemocult test should be taken every year, generally after the age of 50. Hemocult II, more modern, does not require special preparation (meat free diet) and has a better sensitivity, while the Fecal Immunochemical Test (FIT) shows only human hemoglobin in the stool (does not require prior special preparation).

Genetic tests on the stool, which show altered DNA, are modern screening test, much more expensive, but which did not enter yet in the current clinical practice.

Differential diagnosis of colon cancer

The problems of differential diagnosis are related to the differentiation of rectal bleeding causes:

- hemorrhoidal disease and anal fissure
- Crohn's disease
- ulcerative colitis
- colon diverticulosis, complicated with diverticular bleeding
- ischemic and radiation colitis (after radiotherapy)
- colonic angiodysplasia (bleeding from the right colon, in the elderly, by vascular injuries)

In the case of anemic syndrome, we should look if the anemia is iron deficiency anemia, and in this situation (even if rectal bleeding was not present), the most likely cause is in the digestive tract (esogastric, intestine or colon).

Evolution

The evolution of CC depends on the stage at diagnosis. In Dukes A survival rate at 5 years is about 90%, while in Dukes C it is about 50%. In case of a neoplasm with liver metastases (Dukes D), survival rate is very low.

Complications: the most common are metastases, bowel obstruction, perforation.

Treatment

The preferred treatment of colon cancer is *surgery*. The operation will be performed as early as possible, the type of surgery depending on location.

Preoperative assessment will include the evaluation of the extension to the lymph nodes, lung, liver or peritoneal metastases.

Chemotherapy after surgery is indicated in patients with Dukes B2 and C stages. Regiments that include fluorouracil associated with folinic acid or more powerful regiments will be applied. Taking into account the post-chemotherapy survival rates, it is recommended to refer the patient to the oncologist after the operation.

Anti-angiogenic therapy: Bevacizumab (Avastin) inhibits the vascular endothelium growth factor (VEGF). Clinical studies have shown that its association with chemotherapeutic regimens improves survival rates in patients with metastatic CC.

Radiotherapy is mainly indicated for rectal and anal cancers, which, due to the location in the small pelvis, cannot always be resected correctly.

Prevention of colorectal cancer is a medical necessity at present, given its first place among neoplasms in the world.

- *Primary prophylaxy* is represented by education regarding diet, which should include vegetables, fibers (whole bread, cereal), calcium, and should exclude fats and excessive proteins (mainly red meat)
- *Secondary prophylaxy* consists in removing the causes leading to CC, especially finding the polyps and resecting them endoscopically. The detection of polyps in the general population is difficult because of the high number of endoscopic examinations to be performed. Therefore a Hemocult test is recommended every one or two years after the age of 50, followed by colonoscopy in patients that tested positive. Another strategy is to perform screening colonoscopy every 5-10 years after the age of 50.

Colonoscopy should also be performed in high risk individuals: inflammatory bowel diseases, descendants of patients with CC, history of colonic polyps. Molecular genetic screening will represent in the future the ideal method of secondary prevention, by the detection of predisposing genetic factors for colonic neoplasm.

Screening for colon cancer is an expensive method of diagnosing early stages or colonic polyps, but it is mandatory if mortality by this disease is to be lowered.

Screening for CC should be performed according to the financial potential and the access of the gastroenterologist (endoscopist) in every country. The least costly method is the fecal occult blood testing (Hemocult or FIT) performed annually, followed by colonoscopy in those testing positive. The strategy based on colonoscopy at 5-10 years between the ages of 50 and 75 seems to be a better one, but it is expensive as it addresses the whole population of this age.

After the surgical resection of CC, the CEA (carcinoembryonic antigen) dosage may be performed to show possible local recurrence. One year following resection and after that, periodically, a colonoscopy should be performed to find a possible relapse or a new tumor. Ultrasound follow-up (at 3 months) and also CT (6-12 months) in the first 3-5 years to check liver metastases is also necessary.

10. IRRITABLE BOWEL SYNDROME

Definition

The irritable bowel syndrome (IBS) represents a ***functional pathology*** widespread in the population. A large part of the outpatients consulted in gastroenterology present an irritable bowel picture.

Irritable bowel represents *a functional disease, characterized by transit disturbances, which generally consist of constipation alternating with diarrhea, diffuse abdominal pain (generally as cramps), sometimes emission of mucus*. Rectorrhagia, anemia, or weight loss ***are not part of this picture***.

The irritable bowel has many synonyms, such as irritable intestine, nervous diarrhea, but the probably most suggestive name would be the "unhappy colon".

Patients with an irritable bowel generally consult many doctors, from the family doctor to the Internist, gastroenterologist and even the surgeon, on the one hand because of "oncofobia" (fear of cancer), but also because of the long-term evolution of the disease. Usually, they are patients preoccupied with the disease, anxious, depressed or often working under conditions of prolonged stress. Anxious-depressive neurosis is common among these patients, so that they will present a very thorough, detailed history of the disease to their medic, often with dramatic accents. The background of the disease can be constipation (related to the lack of fiber in the diet and sedentary lifestyle), with emergence of stools with a lot of mucus or diarrheal stool, which most often occur in emotional conditions, stress.

The irritable bowel is a *functional disease*, therefore organic lesions, detectable by laboratory techniques, are absent.

The clinical picture of the irritable bowel includes:

- *abdominal pain*, either diffuse, either located on the colon paths. They can be deaf, but they can often have a colicky character (cramps), seconds or minutes long. Other times the patient only feels an abdominal discomfort. Most of the time, the symptoms disappear in periods of relaxing, holidays etc.

- *transit disorders* are frequent, the alternation of constipation with diarrhea being characteristic. Stool is often hard, fragmented, covered with mucus. False diarrhea can often occur, when these hard stools are followed by a liquid stool of irritated colon. Diarrheal stools appear occasionally, most frequently as imperious morning stools, postprandial stools or when the patient is anxious (before exams).

- *emission of mucus* is frequent, accompanying the elimination of stool (especially the hard one). Blood does not appear in the clinical picture of the irritable colon, but hard, rough stools can cause anal fissures that can bleed.

- *bloating* is frequent in patients with IBS colon, being diffusely located, or the patient feeling it especially in specific areas of the abdomen. Gas emission can transitorily ease the patient's suffering.

Diagnosis

The irritable bowel syndrome diagnosis is made by excluding the colon's organic diseases, so it is based on laboratory explorations.

There are certain criteria suggesting IBS, named after the man who had described them - the **Manning criteria:**

-abdominal pain relieved by passage of stool

-more frequent and looser stools with the onset of pain

-bloating, abdominal distention

-sensation of incomplete evacuation of the rectum

-mucus elimination with stool

-imperious character of the stool.

The Manning criteria had been reviewed and slightly modified in Rome (modifications related to the passage of stool), becoming **Rome criteria**, which have been revised several times, the current version being Rome IV, which include in the definition of irritable bowel syndrome - abdominal pain/recurrent abdominal discomfort at least 3 days/month in the last 3 months associated with 2 or several of: improvement after defecation; onset associated with the stool frequency change; onset associated with changing of stools' shape.

Paraclinical diagnosis

The laboratory diagnosis of the irritable bowel consists of *the exclusion of abdominal organic diseases* and follows these investigations:

-anoscopy, rectoscopy, colonoscopy (possibly irigography) to highlight the absence of organic pathology of the colon;

-gastroscopy, to highlight possible gastric diseases;

-abdominal and pelvic ultrasound, to highlight the diseases of the gallbladder, pancreas or genitals;

-radiological evaluation of the bowel (enema or barium passage tracking), capsule endoscopy or enteroscopy for enteric organic pathology.

The IBS diagnosis is established by excluding the organic lesions in these examinations and by the clinical classification criteria of irritable bowel (Manning and Rome criteria).

Differential diagnosis

The differential diagnosis of the irritable bowel is made with:

- anorectal neoplasm and neoplasm colon;
- colonic inflammatory diseases (RUH, Crohn's disease);
- colonic diverticulosis and diverticulitis;
- lactase deficiency;
- functional dyspepsia.

Colonic diverticulosis is frequent in general population, its prevalence increasing with age, so that it is present in more than 50% of the elderly. Usually it is asymptomatic, but complications such as acute diverticulitis or bleeding can occur.

Acute diverticulitis is an acute inflammation of a diverticulum. The clinical signs include local pain, fever, associated with leukocytosis (similar to acute appendicitis, but localized on the left). In a suggestive clinical context, diagnosis is confirmed by abdominal ultrasound (performed by experienced operators) or by contrast enhanced CT. The treatment is usually conservative (fasting + antibiotics), only complicated cases are referred to surgery.

Evolution

The evolution of the irritable bowel syndrome is favorable because there are no complications. Generally, the disease progresses over a long time, with remission periods and exacerbations, usually related to stress. There are some situations where the irritable bowel syndrome is associated with diverticulosis of the colon (given that diverticulosis is a frequent disease especially in older people).

Treatment of IBS

The treatment of this disease is generally difficult, and results are sometimes late. Because this is a functional pathology where the mental component is pretty important, the role of the mental balance is important itself.

1. *Dietary.* Diet, in cases where constipation is predominant, will be rich in dietary fibers. If diet is not enough, constipation will be controlled with laxatives of Forlax type (they raise the volume of the stool). The patient will be indicated to follow a diet s/he tolerates, avoiding products which produce symptoms. In patients with a predominance of diarrhea, the diet will need to be low in dietary fiber.
2. *Medication.* Therapy will consist of:

- *anti-diarrheic agents* (in cases of diarrhea), like Smecta (smectita) or Imodium (loperamid).

- *antispastic:* Pain is controlled with antispasm medication: Spasmosmen (calcium channel blocker), Debridat, Duspatalin, Colospasmin, No-Spa, Meteospasmyl, Ibutin. The medication is administrated if necessary, trying to find the most efficient for the patient (medication is changed until the medication with the maximal effect is found).

-*sedatives*: Sedative medication is often useful, just as psychotherapy. Ruling out the diagnosis of colon neoplasm (imagined by the patient) can often lead to the improvement of symptoms. In case of irritable bowel syndrome, diet and therapy are usually individualized, and the role of the patient's trust in his physician is important.

11. CELIAC DISEASE

Definition

The celiac disease or gluten enteropathy is a chronic intestinal disease characterized by diarrhea, steatorrhea and malabsorption, generated by gluten intolerance (consumption of farinaceous products with gluten content). The morphological element is represented by the atrophy of the jejunum mucosa, and a gluten free diet leads to the clinical and histological improvement of the disease.

Epidemiology

The disease is widespread in places with temperate climate and has a chronic evolution, with onset or exacerbation after the consumption of farinaceous wheat products.

The prevalence of the disease is between 10 and 30 cases in 100.000 inhabitants. The disease was amply described in the Netherlands after the Second World War, because lack of wheat during wartime led to the decrease of the frequency of the disease, and the introduction of wheat after the war favored the recurrence of the symptoms.

In the last 15–20 years, with the typical forms of the disease, which show diarrhea, steatorrhea and malabsorption, latent forms of gluten intolerance have emerged, which do not necessarily lead to villous atrophy, but only to an interstitial or preatrophic jejunum.

The disease is genetically induced, having a familial character; it is 10 times more frequent in the patient's first grade relatives and 30 times more frequent in twins.

Etiopathogenesis

In gluten enteropathy there is an oligopeptidase genetic deficiency in the enterocytes, leading to their sensitization to the alpha-gliadin (third fraction of the gluten). The gliadin, a fraction of the gluten, may be especially found in wheat and rye and less in barley and oats. The immunogenicity of the gluten from different geographical areas varies and this could explain the different spreading of the disease. These immune complexes attach to the intestinal mucosa, they stimulate the aggregation of the K (Killer) lymphocytes, leading to the injury of the mucosa with the loss of villi and proliferation of the cryptic cells.

The interruption of alimentation with gluten favors the restoring of the villous epithelium, improvement of transit disorders and malabsorption, if the diagnosis is made in the first 3–6 years from the clinical onset of the disease. In the advanced forms of the disease, regeneration phenomena of the intestinal mucosa are extremely slow or absent.

Pathology

Macroscopically, the pathological intestinal mucosa is pearly-white, without injured terrain. Lesions are visible at the jejunum and less visible at the level of the ileum.

Microscopically, the lack of normal villi is viewed, these being flat, and in more advanced forms, total villous atrophy occurs.

Clinical picture

Celiac disease can be symptomatic and asymptomatic, and may occur at any age, often even without diarrhea or steatorrhea. In less typical forms, the signs which make us think about the disease are: small stature, infertility, unexplained anemia, recurrent aphthous stomatitis or dermatitis herpetiformis.
In case of celiac disease with *infantile onset*, the child is normal until the introduction of farinaceous products in the diet. Then they start to have soft stools with unpleasant smell and intestinal cramps. Anemia, hypoproteinemia and edema occur.

In *adult onset* diarrhea, steatorrhea and further malabsorption syndrome are progressively reported. Usually the patient present years of diarrheal stool (3–6 stools/day), associated with abdominal discomfort, gurgling. The debut of the diarrheal syndrome is often insidious, it often appears during childhood, other times between ages 20 and 30. Most often, diarrhea occurs 1–2 hours after a meal with wheat pasta (bread, spaghetti, noodles), but in the course of the disease numerous other food intolerances emerge, which make the diagnosis hard. Important clinical elements can be the correlating symptoms with consumption of wheat and their improvement with the 2–3 weeks interruption of it.

Not to forget the asymptomatic forms of celiac disease only manifested by iron deficiency anemia, small stature, hypocalcelmia, dermatological diseases (herpetic dermatitis) etc.

Diagnosis

Diagnosis is made through 2 methods: serology and biopsy.

Serological diagnosis

Determination of anti-gliadin antibodies, antiendomisium, antiterniculin and most recently *anti tissue transglutaminasis antibodies* (with very good sensibility and specificity for this disease).

Determination of antigliadin antibodies has a sensitivity of approx. 80-90% in celiac disease cases. They become undetectable over time in gluten-free diet. Antiendomisium antibodies are very sensitive (more then 90% of cases of the disease have present these antibodies), more sensitive than antigliadin antibodies. More recently we use anti – tissue transglutaminase antibodies in the suspicion of celiac disease. The levels of the 3 antibodies in celiac disease decreases to normal values in a few months, up to a year, under strict gluten-free diet, and this can be a test of patient compliance to the diet.

The evaluation of antibodies in celiac disease is a useful test, especially in family and population screening, as well as in epidemiological studies. But the final test is always the intestinal biopsy.

Histological diagnosis is performed by taking a biopsy of the second duodenum during upper gastrointestinal endoscopy. The characteristic aspects are represented by the flattening of the intestinal villi, "mosaic", "cracked" aspect of the mucosa. The association of the intestinal biopsy with the presence of positive serology for the celiac disease represent the "gold standard" in the diagnosis of the disease. From a histological point of view, lesions are more visible in the proximal area of the small intestine (but in more severe cases they can spread towards the ileum as well).

The biopsy of the duodenum II by duodenoscopy will prove, in typical forms, villous atrophies. Note that the serology of the celiac disease is positive in 90-100% of the cases in more advanced forms, but sometimes more reduced in initial state. This is why the intestinal biopsy (taking 2-4 samples) will be made in every case where we suspect celiac disease.

Other laboratory tests which can be made in case of celiac disease:

- Determination of steatorrhea – which is usually between 7 and 50 grams a day in case of severe celiac disease;
- impaired intestinal absorption tests such the D-xylose test;
- bowel barium x-ray picture of the intestine, which will be slightly modified, usually dilated loops occurring;
- presence of malabsorption syndrome – either selective (iron, folic acid, calcium), either global.

The positive diagnosis is made based on diarrhea, steatorrhea and later, malabsorption syndrome. Food anamnesis, as well as family history can suggest the diagnosis. Positive serology strengthens the diagnosis, which will be confirmed by intestinal biopsy.

Note the need to think about celiac disease when we meet unexplained iron deficiency anemia in women with osteoporosis before 50, in growth retardation in children, in patients with diabetes mellitus or Hashimoto's

thyroiditis (who are 1/30 likely to have celiac disease), in recurrent oral aphthous lesions or dermatitis herpetiformis.

The differential diagnosis is made with diarrhea of other causes: lactase deficiency, Crohn's disease, intestinal tuberculosis, chronic pancreatitis etc.

Prognosis

Prognosis depends on the moment of diagnosis. In undiagnosed cases malabsorption will progressively appear, which will lead, in severe cases, to death. Another cause of death is the development of tumors, especially of intestinal lymphatic lymphoma. Other types of cancer favored by celiac disease are: esophageal cancer and bowel cancer.

In cases diagnosed and subjected to a gluten-free diet, evolution is favorable, with the disappearance of diarrhea, steatorrhea and malabsorption.

Treatment

A. Diet therapy

Celiac disease can have a favorable evolution in case of a complete gluten free diet: wheat flour, barley, oats and rye will be eliminated from the diet. Alimentation with rice flour, cornmeal or consumption of potatoes is allowed. Generally, the disease is completely cured (at the morphopatological examination) in 3–5 years of gluten free diet, but a favorable clinical answer can occur in 3–6 weeks after starting the diet.

Note that gluten free diet is long term (usually lifelong), because reintroducing gluten brings back the symptoms. The supervision of the dietary compliance can be made by dosing the antigliadin antibodies which, in a few months to a year of correct diet, will have normal values, but will increase if the diet stops.

The presence of clearly labeled gluten free products on the market is necessary. Also, the fondation of an Association of people with celiac disease is recommended, where they can discuss their disease related problems, as well as those related to alimentation (associations like this exist in Holland, and more recently also in Romania).

B. ***Drug therapy***

When there is no clear response to the gluten-free diet (the disease may already be in an advanced, refractory phase), addition of low dose of oral corticosteroids (10–20 mg twice a day) can be an option, for a 4–8 weeks period (which can improve clinical symptoms).

12. DISACCHARIDES DEFICIENCY (LACTASE DEFICIENCY)

Definition

The disaccharides deficiency represents a relatively frequent clinical entity, not always recognized, and therefore leading to chronic digestive distress. It exists due to the absent or insufficient secretion of disaccharides at the enteric level.

Disaccharides are compounds formed of two molecules of a monosaccharide (lactose = glucose + galactose), which open in monosaccharides under the action of disaccharidases, which are then absorbed by the intestine. The disaccharides in the intestine are: lactose, maltase, sucrase and trehalose, and the substrate which they act on is made up of lactose, maltose, sucrose and trehalose. The location of the secretory activity of disaccharidases is on the brush border of the enterocytes. There is a genetic programming of the secretion of the disaccharides in the intestinal "brush border" so that the loss of synthesis ability can be the expression of this programming.

Disaccharides deficiency can be:

- *congenital* (congenital lactose deficiency: the newborn does not tolerate milk from the moment of birth; congenital sucrose deficiency; maltose or trehalose).
- *acquired* during lifetime and which can be transient or permanent (the most frequent is the lactase deficiency, with the adult's milk intolerance.)

Pathophysiology

The absence or decrease of disaccharides in the intestine will make impossible the opening of the disaccharide to the monosaccharide and respectively their absorption. The unabsorbed disaccharide determines an increase of the intraluminal osmolarity, with water transfer in the lumen and the increase of the volume of the intestinal chyle. At the same time, the stimulation of the intestinal osmo- and chemoreceptors will produce prokinetic chemical mediators (serotonin, bradykinin). The uncleaved saccharic substrate that reaches the colon, will undergo a bacterial fermentation process with gas production (CO2, hydrogen, methane) and short chain organic acids (acetic acid, propionic acid, butyric acid). All these pathophysiological phenomena will translate clinically by the occurrence of diarrheal stools with gurgling, flatulence after the ingestion of a disaccharide.

Note that the amplitude of clinical manifestations depends on:

- the degree of the disaccharide deficiency (total or partial);
- the amount of the consumed disaccharides one time.

Since the most common deficiency encountered in current clinical practice is lactase deficiency, we will describe this entity, which, by the way, is a model for other dizaharidazice deficiencies as well.

LACTASE DEFICIENCY

Epidemiology

From an epidemiological point of view, there is great variability in lactase deficiency depending on the geographical area. Thus, populations that do not consume milk traditionally (the Australian aborigines, Eskimos, American Indians, the Chinese) have a lactase deficiency of 40-90% in adults.

Populations that, throughout history, have grown animals (Europeans and their descendants) have a fairly low percentage of lactase deficiency in adults (5-15% in Northern Europe).

Thus, there is a *congenital lactase deficiency* occurring immediately after birth, with the apparition of diarrhea.

Primary lactase deficiency with late onset is a relatively normal situation. Thus, after stopping breastfeeding the infant, there is a repression of the lactase activity. An adult has aprox. 5-10% of the lactase level of a newborn. This primary deficiency is a hereditary ethnical group condition, unrelated to geographic location, environment conditions or actual milk consumption. It is considered that the persistence of lactase activity is an *adaptive genetic mutation* (produced in populations who grow animals and drink milk), and the deficiency is thus a relatively normal condition.

Acquired lactase deficiency (secondary) occurs in some inflammatory intestinal diseases: gluten enteropathy, Crohn's disease, RUH, giardiasis, radiation enteritis, short bowel syndrome.

Pathology

On microscopic examination, intestinal mucosa looks normal, including the villi and the "brush border". The use of immunohistochemical techniques highlights the decrease or absence of the enzymatic apparatus at the level of the brush border. Changes in the primary disease occur only in secondary lactase deficiencies.

Clinical picture

The clinical signs of the disease are relatively typical, but they are still often ignored by the patient for years. The signs of the disease differ depending on the intensity of the lactase deficiency and on the amount of the consumed

lactose. Typically, after milk or milk derivatives consumption the patient feels bloating, gurgling, explosive watery stools, flatulence in a few tens of minutes.

Diagnosis

Starting from the obvious clinical signs or clinical suspicion, a food test can be made, asking the outpatient to ingest 250-300 ml milk on an empty stomach, and tracking the effect for 2-3 hours. If the described clinical signs appear, the diagnosis is clear.

Lactose tolerance test (LTT) which consists of 3 phases: clinical, biological and radiological. The patient's blood sugar concentration is determined, then they get administered 50 g of lactose in 40 ml of water and a sulfate barium package. Blood sugar samples are taken at 30, 60, 90 and 120 minutes (only at 1 and 2 hours simplified) and an abdominal radiography is performed on an empty stomach every/after 1 hour.

Interpretation of results:

- *clinical*: occurrence of diarrhea in a few minutes, with flatulence, gurgling indicates a positive clinical test (error possibility after gastrectomy, when no longer having a pyloric brake, osmotic diarrhea occurs because of milk);
- *biological*: the absence of the increase of the blood sugar level to more than 25% of the fasting value is a positive test (the lactose not dissolving in glucose and galactose, the blood sugar level will remain in the plateau);
- *radiological*: lactase deficiency will appear in dilution of barium (through hypersecretion), bowel gas with distension and very fast bowel loops; usually, the barium column reaches the colon in an hour.

Respiratory tests to determine lactase deficiency are very modern, but they require relatively complex equipment. The lactose is marked with 14C, with the determination of marked CO2 in the exhaled air, or only lactose, with the determination of H2 in the exhaled air (an increase of the exhaled H2 > 20 ppm in 3-6 hours after ingestion suggests a lactase deficiency.)

Determination of lactase in biopsy requires, ideally, a jejunal biopsy (through intestinal biopsy) or maybe a duodenal biopsy at the gastroduodenoscopy, with the determination of the lactase value (allows a quantitative assessment of the deficiency). The method is laborious and expensive, requires biopsy.

Positive diagnosis is made based on the clinical signs and then on the tests described above. Milder forms are harder to diagnose.

Differential diagnosis has to be made with milk allergy (sometimes in children), osmotic intolerance to milk (resected stomach), psychogenic intolerance to milk (patients are disgusted by milk).

Evolution

The course of the disease in adults is favorable, as most patients restrict their diet themselves, avoiding dairy products. In some cases, especially undiagnosed, multiple conditioning may occur, with prolonged diarrhea, sometimes even malabsorption.

Treatment

Hygienic-dietary: In the case of this disease, treatment is obvious and it consists of reduction or complete elimination of milk and dairy products from the alimentation (depending on the existing lactase supply). Thus, a cup of milk contains aprox. 12 g lactose, and in the decreasing order regarding the lactase content lies yoghurt, fresh cheese and fermented cheese. The patient will have to be educated about alimentation where milk is not obvious (puddings, mashed potatoes, chocolate, candy, some creamy soups etc.). Milk without lactose can be used (especially for congenital lactose deficiency when the newborn's diet is very restrictive). For adults, solution came not long ago, through the apparition on the market of the products containing lactose (with bacterial origin), such as Laluk or Lact-Aid. Administration of 2-3 tb. of Laluk or Lact-Aid, together with the meal, will ensure the assimilation of the lactose and will prevent the occurrence of the clinical symptoms so well known to the patient.

The other disaccharides deficiencies are very rare; thus, in sucrose deficiency sugar is excluded, and in case of maltose deficiency starch is excluded, and in case of trehalose deficiency young mushrooms.

13. MALABSORPTION SYNDROME (MS)

Definition

Malabsorption syndrome (MS) represents a pathological condition characterized by the disturbance of the absorption of certain nutritive components in the small intestine.

A wide variety of diseases can cause primary or secondary malabsorption. Thus, malabsorption can be of pancreatic, hepatic, or of intestinal origin. MS can be caused by certain **digestive disorders** (maldigestion), with the secondary damage of the absorption (in hepatic, pancreatic causes) or can be caused directly by certain **absorption** disorders at the enteric level (in case of intestinal diseases, where the digestion was correctly done).

In malabsorption, the most typical sign is steatorrhea, defined as a loss bigger than 5 g fat/24 hours through stool.

The physiology of digestion

Alimentary proteins suffer in the stomach, under the action of pepsin and hydrochloric acid, a transformation into tryptones. In the duodenum, pancreatic proteases loosen the tryptone to amino acids and bi- or oligopeptides; these will be turned to amino acids by oligopeptidases in the intestinal brush border.

Alimentary carbohydrates.

They are not affected by the salivary amylase (inactivated by the gastric Ph-acid). Pancreatic amylase will act upon the carbohydrates in the intestine, transforming them into disaccharides, which, reacting to the disaccharides in the intestinal brush border, will transform into monosaccharides (glucose, fructose, galactose).

Alimentary lipids.

They are emulsified and micellized under the action of bile salts. Under the action of pancreatic lipase, at a neutral pH (resulting from neutralization of gastric acidity by pancreatic carbonates), triglycerides are opened to monoglycerides and free fatty acids.

The physiology of absorption

Proteins are absorbed actively, like amino acids, predominantly in the proximal jejunum.

Carbohydrates are absorbed like monosaccharides, actively for the glucose and galactose and passively for fructose (the active mechanism is energy-dependent and the passive one – energy-independent).

Xylose (pentose monosaccharide) is actively absorbed at low concentrations and passively through diffusion at high concentrations. Carbohydrate absorption usually happens in the proximal jejunum.

Lipids, opened in monoglycerides and fatty acids, are absorbed mainly in the first 100 cm of jejunum and less in the ileum. The mechanism is passive for crossing the cell membrane, but then requires energetic processes.

The absorption of *iron* is made in the duodenum and in the first intestinal loops, in reduced form. The enterocyte transport is done with the help of the ferritin, and in circulation, the iron is taken by the siderophilin.

Vitamin B12 (the extrinsical factor) binds to the gastric intrinsic factor helped by a protein which can be found in the gastric juice: protein R.

The absorption of vitamin B12 is made in the terminal ileum, where there are receptors which recognize the complex intrinsic-extrinsic factors.

Electrolytes and water are usually absorbed both passively and actively, in the duodenum and ileum, but in the colon for Na and K.

Etiopathogenesis of the malabsorption syndrome

Various diseases of the digestive tract can cause ***digestive*** disorders of food digestion and/or ***absorption***.

Digestion of proteins is modified in pancreatic insufficiency (decrease of trypsin and chymotrypsin), when transit speed is accelerated (reduced enzyme contact time). The poor absorption of amino acids appears in various digestive diseases.

Carbohydrate malabsorption is generated by maldigestion, especially by disaccharides deficiency (lactose, maltose, sucrase) or in case chronic pancreatic disease (pancreatic amylase). Chronic intestinal illness generates disorders in the absorption of monosaccharides.

Malabsorption of lipids is generated by lipid maldigestion (gastrectomy resection with anastomosis Billroth II, where bile salts and lipase come into non-physiological contact with aliments; Zollinger Ellison syndrome, where excessive gastric acidity inactivates pancreatic lipase; insufficiency of the pancreatic lipase in chronic pancreatitis; the lack of micellization of the lipids by reducing the pool of bile acids - chronic liver disease, intestinal bacterial overpopulation or insufficient re-absorption from the inflammations of the terminal ileum). The actual lipid malabsorption is the result of maldigestion, as well as the presence of an accelerated intestinal transit or of certain intestinal diseases.

The etiology of malabsorption

Causes of maldigestion:

a. Gastric causes
- Billroth II gastrectomy;
- gastroenteroanastomosis (GEP);
- Zollinger Ellison syndrome.

b. Biliary causes:
- chronic liver diseases;
- chronic biliary obstruction.

c. Pancreatic causes:
- chronic pancreatitis;
- pancreatic cystic fibrosis.

d. Intestinal causes:
- disaccharides deficiency (lactase, maltase, sucrase, trehalose);
- blind loop syndrome – through bacterial overpopulation.

Causes of intestinal malabsorption

a. The intestinal epithelium of absorption abnormal – as it happens in:
- celiac disease;
- Whipple's disease;
- intestinal amyloidosis;
- chronic intestinal ischemia;
- Bowel Crohn's disease;
- tropical sprue;
- intestinal TBC.

b. Short bowel syndrome:
- post surgery;
- fistulas enterocolitis;
- intestinal bypass surgery.

c. Abnormal intestinal transport:
- intestinal lymphoma;
- idiopathic intestinal lymphangiectasia;
- congenital cystic pneumatosis.

d. Increased intestinal transit rate:
- hyperthyroidism;
- chronic diarrhea (hemorrhagic ulceration, Verner Morrison syndrome = pancreatic cholera).

Clinical forms of MS

- MS through maldigestion
- MS through intestinal absorption disorders (***malabsorption***)
- ***Mixed MS*** – where both digestion and absorption disorders occur.

The syndrome of malabsorption can be:

- ***Global MS***, when disorders occur in the absorption of all alimentary components.
- ***Selective MS***, when the absorption of a single principle is problematic: MS selective for lactose (lactose deficiency), MS selective for B12 (inflammatory diseases of the terminal ileum or the resection of terminal ileum), MS selective for fats in Zollinger Ellison syndrome (by inactivation of the pancreatic lipase from the excessive gastric acidity etc.).

Clinical picture

The clinical picture of MS is generally dominated by chronic diarrhea, weight loss up to cachexia, steatorrhea (soft, light colored, smelly stools adherent to the toilet). Abdominal distension, bloating, flatulence, abdominal discomfort are frequent. Weight loss is a rule, with varying degrees of denutrition. The reduction of the cellulo-adipose tissue (disappearance of *Bichat's* fat pad) and of the muscle mass (muscle atrophy). Tegumental changes occur, pallor, dry and rough skin, sometimes with pellagroid pigmentation). Lingual mucosa is red, depapillated, oral rhagades appear. Nails suffer discoloration and break, axillary and pubic hair growth is reduced, later alopecia sets in. Of course, these lesions develop in parallel with the duration and severity of the disease.

Calcium absorption disorders can cause osteomalacia or bone pain and tetany. Vitamin K absorption deficiency causes bleeding tendencies. Hypoalbuminemia secondary to protein malabsorption generates edema, possibly ascites. Anemia can be caused by iron absorption deficiency (hypochromic, microcytic) or impaired absorption of vitamin B12 and folic acid (macrocytic).

Endocrine disorders are common, they relate to the absence of substrate protein or lipid hormones. Pituitary insufficiency may occur (with growth disorders in children), adrenal insufficiency (Addison's disease), gonadal failure (impotence and sterility).

Besides the clinical signs related to malabsorption syndrome, signs of the disease that caused the malabsorption also appear. These can be pain "in the duct" in chronic pancreatitis, abdominal angina in mesenteric ischemia, persistent ulcer pain in Zollinger-Ellison syndrome etc.

Diagnosis

MS diagnosis is established based on clinical signs and laboratory tests. Presence of chronic diarrhea combined with weight loss and anemia may evoke the MS diagnosis. Laboratory tests will confirm this diagnosis.

Steatorrhea is a crucial sign of MS. Determining fat loss through stool over a 3 day period is a standard test ("gold standard").

Steatorrhea represents the elimination of more than 5 g lipids/24 hours. Besides this quantitative steatorrhea, the coloring of a stool smear with Sudan III and counting the fat globules may be a useful test (significant).

After diagnosing malabsorption through steatorrhea, 2 mandatory steps follow:

a) determining the etiology (location of production) of malabsorption;

b) the biological consequences of malabsorption;

a) **Determining the etiology of MS** requires the following evaluations:

- ***gastric***: barium passage for the diagnosis of gastrocolic fistula, gastroenteroanastomosis, gastrectomy with Billroth II anastomosis; gastroscopy: multiple ulcers of Zollinger-Ellison syndrome; dosage of gastrinemia (diagnosis of gastrinoma), possibly gastric chemistry stimulation with Pentagastrin.

- ***biliary***: biological diagnosis of cholestasis syndrome (alkaline phosphatase, gamma-glutamyl transpeptidase, elevated bilirubin) in primary biliary cirrhosis; ultrasound signs of biliary obstruction, possibly complemented with MRI cholangiography or pancreatic computed tomography and endoscopic retrograde cholangiopancreatography (ERCP).

- ***pancreatic***: pancreatic enzymes (amylase, lipase can be increased if necessary); modified appearance of the pancreas (ultrasound, CT) or CPER evaluation or MRI pancreatography of the pancreatic duct appearance; impaired pancreatic function tests (PABA test or Fluorescein dilaurate test); more recently, determination of fecal elastase I may reveal pancreatic insufficiency in early stages; VIP level dosage (vasoactive intestinal polypeptide) can diagnose pancreatic VIPom or pancreatic cholera (severe diarrhea, aqueous), with hypokalemia.

- ***intestinal***: barium passage, with intestinal or entero-enema tracking, can evaluate the intestinal aspect and motility; duodenoscopy with duodenal biopsy (very useful for celiac disease) or enteroscopy can view the appearance of the mucosa (+ biopsy); the test with D-xylose (pentose monosaccharide) differentiates pancreatogenic MS (the test is normal) from the intestinal one (where the test is altered).

The test consists in the oral administration of 25 g of D-xylose and collecting the urine for 5 hours. A urinary elimination under 5 g indicates an intestinal absorption disorder; the Schilling test evaluates the absorption of Vitamin B12. Reduced urinary excretion (under 5%) of Vitamin B12 radioactively labeled, administered orally, shows a disorder of production of intrinsic gastric factor or (if it has corrected orally), an inadequate absorption; biopsy of the small intestine (with Quinton's catheter) from the jejunal area may reveal villous atrophies from the celiac disease or it may diagnose a Whipple disease or a lymphangiectasia. Harvesting jejunal juice through the same

catheter for culture can reveal aspects of dysmicrobism. Colonoscopy may reveal changes in ulcerative colitis or Crohn's disease. Examining the terminal ileum can help diagnose a Chron's disease located at that level. Colonoscopy can show the collagenous colitis or lymphocytic colitis macroscopic as appearing normal, but biopsy can reveal the presence of collagen bands or lymphocytic infiltrates.

Lactose tolerance test (LTT) which can highlight a lactose deficiency (a test that uses barium sulfate together with 50 g of lactose). The same lactase deficiency can be highlighted also by respiratory tests with hydrogen (based on the excretion of respiratory hydrogen after administering lactose, which does not loosen jejunally through lack of lactose, but is fermented, with the formation of hydrogen in the colon). The respiratory test with hydrogen can be useful also in diagnosing intestinal bacterial overpopulation (after administering glucose).

b) Biological consequences of malabsorption are represented by the reduction of various biological parameters. Hypoproteinemia with hypoalbuminemia, iron deficiency and/or macrocytic anemia, hypocholesterolaemia with hypolipemia, decreased prothrombin index, hypokaliemia, hypocalcemia, hyponatremia appear.

Differential diagnosis

The differential diagnosis of MS is made with various causes of chronic diarrhea which did not reach malabsorption. In these cases, biological parameters of weight deficit and blood change (proteinemia, albumin etc.) do not occur. Colon neoplasm (especially the ceco-ascending one) is accompanied by weight loss, diarrhea, iron deficiency anemia and has to be distinguished from MS. If hepatic metastases also appear, the jaundice can occure and a liver tumor will be palpable. Neoplastic syndromes of various causes generally go with cachexia, hypoproteinemia and hypoalbuminemia, but without diarrhea.

Evolution

Evolution of MS is chronic and progressive, if the etiology is not discovered and treated. Malnutrition evolves towards cachexia, uncorrected biological disorders worsen. An eloquent example is celiac disease (gluten enteropathy), which is accompanied by anemia, malabsorption and diarrhea. Not recognized, the disease progresses gradually to cachexia.

Correct diagnosis through jejunal or duodenal biopsy (villous atrophies) will require a diet without gluten ("gluten free diet"), which will arrest the clinical symptoms, will lead to villous restoration and to the disappearance of malabsorption syndrome.

Complications

MS complications are related to the progressive evolution towards cachexia, as well as to the advanced consequences of the disease:

- hypoalbuminemia with edema and even ascites
- decreased prothrombin index with multiple bleeding
- joint anemia (iron and macrocytic deficiency), which may be severe
- serum electrolytes decreasing severely: K, Na, Ca, Mg
- decrease of the level of lipo- and/or water-soluble vitamins, with the multiple related complications.

Prognosis

MS prognosis depends on the base disease. If this is recognized, diagnosed and medically or surgically solvable, evolution is favorable (celiac disease, resectable gastrinoma etc.) If the MS generating disease is not diagnosed or if it is hard to influence therapeutically, the prognosis is reserved (chronic severe pancreatitis, intestinal lymphoma, short bowel syndrome, etc.).

Treatment

Therapeutic approach to MS is mostly related to its etiology.

A.Diet therapy is very important in certain specific diseases, *celiac disease* (where aliments like wheat, barley, oats and rye will be mandatorily removed from the diet, but use of rice and rice flour, corn flour, potatoes will be allowed) or *lactose deficiency* (where milk and milk derivates will be removed).

In *chronic pancreatitis*, the diet will completely avoid alcohol consumption and will have a small amount of fat. In *chronic diarrheas* food rich in hard vegetal fibers will be avoided (radishes, cabbage, kale, etc.).

B.Drug therapy is related to MS etiology.

Thus, in *Zollinger-Ellison syndrome* (gastrinoma), the therapy of choice is resecting the gastrinoma (tissue that produces excessive gastrin). Because the origin of this tissue has not been discovered, a prolonged and intense blockage of the acid secretion will be necessary, with H + / K+ ATPase proton pump inhibitors. Thus, high doses of Esomeprazole 80 mg/day, Omeprazole 40-160 mg/day, 80 mg/day on average, Lansoprazole or Pantoprazole will be administered. Another alternative is octreotide (Sandostatin) 200 ug/day subcutaneously, which provides a reduction of 95% of the acid secretion.

In the presence of a *chronic pancreatitis*, enzyme substitution is important. It will reduce pain by inhibiting phenomena through feed-back of the pancreatic secretion and will reduce steatorrhea. What is very important is that the dosage of administered ferments to be high enough (choosing the lipase content as guidance element, which, in case of pancroatogenic MS, has to be at

least 20,000 IU of lipase/meal). As products we can choose: Creon, Nutrizym, Cotazym, Panzytrat, Digestal forte, Mezym forte etc. Another factor that has to be followed is that the products have to be gastro-protected, microgranulated, so that the substrate of the enzyme is released only in the intestine and is released progressively. If the enzyme products are not gastro-protected (or acidity is not neutralized prior to administration), the lipase in the product is neutralized.

In *intestinal causes* of malabsorption, the medical treatment will focus on one hand on dysmicrobism (which is treated with intestinal eubiotics: Normix 3-6 tb/day, Saprosan 3 x 1 cp/day, Antin 4 x 1 cp/day, Intetrix 4 x 1 cp/day), and then intestinal protection with products like Smecta (Diosmectita) 3 x 1 sachet/day or reducing the speed of transit in case of acute diarrhea (exacerbated), with Loperamide (Imodium) 1-2 cp if needed. In case of excessive bloating, aerocolia, Dimethicone (SAB -simplex) can be used. In Crohn's disease treatment will be with corticosteroids or azathioprine.

In case of the *Verner-Morisson syndrome* (VIPom), treatment of choice is made with octreotide (Sandostatin) at a dose of 200-300 mg/day.

In the case of patients diagnosed with Whipple's disease, the treatment is made with antibiotics (Tetracycline, Ampicillin, Trimethoprim sulfametoxazole - Biseptol). Treatment is long term, lasting 10-12 months and the dose, in the case of Tetracycline, will be of 4 x 250 mg/day. Clinical symptoms resolve relatively quickly with treatment, but histological recovery may last up to 2 years. Besides etiopathogenetic treatment, in case of malabsorption syndrome (especially severe forms), the following deficiencies have to be corrected: hypoalbuminemia by administration of plasma, iron deficiency anemia by oral or intramuscular administration of iron, macrocytic anemia by administration of vitamin B12 and/or folic acid. Electrolyte deficiencies (Na, K) will be corrected parenterally and those of Ca and Mg usually orally. Vitamin deficiencies (B, D and K complex), as well as hormonal ones will be corrected when they occur.

The goal of therapy in MS targets the source of the condition and the correction of secondary biological disturbances that occurred.

14. ACUTE PANCREATITIS (AP)

Definition

AP it is an acute inflammatory disease that affects the pancreas and peripancreatic tissues, with possible damage to other organs.

The **incidence** of the disease is difficult to be evaluated, being between 5-73 new cases/100.000 people/year, with an increasing trend in the last 20 years. It is a relatively frequent disease representing 2% - 3% of acute abdominal pathologies.

AP is a disease with unpredictable evolution, with general mortality rate of almost 5%, depending on severity. Thus, in mild forms, the mortality is around 3%, while in severe forms it goes up to 17% (30% in infected necrosis). Most cases are mild forms (only in 20% we encounter necrotico-hemorrhagic forms).

Etiology

The most frequent causes of acute pancreatitis are:

- Alcoholic (30-45% of cases)
- Biliary (30-45% of cases) – appears when a small gallstone passes the common bile duct down to the papila and temporary or completely obstructs the pancreatic duct
- Hypertriglyceridemia– TG > 1000 mg%
- Iatrogenic:
  - After ERCP (5-8%)
  - After surgery
- Viral (mumps virus)
- Drug-induced - **Certain association:** furosemide, metronidazole, tetracycline, azathioprine, 6 mercaptopurine, salicylates, estrogens, sulfonamides. **Probably associated:** amiodarone, ampicillin, erythromycin, paracetamol, piroxicam, ketoprofen, carbamazepine, etc.
- Hereditary (<20 years, familial aggregation)
- Structural causes (pancreas divisum, annular pancreas, sphincter of Oddi dysfunction)
- Autoimmune pancreatitis - in patients with an elevated serum IgG4 level, with suggestive histopathological examination, and with a “sausage like” appearance of the pancreas on CT and ultrasound examination

Pathogenesis

The destructive process in acute pancreatitis is initiated by the intracellular premature activation of trypsinogen that leads to the damage of pancreatic cells ("auto digestion of the pancreas") with the release of chemokines and cytokines and the attraction of neutrophils and macrophages. The premature activation of enzymes is determined:

- In alcoholic acute pancreatitis by the non-oxidative alcohol metabolism with accumulation of ethyl esters and fatty acids
- In acute biliary pancreatitis- the gallstone in the common bile duct can block the Wirsung duct and generate biliary reflux into the Wirsung duct

Clinical signs

The main symptom in acute pancreatitis is ***epigastric severe pain***, irradiated to the left and the right side of the upper abdomen and also to the back (belt pain). This is the cardinal symptom for the positive diagnosis. It can be associated with *nausea and vomiting* (85% of cases), epigastric rebound *tenderness* on palpation, low grade *fever*, usually due to necrosis, High fever ≥ 38°C is usually associated with the suspicion of infection. In severe cases we can encounter *signs of shock*: tachypnea, respiratory distress, tachycardia, hypotension, deep sweating, altered state of consciousness, oliguria, anuria. We can also find in these patients *dynamic ileus, the Cullen sign* – peri-umbilical ecchymosis, or the Grey-Turner sign – ecchymosis in the flanks.

The **positive diagnosis** is based on the presence of pain in the upper abdomen and the presence of elevated levels of serum lipase ≥ 3 times normal values. We can also observe elevated serum and urine amylase (not so specific), presence of leukocytosis, signs of hemoconcentration (increased hematocrit), cytolysis, cholestasis, hyperglycemia as indicator of severity, hypocalcemia and elevated creatinine and urea, also signs of severity.

The **imaging techniques** are also useful for the acute pancreatitis diagnosis.

Ultrasound is a inexpensive method, non-irradiating, can be repeated, accessible, easy to use in patients follow-up, but sometimes difficult to use at the onset of acute pancreatitis due to lack of acoustic window. It can show also suggestive elements for etiology (gallbladder stones, dilated common bile duct, suggestive elements for chronic pancreatitis), elements of severity (ascites, hyperreflectivity of omental bursa, collections). This is why ultrasound should be the first line imaging method in all patients suspected to have acute pancreatitis, starting from the emergency room.

In mild forms we can find the pancreas increased in size, with hypoechogenic +/-inhomogeneous aspect, while in severe forms we can observe

inhomogeneous aspect of the gland, hyperreflectivity of omental bursa, pancreatic and peripancreatic collections or vascular complications (splenic thrombosis).

Contrast-enhanced computed tomography (CECT) is the standard imaging modality for the evaluation of acute pancreatitis. It shows necrotic areas and possible complications (peripancreatic collections, pseudocysts, vascular damage).

CECT allows the assessment of severity using the Balthazar score

• Normal pancreas	0 points	(Stage A)
• Pancreatic edema	1 point	(Stage B)
• Peripancreatic inflammation	2 points	(Stage C)
• One single collection	3 points	(Stage D)
• Two or more collections	4 points	(Stage E)
• Necrosis ≤ 30%	2 points	
• Necrosis 30-50%	4 points	
• Necrosis ≥ 50%	6 points	

Mild acute pancreatitis: 0-3 points
Moderate acute pancreatitis: 4-6 points
Severe acute pancreatitis: 7-10 points

In acute pancreatitis, CECT should be performed initially in severe forms which didn't improve after 72 hours of conservative treatment and in patients with good initial evolution, but who subsequently developed signs of poor progression (fever, gastrointestinal intolerance, hypotension).

CECT should also be performed when the clinical status of the patient is worsening and after 7-10 days of the first CT for patients with necrosis.

Other imaging methods are also useful for evaluation in AP:

- ***Plain abdominal X ray*** is normal in most cases, but can show small bowel ileus with "sentinel loop"
- ***MRI*** is a non-irradiating method that can diagnose a rupture of the pancreatic duct and choledocholithiasis (MBD stones) (MRCP)
- ***Endoscopic ultrasonography*** (EUS) is a non-invasive method, first line for the evaluation of MBD and also for the diagnosis of chronic pancreatitis.

The **differential diagnosis** should be made with biliary colic, perforated duodenal ulcer, acute appendicitis, peritonitis, diverticulitis, renal colic, intestinal obstruction, Inferior myocardial infarction, chronic mesenteric ischemia, mesenteric infarction, aortic aneurysm, basal pneumonia.

Evolution, prognosis:

Acute pancreatitis is a disease with an unpredictable evolution. Approximately 80% of cases are mild forms that will clinically improve in 48-72h, with good clinical progression and restitutio ad integrum (full recovery). On the other hand, approximately 20% of cases are severe forms with complications. These forms are associated with organ dysfunction and / or local complications: necrosis, abscess, pseudocysts.

The assessment of severity should be done for all patients within 48 hours after the diagnosis. For this we can use:

- RANSON criteria with 11 criteria (5 admission, 6- 48 hrs)

At admission	**Within 48 hours**
Age > 55 years	Hematocrit fall > 10%
Leukocytes > 16000/mm^3	↑ urea > 5 mg %
Glycemia > 200 mg%	Serum calcium < 8 mg %
LDH > 350 U/l	PaO_2 < 60 mmHg
AST > 250 U/l	Base deficit > 4 mEq/l
	Sequestration of fluids > 6l

- APACHE II score that use 12 variables, age, past medical history; it is more accurate but complicated to determine
- Atlanta score with severity criteria:
  - Organ dysfunction (systolic BP <90 mmHg, PaO 2 <60 mmHg, creatinine> 2 mg% UGIB > 500 ml/24 h)
  - Local complications (pseudocyst, abscess, necrosis)
  - 3 or more Ranson criteria
  - 8 or more APACHE II score
- **PCR > 150 mg%** within 48 hours of onset has a good positive predictive value for a severe form and it easy to use in clinical practice

Complications that frequently appear in moderate and severe forms of acute pancreatitis are either:

- local complications: necrosis, pseudocyst, abscess, peritoneal collections ± infection, vein thrombosis, paralytic ileus, mesenteric infarction, or
- systemic complications: shock; pulmonary complications: pleural effusion, pneumonia, mediastinal abscess; acute renal failure, encephalopathy; retinopathy; fat tissue necrosis.

Treatment:

There is no etiological treatment in acute pancreatitis. The treatment is based on supportive measures and treatment of complications, if they appear.

Supportive measures:

- Monitoring of vital signs
- Aggressive fluid resuscitation (250-300 ml / h) with Ringer Lactate or Normal Saline within first 24-48 hours
- Pain management
- Correction of electrolyte and metabolic disorders

Dietary treatment:

- Fasting (nil per os - NPO)
- Resumption of food, 24 hours after the pain relieved
- Fat-free diet, depending on the patient's tolerance
- In severe forms, without digestive tolerance parenteral nutrition is needed.

Specific therapies

- In acute biliary pancreatitis with obstructive jaundice ± angiocholitis the drainage of the common bile duct should be done as soon as possible by ERCP, preferably within 72 hours from the onset.
- Pancreatic pseudocysts if they are asymptomatic, they should be treated conservatively, while if they are symptomatic (> 6 cm in general) they need percutaneous or endoscopic drainage
- Sterile pancreatic necrosis requires conservative treatment, while infected pancreatic necrosis requires endoscopic, percutaneous or surgical drainage (the surgical drainage is preferable to be done after 2 weeks) and antibiotic therapy.

Acute pancreatitis still has rather high mortality especially in severe forms despite the progress made in medicine.

15. CHRONIC PANCREATITIS

Definition

Chronic pancreatitis (CP) is a chronic inflammatory disease of the pancreas, with progressive evolution to exocrine and endocrine pancreatic destruction, ending in pancreatic insufficiency.

It is a disease with slow, but progressive onset, needing several years (usually more than 10) for complete onset.

CP is a condition different from acute pancreatitis (AP) and is not a result of it. AP usually develops to complications or to "restitutio ad integrum".

Clinical signs

The clinical picture suggestive of pancreatitis is generally (but not necessarily) dominated by abdominal pain, with epigastric or periumbilical location, or sometimes extending to the back, often set on by abundant meals.
Presence of steatorrhea (pasty, voluminous, especially foul-smelling stools) is a late sign, when malabsorption is already present, and it is always accompanied by weight loss.

A history of chronic alcoholism (whether admitted or not by the patient) is an important element of diagnosis. Collateral anamnesis (from the relatives) is very important in order to find out if the patient has a history of excessive and sustained alcohol consumption.

Etiology

a) Chronic alcoholism is the most important cause of chronic pancreatitis, accounting for over 90% of CP. The toxic dose of pure alcohol is over 60-40 ml alcohol/day for men, and over 40 ml alcohol/day for women. Over 45 % of chronic alcoholics present morphological changes of CP at autopsy, even if clinically they had no signs of the disease. The clinical symptoms of CP in general appear late in time, after 10-20 years of considerable alcohol consumption.

Some patients have also been diagnosed with alcoholic liver disease type lesions (steatosis, alcoholic hepatitis, or even alcoholic liver cirrhosis).

b) Gallbladder lithiasis

Although it is a common factor for AP, it does not generate CP. Therefore, it is unjustified to perform a cholecystectomy for asymptomatic patients in order to prevent the onset of CP, as it is also unjustified to relate chronic pancreatic lesions found at cholecystectomy with an earlier gallbladder lithiasis.

c) Hypercalcemia in hyperparathyroidism is another possible etiological factor of AP.

d) Ductal obstruction caused by: pancreatic trauma, pancreatic tumors, Oddian stenosis, calculus in Wirsung's canal, congenital duct anomalies such as "pancreas divisum" (a congenital anomaly caused by the insufficient fusion of ventral and dorsal embryonic ducts).

e) Hereditary pancreatitis implies a dominant autosomal gene. In this case family history is important.

f) Various conditions such as malnutrition (tropical CP in India, Africa, South-East Asia), hemochromatosis (bronze diabetes – the cause is iron deposit in the liver, pancreas, myocardium).

In conclusion, the almost exclusive cause of CP is chronic alcoholism.

Pathogenesis

In chronic alcoholism, the pancreas secretes a pancreatic juice with protein concentrations higher than normal. These proteins may precipitate, forming protein plugs which will cause duct obstruction (the obstruction of small ducts) with a retrograde activation of pancreatic enzymes. Some protein plugs are calcified by impregnation with calcium carbonate.

Calculus formation is favored by the alteration of the pancreatic synthesis of "**lithostatin**" due to alcohol (initially called "PSP – pancreatic stone protein"), which inhibits the nucleation and precipitation of calcium carbonate crystals of the pancreatic juice. As a consequence of obstructions, some ducts are broken and activate enzymes, other ducts are dilated and periductal fibrosis occurs with new stenosis. Tissue destruction and calcium deposits also occur.

Morphopathology

Macroscopically.

The pancreas is hard at palpation, most often small, rarely hypertrophic, sometimes even pseudotumoral (causing intraoperative diagnostic errors in the absence of biopsy).

Microscopically, there is fibrosis and lympho-plasmocytic infiltration around the acini. Ducts are dilated unevenly, with protein plugs and several mm large Wirsung calculi.

Diagnosis

The disease most often starts insidiously, it is sometimes difficult to differentiate it from repeated relapse of alcohol-based acute pancreatitis. CP is at least 3-4 times more frequent (or even more) in men than women. It is usually diagnosed after the age of 40, but some cases may be diagnosed as early as around age 30 (with a possible existence of a genetic factor).

Clinical picture

The clinical picture is dominated by *pain* that can be epigastric, periumbilical or right-to-left and radiating to the back. The pain can be monotonous, irritating, rarely occasional, but in some cases intense, quasi-permanent, disabling. Pain is often triggered by eating (stimulation of enzymatic secretion), therefore CP patients prefer not to eat, only to drink alcohol, which may have an analgesic effect. In 10-20% of CP cases pain may be absent, and the disease is only diagnosed accidentally by imaging techniques (ultrasound). Other symptoms may include *obstructive jaundice* caused by the compression of the pancreatic head on the bile duct, the malabsorption with steatorrhea, or type 2 diabetes mellitus which occurs in 50-70% of calcific CP.

Clinical examination usually provides no relevant data, as the pain is localized in the upper abdomen. Rarely, a large pancreatic pseudocyst can be palpated or there is a suspicion of pancreatic pleural or peritoneal effusion (rich in pancreatic enzymes).

Paraclinical examinations

Biologically**,** there may be a small to moderate elevation of *amylasemia, amylasuria*, or **serum lipase**. Values are not as high as in acute pancreatitis (perhaps only in relapses of acute pancreatitis occurring in chronic pancreatitis), but there are severe forms of CP with quasi normal levels of serum or urinary enzymes (the mass of residual pancreatic tissue is decreasing).

Fat dosage in stools may show *steatorrhea* (more than 7 g lipids lost by feces/day) by a quantitative or semiquantitative test (staining of feces with Sudan red).

Protein loss dosage in stools – *creatorrhea* of over 2.5 g/day means protein maldigestion. Glycemia levels may be elevated because of type 2 diabetes; an OGTT (oral glucose tolerance test) may document an infraclinical diabetes.

Imaging examination

It is currently the most common method to diagnose CP. Incidental imaging examinations may often diagnose asymptomatic CP or may discover the reasons of long-lasting atypical abdominal pain.

- *Radiology* by abdominal X-ray on empty abdomen may reveal pancreatic calculi in about. 30% of calcific pancreatitis. The radiological image must be centered on the epigastric (pancreatic) region, and in case of doubt a profile radiography may demonstrate the localization of calcification on the spinal cord.
- *Ultrasound* is the most common diagnosis method for advanced chronic pancreatitis. Ultrasound may reveal diffuse pancreatic calcifications, pancreatic heterogeneity (the inhomogeneous aspect of the pancreas), the dilation of Wirsung's duct over 3 mm (in pathological conditions it can dilate to 7-10 mm) with presence of Wirsung calculi (hyperechogenic

images in the duct with posterior shadow), presence of pancreatic pseudocysts (transonic images with variable sizes, usually 1 to 10 cm, but sometimes with huge sizes) in the head, body or tail. Not all CP cases display these ultrasound signs, but they can often be associated. The imaging specialist's experience is important for an ultrasound diagnosis of CP.

- *Computed tomography* is an accurate and precise method for diagnosing morphological modifications in CP and following up its evolution in time. It is indicated in all cases of initial evaluation or in cases when the ultrasound is not conclusive. It allows visualization of minor calcifications, evaluation of obese or bloated patients, therefore it is superior to ultrasound (but so is also its price).
- *Endoscopic retrograde cholangiopancreatography* (ERCP) highlights the morphological aspect of the pancreatic duct: irregular, with stenoses and dilations that occur in CP. It is a useful method even at an early stage of the disease, but complications may follow in approx. 5% of cases. The aspect of the pancreatic duct can also be evaluated through *MR pancreatography*.
- *Endoscopic ultrasound (EUS)* combines endoscopy with ultrasound and it is a useful and faithful method for diagnosing CP, revealing the lack of homogeneity of the pancreatic tissue, dilation of the Wirsung duct, calcifications of the pancreatic parenchyma, and possible Wirsung calculi. This is the most accurate method of diagnosing chronic pancreatitis, even at an early stage.

Pancreatic secretion tests evaluate the pancreatic functional reserve. They are rarely used in daily clinical practice. These tests are:

- Lundh test
- secretin test
- PABA test
- pancreolauryl test
- fecal elastase-1 test

The Lundh test is used for the dosage of pancreatic enzymes (lipase, trypsin and amylase) in the pancreatic juice obtained by duodenal intubation after a test meal.

The secretin test stimulates the pancreatic secretion with the help of secretin (which normally elevates the volume of secretion as well as the secretion of bicarbonate). In chronic pancreatitis the volume of secretion and bicarbonate discharge both decreased. This test can also be done in combination, used together with cerulean as secretin secretion stimulation (secretin-cerulean test).

The PABA test (or bentiromide test) administers a polypeptide attached to PABA (para aminobenzoic acid). Under the effect of chymotrypsine, the peptide

detaches from PABA which is reabsorbed and eliminated through urine. So, the decrease of PABA elimination is an indirect sign of pancreatic distress.

Pancreolauryl test: the substrate is lipidic, marked with fluorescein. Under the effect of pancreatic esterase, fluorescein is detached, reabsorbed and eliminated in the urine, when it can be dosed.

These pancreatic secretion tests are laborious and therefore relatively rarely performed.

Fecal elastase-1 test is a ***functional pancreatic test*** which detects early pancreatic insufficiency and it is *the standard test currently used*.

Classification of chronic pancreatitis

Clinical forms of CP:

- CP with pain (intermittent or continuous)
- asymptomatic CP

Morphopahological forms of CP:

- obstructive CP – with significant Wirsung duct dilation
- calcific CP – with predominant calcification of the pancreatic parenchyma;
- mixed CP – with calcifications and duct dilation

Evolution

The evolution of the disease is chronic, with recurrent acute bouts. At first it can be asymptomatic, but it becomes symptomatic in time, and the most important element is often the pain. The complete discontinuation of alcohol consumption may have a beneficial effect on the pain, but not always. Maldigestion occurs in time with secondary undernutrition.

Complications

CP complications can be:

- pancreatic pseudocyst, sometimes compressive;
- pancreatic abscess produced by the infection of a pancreatic pseudocyst;
- recurrent ascites rich in amylase, usually not very abundant, which can be serous citrine fluid or occasionally hemorrhagic (therefore in case of unclear ascites the amylase in the ascitic fluid will always be determined);
- obstructive jaundice by the compression of the bile duct to the hypertrophic pancreatic head (difficult differential diagnosis with pancreatic cephalic neoplasm);
- thrombosis of the splenic vein or the portal vein by neighborhood inflammation.

Treatment

A. Diet

Treatment begins with dietetic measures, among which most importantly the complete and definitive stop of alcohol consumption. Abundant meals rich in fats and also in proteins which stimulate pancreatic secretion, intensifying the pain, must be avoided. Acute episodes of AP in chronic pancreatitis are treated in hospital care, strict diet, parenteral nutrition or occasionally nasogastric tube, analgesic medication, anti acid secretion medication (duodenal acidity may stimulate pancreatic secretion).

B. Medication

Medical treatment of CP consists of:

- analgesics for the painful periods (Algocalmin, Piafen, Tramal, Fortral);
- pancreatic enzyme substitution which may improve symptoms by reducing pancreatic secretion, having a negative bio-feedback effect. Dosage must be large, even in the absence of malabsorbtion. High lipase concentration products must be used: Creon, Mezym forte, Panyztrat, Festal, Cotazym, Nutryzym, Digestal forte, etc. Gastro-protected (enterosoluble) products are to be preferred because of the neutralization of lipase by the gastric acid juice. In case of maldigestion with malabsorbtion the dose of substitution ferments must be high, at least 20.000 U lipase/meal. If the product is not gastro-protected, an anti-secretory (Ranitidine, Cimetidine) must be administered 30 minutes before meals. If maldigestion cannot be countered this way, medium chain triglycerides can be added in a dose of 40g/day (coconut oil which is easily absorbed, partially preventing malabsorbtion).

C. Alternative therapy

It can be:

1. ***Endoscopic:*** endoscopic therapy in CP gains increasingly more ground in treating patients. For satisfactory results, patients must be carefully selected in terms of the type of endoscopic intervention.

The practiced techniques:

- papillotomy
- biliary or Wirsung duct prosthesis in case of benign strictures (due to inflammation or necrosis around Wirsung duct). From a technical point of view, papillary sphincterotomy is performed, then the stents are placed using a guiding wire up to above the stenosis (sometimes in case of tight stenosis they need to be dilated). Evolution after placements of stents is favorable in 85-100% of cases.
- calculus extraction from Wirsung duct: the presence of calculi increases intraductal pressure, increasing the pain and causing pancreatic ischemia. Sphincterotomy is performed just before the extraction to allow papillary access. Devices used for extraction are extraction “balloons” and “baskets”. In case of large calculi lithotripsy may be attempted to extract fragments of calculi.

Lithotripsy (ESWL) is an adjuvant technique frequently used, as it permits the fragmentation of large calculi and extraction of smaller ones.

- echoendoscopic drainage of pancreatic pseudocysts. These appear as complications in CP in 20-40% of cases. The use of drainage with echoendoscopic guiding of pseudocysts is a nonsurgical alternative for these patients. The purpose of transmural drainage is to make communication between the pseudocyst cavity and the digestive lumen (cystogastrostomy or cystoduodenostomy), draining the content of the cyst into the intestinal lumen.

2. ***Surgical***: in very painful forms the celiac plexus can be blocked (also echoendoscopically), total or subtotal pancreatectomy is performed, using various techniques of derivation or decompression (lateral pancreatojejunostomy).

16. BILIARY LITHIASIS

Epidemiology

Biliary lithiasis has a relatively frequent condition, present in over 10% of the adult population of European countries. In the Banat region, a prospective study showed that 13% of adults over the age of 20 had biliary lithiasis. Diagnosis is often accidental, by routine ultrasound. Biliary lithiasis is often clinically manifest.

Etiopathology of biliary lithiasis

Etiological factors

The main responsible factors for cholesterolotic biliary lithiasis are: genetic predisposition, female gender (proportion of women/men suffering of biliary lithiasis: 2-3/1), obesity, age, hyperlipoproteinemia, parity, diabetes mellitus, etc.

Pathogenesis of cholesterolic biliary lithiasis: the balance of cholesterol, bile acids and lecithin in the gallbladder is broken. This balance ensures the solubilization of cholesterol. An increase in cholesterol elimination (in hyperlipoproteinemia, sudden loss of weight, diabetes mellitus, obesity), or, on the contrary, a decrease in bile acid elimination lead to this imbalance which ensures the solubilization of cholesterol, precipitating it and nucleating cholesterol crystals. Biliary stasis (for instance during pregnancy) is another factor that favors the formation of calculi. In case of calcium bilirubinate lithiasis the mechanism of calculus formation is different: an increased bilirubinate elimination, as in chronic hemolysis, liver cirrhosis, Clonoris infections (in Asian countries where calcium bilirubinate lithiasis predominates).

Diagnosis

The diagnosis of biliary lithiasis can be ***clinical***, when biliary colic or a dyspeptic symptom occurs which may indicate biliary distress. It must be emphasized that biliary lithiasis is often asymptomatic either completely or partially (showing only vague dyspeptic symptoms), and its diagnosis is accidental.

Paraclinical diagnosis of biliary lithiasis is established by *ultrasound*. Biliary lithiasis in ultrasound examination appears as one or more hyperreflective images, moving with the position of the patient, presenting "posterior shadow". The size and approximate number of calculi can be evaluated by ultrasound.

Echoendoscopy can be used for diagnosing biliary lithiasis in cases with uncertain diagnosis.

Computed tomography in a non-surgical therapy (medicated litholysis) can evaluate the presence of calcification of biliary calculi.

A modern concept of biliary lithiasis is to classify biliary lithiasis as:

- symptomatic biliary lithiasis
- asymptomatic biliary lithiasis

Symptomatic biliary lithiasis is the one which generates biliary colic (biliary colic means an intense or violent pain localized in the epigastrium or the right hypochondrium, perhaps with subscapular radiation, usually lasting over half an hour). Nausea or vomiting (and also headache or migraine) unaccompanied by colic-type pain do not classify a lithiasis as symptomatic.

Asymptomatic biliary lithiasis is lithiasis which does not generate biliary colic.

Differential diagnosis

The differential diagnosis of biliary lithiasis from a clinical point of view is made with ulcer pain, renal colic, chronic pancreatitis pain, dysmotility dyspepsia, etc. The ultrasound differential diagnosis of biliary lithiasis is made with gallbladder polyp, gallbladder neoplasm, biliary sludge.

Evolution

The evolution of biliary lithiasis is often unpredictable. In general, symptomatic biliary lithiasis generates relatively frequent colics which can be complicated with vesicular hydrops, acute cholecystitis, etc. Asymptomatic biliary lithiasis often lacks symptoms throughout one's lifetime, and some prospective studies have shown that only approximately 20% of asymptomatic biliary lithiases became symptomatic (exhibiting biliary colics) in 10 years of follow-up.

Complications

Complications of biliary lithiasis are: biliary colic, vesicular hydrops, acute cholecystitis, calculus migration in the bile duct - choledocholithiasis, acute biliary pancreatitis, biliary ileus, neoplasm of the gallbladder.

Obstructive jaundice by calculus migration in the bile duct is treated by endoscopic sphincterotomy with subsequent extraction of the calculus (calculi) in the bile duct with balloon or Dormia catheter.

Prognosis

The prognosis of biliary lithiasis is good, symptomatic cases are usually treated surgically, while asymptomatic cases are monitored.

Treatment of biliary lithiasis

There is almost unanimous consensus at present that asymptomatic biliary lithiasis should only be monitored and not treated surgically (World Gastroenterology Organization – WGO). Taking into account that only 1-2% of asymptomatic cases become symptomatic a year, watchful waiting seems the most logical and economic solution, with decision of therapy only taken when symptoms appear. It must be said that cholecystectomy, although a relatively simple surgical gesture, may have complications.

Symptomatic biliary lithiasis must be treated. Most often, the treatment is **surgical**, but sometimes can be made with nonsurgical techniques. With the introduction of laparoscopic cholecystectomy, patients are more willing to accept the intervention. It is a safe intervention, with short hospitalization and minimal post-surgical complications (if made by surgeons well trained in this technique). This technique is primarily used for uncomplicated biliary lithiasis, and also acute cholecystitis or vesicular hydrops. In scleroatrophic lithiasic cholecystitis or in suspicion of common bile duct lithiasis the traditional technique of open cholecystectomy is preferred. In suspicion of choledochian lithiasis the exploration of the bile duct by echoendoscopy (or MRI cholangiography) or more rarely endoscopic retrograde cholangiography (ERC) is compulsory, the calculi discovered can be extracted by endoscopy.

Non-surgical treatment techniques of biliary lithiasis are ***medicated litholysis and extracorporeal lithotripsy*** (less used lately).

Medicated litholysis:

It is used for cholesterol gallstones, preferably small sized, which fill less than half of the gallbladder volume, and a gallbladder with permeable infundibular cystic area. The treatment consists in the administration of ursodeoxycholic acid (10 mg/ body kg/day) as product Ursofalk or its combination with chenodeoxycholic acid (10-15 mg/body kg/day), the product Litofalk for a period of 6-24 months, until the complete dissolution of calculi (the chance of success is 50% and there is a risk of relapse of approx. 10% in the first 5 years). Results are monitored by ultrasound. The use of the method of medicated dissolution of calculi has decreased in recent years.

Extracorporeal shock wave lithotripsy (ESWL) consists in bombing cholesterol calculi with shock waves; it is used in case of unique or small number of calculi, preferably under 15 mm. The fragments resulting from lithotripsy are dissolved by administration of biliary acids (especially ursodeoxycholic acid), until the complete disappearance of all fragments of calculi in the gallbladder. Both non-surgical techniques (medicated litholysis and ESWL) are relatively expensive and their use has been decreasing in recent years.

B. HEPATOLOGY

1. CHRONIC HEPATITIS

Definition

Chronic hepatitis is represented by necro-inflammatory and fibrotic hepatic processes *with an evolution of more than 6 months*.

Diagnosis

The diagnosis of chronic hepatitis is clinico-biological, and, especially, histological. This is due to the fact that chronic hepatitis can frequently be completely asymptomatic, or a completely non-suggestive clinical picture can be present, which is why it is sometimes detected on the occasion of routine biological investigations.

Almost in half of the patients with chronic hepatitis, the disease is detected on the occasion of periodic check-ups (which will evidence changes in biological parameters – most frequently in transaminases), or on the occasion of routine ultrasound, which can demonstrate splenomegaly. When there is a suspicion of chronic hepatitis, accurate etiological anamnesis, adequate clinical examination (for hepatomegaly and splenomegaly), biological evaluation for liver involvement (with the 4 biological syndromes: hepatocytolytic, impaired liver synthesis, inflammatory and biliary excretory), abdominal ultrasound for assessing the size of the spleen and possible signs of portal hypertension will be performed.

The staging of chronic hepatitis will be carried out through ***liver biopsy puncture*** (LBP) or through a ***non-invasive evaluation of liver fibrosis***.

Biopsy will allow for correct histological grading, accurate prognosis, and will sometimes provide important etiological elements (in virus B hepatitis – the "dull glass" appearance of the hepatocyte, or in primitive biliary cirrhosis - periductullar inflammatory infiltrate) and will allow at the same time to make a therapeutic decision (depending on the detected lesions).

Lately, it has been attempted to use some **non-invasive markers for the determination of liver fibrosis**: **FibroTest-ActiTest** (using biological tests) or ultrasound based elastographic techniques (**FibroScan, ARFI, 2D-SWE).** In some hepatology centers these non-invasive fibrosis tests replaced a high number of liver biopsies.

The histological staging of chronic hepatitis requires liver biopsy puncture (LBP). This is a low invasive technique with a minimum risk (in approximately 1-2% of the cases, post-biopsy pain in the shoulder blade or very rarely, hemoperitoneum may occur), which has lately been performed under ultrasound-guided control. The biopsy fragment, after being fixed and stained with HE or special stains for fibrosis, will be read by a morphopathologist experienced in hepatology.

There are currently several histological grading scores: the Knodell score, the Metavir score or the HAI (Histologic Activity Index) score.

In general, all these scores assess necroinflammatory activity *(grading*) and fibrosis (*staging*).

Thus, the **Knodell score** uses for necroinflammation (periportal necrosis and bridging necrosis, portal necrosis and portal inflammation) a maximum score of 18, and for fibrosis, a score ranging from 0 (absent) to 4 (cirrhogenic evolution). It is used for patients with chronic hepatitis B.

The **Metavir score** is used for activity from 0 to 4, as well as for fibrosis (0-4). It is used for patients with chronic hepatitis C.

Ultrasound based elastography techniques have been intensely developed in the last years. Liver tissue is stimulated by ultrasound waves and thus, liver stiffness is assessed. Liver stiffness (LS) is a marker of fibrosis and is measured either in kiloPascals (kPa) or in meters/second (m/s). The stiffer the liver, the more severe fibrosis. Even if elastographic techniques have difficulties to discriminate contiguous stages of fibrosis, they are accurate enough to diagnose significant fibrosis (F=2), severe fibrosis (F=3) or cirrhosis.

The first elastographic technique was Transient Elastography (performed with a FibroScan device). It is a painless, reproducible technique, performed in less than 5 minutes, but it cannot be done in patients with ascites. M probe is used in normal weight patients, and XL probe in overweight and obese. LS values lower than 6 kPa are considered normal; > 7.6 kPa suggestive for at least significant fibrosis (F=2); > 9.5 kPa for at least severe fibrosis (F=3); while > 13 kPa for cirrhosis.

Other elastographic techniques are ***"point shear wave elastography" using ARFI*** technique (VTQ from Siemens or ElastPQ from Philips) or ***"2D SWE"*** from SuperSonic Imagine-Aixplorer™ and 2D SWE-General Electric (they are real-time elastography techniques, the result being displayed both as a color-coded image, and as a numeric value). The cut-off values for different stages of fibrosis are similar but not identical with those from FibroScan.

Fibrotest-Actitest (and FibroMax) are serologic tests in which 6 biologic parameters are combined in a patented formula with the subject's age and gender, to obtain a rather good prediction of the severity of fibrosis and necroinflammation. ***FibroMax*** also evaluates the severity of steatosis in non-alcoholic (NASH) and alcoholic (ASH) steatohepatitis. This is relatively expensive test.

Etiology of chronic hepatitis

Without any doubt, the most frequent etiology of chronic hepatitis is viral etiology. Thus, B virus (possibly associated with D virus) and C virus are the main causes of chronic hepatitis. Other possible, but clearly more rare causes are autoimmune hepatitis, followed by Wilson disease hepatitis (ceruloplasmin deficiency), drugs, and alpha-1 antitrypsin deficiency. In the presence of a patient with chronic hepatitis, in order to establish etiology, viral markers will be first searched for: HBsAg (when positive, anti-D antibodies will also be looked for), and anti-HCV. If these viral markers are negative, other possible etiologies will be investigated (antinuclear antibodies, LKM1 and SMA – smooth muscle antibodies for autoimmune hepatitis, measurement of ceruloplasmin for Wilson disease, measurement of alpha-1 antitrypsin for determining its deficit). So, the main *etiologies* of chronic hepatitis are:

1. hepatitis B virus
2. hepatitis D virus (only in association with B virus)
3. hepatitis C virus
4. autoimmune cause
5. Wilson disease (ceruloplasmin deficiency)
6. alpha-1 antitrypsin deficiency
7. chronic cholestatic hepatitis
8. drug cause (oxyphenisatine, isoniazid, nitrofurantoin, alpha-methyldopa as main drugs).
9. Non-alcoholic steatohepatitis (NASH) - a growing cause frequent, with the increase of its etiological factors (obesity, dyslipidemia, diabetes mellitus)
10. alcoholic steatohepatitis

I. Chronic B virus hepatitis

It is a public health problem in Romania because of the relatively high proportion of B virus (approximately 5% of the population).

Epidemiology. Incidence is estimated between 5 and 8% in our country, which places Romania in the category of moderate endemic countries.

Acute virus B hepatitis becomes chronic in about 5-10% of the cases, which allows for the presence of a sufficiently important virus reservoir.

It is estimated that more than 2 billion people have been infected with hepatitis B virus worldwide; only in Europe, more than 1 million new cases occur every year. At global level, there are currently more than 350 million chronic HBV carriers, with an increasing tendency towards 400 millions. Most chronic carriers are in Asia and Africa, where prevalence is high (over 8-10%). Romania is considered to be a moderate endemic country (5-7%). Regions with a low prevalence (less than 2%) include Australia, USA and Western Europe.

The natural reservoir of HBV infection is represented by infected persons, the virus being located in the blood, saliva and other secretions (seminal, vaginal, breast milk). The main source of infection is infected blood. So, the insufficiently controlled administration of blood (transfusion) or blood derived products (thrombocyte mass, cryoprecipitate, antihemophilic factors, etc.) may cause the infection. This can also be transmitted by sexual route (through sperm), through different secretions, or perinatally. Receptivity is general, except for those who had the disease or vaccinated subjects.

The virus can be transmitted by various routes:

A. Horizontal

- Parenteral or percutaneous (blood, blood derived products, contact with infected instruments, including from tattooing).
- Non-sexual physical contact (intrafamilial, children communities).
- Sexual contact.

B. Vertical

- Perinatal (from an infected mother to her child).

In high endemic areas, transmission is predominantly vertical, while in moderate and low endemic areas, transmission is mainly horizontal. The serological triage of blood collected for transfusion has led to a decrease of HBsAg incidence and residual HBV transmission risk.

Pathogenesis

Hepatitis B virus (HBV) is a small size virus of the Hepatnaviridae family. It is formed by an external envelope that contains HBsAg in the three forms, and the nucleocapsid with double-stranded genomic DNA (HBV DNA) and DNA polymerase. The genome contains 4 genes (S, pre-C, P and X).

Structure of hepatitis B virus: 1–"CORE"- the heart of the virus includes:

- double-stranded DNA
- DNA polymerase
- Ag (antigens)

2 – Nucleocapsid

Hepatitis B virus has hepatocellular tropism, but it can also be found in monocytes; its replication occurs in the hepatocyte, producing large amounts of HBsAg. Only a small part of HBsAg enter a completely new virus, the rest being released into blood circulation as spherical filaments and representing serological markers for hepatitis B infection.

Liver injury by HBV does not occur through direct cytopathic action, but through the induction of a cell mediated immune response. In chronically infected subjects, this response is deficient towards the virus and the infected hepatocytes, leading to an incapacity for the immune elimination of HBV in the acute phase of the disease and to a progressive liver alteration by further destruction of the infected hepatocytes. Thus, a potentially reversible

inflammatory and hepatocyte necrosis process develops. The continuation of this process for a prolonged time period leads to fibrosis, and in the last stage, even to hepatocyte carcinoma.

Natural history of HBV infection

Chronic HBV infection occurs in the absence of a spontaneous elimination of HBV infected hepatocytes and of HBeAg/anti-HBe seroconversion. The age of the infected person at the time of the primary infection appears as the best determining factor for chronicization. Infection chronicization may exceed 90% in perinatally infected children of HBeAg positive mothers, with a frequently subclinical evolution of acute hepatitis. In contrast, in children aged over 5 years and young adults, acute infection may be clinically apparent, while chronicization decreases.

The evolution of chronic hepatitis B towards cirrhosis occurs in 40% of children and 14-20% of adults, with an annual progression of about 2%. There are a number of factors favoring the evolution towards cirrhosis: age over 30 years, duration of HBV replication, and severity of liver disease and viral reactivation.

Hepatocellular carcinoma develops on the background of liver cirrhosis with an annual rate of ~ 3% and after an evolution of chronic HBV infection of more than 25 years. After chronic hepatitis B is resolved, a progressive decrease of oncogenic risk occurs.

The main ***serological markers*** of hepatitis B are as follows:

- HBsAg (diagnosed using Elisa techniques) *represents a marker of infectiousness* and occurs both in the acute phase of the disease and in patients with chronic hepatitis. *The persistence of this antigen for more than 6 months, after acute hepatitis, indicates chronicization.* Its disappearance, along with the appearance of anti-HBs Ab, indicates HBsAg seroconversion. Significance:

- Anti-HBs Ab signify immunization through infection or vaccination.

- Anti-HBc Ab *signify a subject having undergone the disease*. Anti-HBc Ab occur in the serum of patients with chronic infection (anti-HBc IgG) or are acute infection of viral replication markers (anti-HBc IgM).

- HBeAg (replication antigen) *signifies the replication phase of the infection*. It can be detected in about 25% of patients with chronic B hepatitis. Its presence signifies *wild virus infection*.

- Anti-HBe Ab *occur at the time of HBeAg/anti-HBe seroconversion* and indicate reduced viral replication in subjects with chronic infection, with the improvement of clinical prognosis.

The presence of anti-HBe and *HBV DNA* in HBeAg negative patients is found in patients with pre-Core mutant HBV.

- HBV DNA *is the most sensitive marker of viral replication.*

Its quantitative measurement allows to evaluate the progressiveness of chronic hepatitis B and antiviral treatment response. The most sensitive tests for detecting HBV DNA are PCR techniques.

- Anti-HBs Ab – signify the healing of hepatitis B or vaccination against hepatitis B.

The first element to be searched for in chronic hepatitis is HBsAg. If positive, it will be established whether the virus is wild or mutant (HBeAg or Anti-Hbe) and viral replication (HBV DNA) will be determined. If HBsAg is present, HBeAg is positive (***wild virus***) or HBeAg is negative, HBV DNA is positive (***pre-core mutant virus***), active viral replication represents a potential evolution of chronic hepatitis.

The clinical picture of hepatitis B virus is most frequently effaced. In most chronic patients, the disease is detected incidentally, when on the occasion of routine biological investigations, increased transaminases are found. An occasional clinical examination can detect hepatomegaly or possibly, splenomegaly. The majority of the patients are completely asymptomatic or may complain of asthenia, adynamia, decreased work capacity. Jaundice or subjaundice episodes occur more rarely, usually in more advanced stages of the disease.

Patient *anamnesis* may only quite rarely reveal a history of acute jaundice-causing hepatitis with HBsAg, but other events with infectious potential may be discovered: injections, vaccinations, tattoos, small or large surgery, etc. If the discovery is made in childhood, the problem of vertical maternal-fetal transmission may be posed.

The *clinical examination* of a patient with chronic hepatitis can detect hepatomegaly and sometimes splenomegaly. Liver consistency is moderately increased, which is different from the firm consistency found in liver cirrhosis. Jaundice or subjaundice is less common.

The biological picture can be more or less changed. Thus, there are chronic hepatitis cases with a minimally changed biological picture, while others (usually active forms) show obvious changes.

The hepatocytolytic syndrome translates into GPT, GOT (ALAT, ASAT) transaminases that are increased several times (in general 2-3xN), but there are also chronic hepatitis cases with quasi-normal transaminases.

Inflammatory syndrome. There is a certain correlation between their levels and the biological activity of the disease.

Impaired liver synthesis syndrome (decrease of QI, QT, albuminemia) is little changed.

Biliary-excretory syndrome, with the increase of bilirubin, is uncommon.

The required hepatic viral markers are HBsAg, as an expression of B virus, as well as replication markers HBV DNA, HBeAg (or non-replication markers – anti-HBe).

The investigation of D (delta) virus in the presence of B virus is compulsory, given the association of the two (D virus is a defective virus, which cannot exist in the absence of *B virus infection*).

Chronic B virus hepatitis can have ***two forms***:

- **the "e" positive form** (positive HBeAg = wild virus)
- **the "e" negative form** (negative HBeAg, replicative HBV DNA = pre-core mutant virus).

Lately, the mutant virus form of chronic hepatitis has been predominant (in Romania, about 80% of chronic B hepatitis cases are "e" negative).

Hepatitis B virus genotyping: the main genotypes are A, B, C and D. Genotype A has a better response to interferon, while genotype D is associated with a better response to nucleoside analogues. In Romania, genotype D virus is predominant (approx. 80%).

Non-replicative hepatitis B virus carriers: subjects with chronic HBV infection, without hepatic disease, where only HBsAg is present, HBV DNA replication and HBeAg being absent, with persistently normal aminotransferases (and normal values of the other hepatic tests), under the conditions of an asymptomatic evolution, are ***"non-replicative hepatitis B virus carriers"*** (the old term was "healthy hepatitis B virus carrier").

The staging of chronic hepatitis is performed through liver biopsy. This will assess the staging and grading of the disease. The presence of the virus B infection marker is detected by orcein staining, which will confer a "dull glass" appearance to the infected hepatocytes. A staging alternative can be FibroTest/Actitest or FibroScan or ARFI.

Treatment of chronic virus B hepatitis

The general measures for these patients include a lifestyle similar to that of a normal individual. Mild physical activity will not be contraindicated. Prolonged bed rest has not proved to be beneficial. In mild and moderate forms, patients can continue their professional activity, especially in professions without particular physical effort. Alcohol use will be an absolute contraindication because of its synergistic hepatotoxic effect.

Diet is close to that of normal individuals; a sufficient protein, vegetal and fruit intake is recommended. Drug administration will be avoided as much as possible, because of the hepatotoxic effect of many drugs.

"Hepatotropic" drugs do not change the evolution of the disease and have no antiviral effect. The following can be used: Essentiale forte, Liv 52, Lagossa, Endonal, etc.

People in contact with hepatitis B patients (family members) will be *vaccinated* against hepatitis B, with the **Engerix B vaccine**. In adults, 3 Engerix

B doses of 1 ml at 0.1 and 6 months are used, by injection in the deltoid muscle. At the same time, the vaccination of all persons at risk for hepatitis B is compulsory: medical staff, dentists, chronic hemodialysis patients, etc.

Antiviral medication currently represents the basis of therapy in hepatitis B, with ***interferon or nucleoside analogues***. These therapies are indicated in the replicative forms (viremia >2,000 UI/ml or >10,000 copies/ml) of hepatitis B (infecting forms with evolutive potential), with increased transaminase levels. The forms with normal transaminase values usually have a weak or no response to therapy and will not be treated, except when there are important histological lesions.

The main objectives of treatment are the suppression of replication or the elimination of HBV, as well as the reduction or stopping of the necroinflammatory process, through the diminution of pathogenicity and infectivity. The long term goal is to prevent recurrences, to stop evolution towards cirrhosis and progression to hepatocellular carcinoma.

Patients with antiviral treatment indications should meet a number of requirements:

a) virological – positive HBsAg, positive HBeAg/ positive anti-HBe (mutant HBV), positive HBV DNA in the serum;
b) biological – increased ASAT and ALAT;
c) histological – Knodell activity score over 5.

1. Peginterferon (PegIFN-Pegasys) is a retard interferon, which is administered subcutaneously once a week; it has an antiviral as well as immunomodulatory effect. Interferon treatment is contraindicated in non-replicative patients, patients with leuko-thrombocytopenia, mental disorders (severe depression), as well as decompensated cirrhosis.

The administered interferon dose will be: Pegasys 180 micrograms/week, subcutaneously, for 48 weeks (can sometimes be extended to 72 weeks).

The leukocytes and thrombocytes counts will be monitored monthly (interferon may cause leukopenia and thrombocytopenia), and transaminase values will also be monitored monthly. Usually, at 2 months, transaminases can reach high values, through the hepatocytolysis of the infected cells.

The disappearance of HBsAg after treatment occurs only in about 10% of the patients, but in more than half of the cases, “e” seroconversion develops, which is frequently followed in time by the spontaneous disappearance of HBsAg.

Complete therapeutic response involves the disappearance of viral replication markers from the serum and the HBeAg/anti-HBe seroconversion, the normalization of ALAT, ASAT, and the reduction of the Knodell score by at least two points.

In the pre-treatment phase, the following are predictive for a favorable response to interferon: high transaminase levels, low viral replication, a Knodell score higher than 6, absence of HIV co-infection, and an infecting contact with HBV at adult age.

The main adverse reactions of interferon treatment are: pseudo-influenza syndrome (post-injection), leuko- and thrombocytopenia, thyroid involvement (hypothyroidism), depression (even severe, sometimes with suicidal tendencies).

***2. Nucleoside analogues (*lamivudine, adefovir, entecavir and tenofovir)** are used in clinical practice for the treatment of chronic hepatitis B.

Initially, lamivudine was used, but entecavir and tenofovir are currently the drugs of choice since viral resistance doesn't occur during therapy (all four preparations are reimbursed by the Romanian National Health Insurance House). Treatment will be administered for an indefinite time period, and will usually stop viral replication. The cessation of therapy usually leads to the resumption of viral replication.

Entecavir (Baraclude**) or tenofovir** are the therapy of choice in patients in whom we decided to administer oral therapy since patients will seldom develop drug resistance. In patients who have developed lamivudine resistance, adefovir or tenofovir will be added. Analogues treatment is easy (one tablet daily) but for an indefinite duration.

The advantage of interferon is its administration for a definite time period (48 weeks), with important adverse effects; the advantage of nucleoside analogues is an easy way of administration (oral), with minimum adverse effects, but the duration of administration is very long (life-long).

Current therapy in chronic hepatitis B has somewhat disappointing results, because it can induce seroconversion and transaminase normalization, but the disappearance of HBsAg occurs only in approx. 10% of the treated cases. Hopefully, better results will be achieved in the future, either through drug associations or through the introduction of new therapies.

II. Chronic hepatitis B associated with D virus

HDV superinfects 5-10% of the carriers of a chronic HBV infection in our geographical area.

Epidemiology

The prevalence of HDV infection varies depending on the geographical region. Thus, low endemic areas (less than 10%) include USA, northern European countries and the Far East, moderate endemic areas (10-30%) include the Mediterranean Basin, the Middle East and Asia, hyperendemic areas are

Africa, South America. In Romania, about 25% of the patients with B virus are also infected with D virus (in Timișoara approx. 10%).

HDV is transmitted from persons infected with this virus, which represent the infection source. The transmission route is similar to that of HBV, i.e. parenteral/through blood or sexual.

Pathogenesis

Hepatitis D virus is a small size virus.

HDV is a cytopathogenic virus, being present only in subjects infected with HBV, its presence being required for HDV replication. In active replication/acute infection phases, it can inhibit HBV replication, with the serological absence of HBsAg through a hepatic interferon synthesis stimulation mechanism.

HDV is a defective virus, which either infects the host concomitantly with HBV (*co-infection*) or occurs in a HBV carrier (*superinfection*).

HDV superinfection aggravates the evolution of hepatitis B or cirrhosis of this etiology and leads to the chronicization of HDV infection in 75% of the cases. Cirrhogenic evolution in the chronic infection form is rapidly progressive (2-10 years). In a similar percentage (15%), death through liver failure after 1-2 years or disease remission occurs.

HDV superinfection is suggested by the occurrence of an acute episode with jaundice on the background of chronic B hepatitis, which has no signs of activity and whose subsequent evolution is severe. In chronic HBsAg carriers, without hepatic disease, it manifests as an acute hepatitis episode.

Clinical picture

Clinically, it has no particular signs that might differentiate it from chronic viral hepatitis of other etiology.

Diagnosis

Serological markers

The diagnosis of superinfection is based on the de novo serum appearance of antiHD antibodies in a known patient with HBsAg +.

Coinfection is diagnosed by detecting de novo of both HBsAg as well as IgM-type antiHD antibodies in the serum.

Functional hepatic tests

Their change reflects the degree of hepatic involvement, without indicating a specific etiology.

Hepatic histology

The aggressiveness of hepatocytic necrosis is striking, with bridging and spotty necrosis, multilobular involvement. Using special techniques, the presence of HDAg can be evidenced in hepatocytes.

Treatment

This type of hepatitis has poorer therapeutic results with **interferon (IFN).**

The preparations are Intron A (Merck) or Roferon (Roche). The IFN doses used are large, 3 x 10 MU/week for 1 year, but the rate of disappearance of HBsAG remains low (and the disappearance of HDV RNA very low, max. 25%). However, therapy is useful, as it can stop or slow the evolution of chronic hepatitis.

Currently, D virus hepatitis is also treated with **pegylated interferon (PEG-IFN)**, which seems to improve therapeutic results.

Peginterferon doses are: Pegasys 180 micrograms/week or PegIntron 1.5 micrograms/kg body weight/week administered for one year.

The disappearance of HDVAg occurs in approx. 25-40% of the treated cases.

III. Chronic C virus hepatitis

Chronic C virus hepatitis is a health problem known as such since 1990, when this virus was discovered. Before this date, the concept of non-A or non-B hepatitis was known. It is an important problem, because chronic hepatitis cases due to transfusions performed before this virus was known and tested are now detected. After acute C virus hepatitis (most frequently anicteric and consequently frequently undiagnosed), the rate of chronicity is very high, up to 70-80%. The natural evolution towards liver cirrhosis occurs in approx. 20-30% of the cases.

Epidemiology. It is estimated that 170 million people are infected with HCV worldwide, with a prevalence of 3%. In Romania, a recent study has demonstrated a 3.5% prevalence.

Transmission of HCV

Persons infected with HCV represent the source of infection with this virus, no matter if they have or not hepatic disease manifestations. Parenteral transmission is the main cause of infection, through transfusion with anti-HCV unscreened blood or the use of injectable drugs. The introduction of the screening of transfusion blood has considerably reduced this risk; prior to 1990, the incidence of posttransfusion hepatitis C reached 90-95% of the cases.

Injectable drug users are infected with HCV in a proportion of 50-80%, similarly to hemophilic subjects (60-80%). Other parenteral transmission routes of HCV include organ transplantation, hemodialysis, nosocomial infections (non-sterilized instruments) with a very low frequency, as well as occupational exposure (in general surgery, orthopedic surgery, dentistry).

Non-parenteral transmission occurs by two routes: sexual (which has a low frequency and seems to be facilitated by HIV co-infection) and vertical transmission. This occurs from mother to newborn, with a frequency of 3-6% or 10-17%, depending on the absence or presence of HIV co-infection in the mother. Non-sexual intrafamilial transmission (3-10%) occurs particularly under the conditions of high viremia. In 30-40% of the cases, the HCV transmission route cannot be demonstrated.

The source of infection is represented by sick persons. Despite accurate anamnesis, in approximately 30-40% of the cases, no potentially infecting source can be detected, which is why other possible transmission routes of the infection are investigated.

The population receptivity to infection is general, given that there is no hepatitis C vaccination. Regarding the prevalence of C virus infection in the population, Romanian epidemiological studies have shown a 3.2% prevalence in the population.

Pathogenesis

Hepatitis C virus is an RNA virus related to viruses of the Flaviviridae and Pestiviridae families, which is formed by an external lipid envelope and a nucleocapsid containing HCV RNA. It has a high genetic variability; there are at least six genotypes, with different geographical distributions and clinical implications. This explains the difficulty of developing vaccines, the response after interferon therapy, the sometimes severe evolution of hepatic disease, the increased frequency of chronic HCV infection, all of which are found particularly in genotype Ib.

HCV is a cytopathogenic virus that induces hepatocytic lesions through direct toxic viral action and through an immune mediated mechanism. Cell mediated immunity, through a specific antigen dependent mechanism, a non-specific mechanism, respectively, is mainly involved. The failure to eliminate HCV leads to the progress of lesions in chronic hepatitis and subsequently, to liver cirrhosis.

Natural history of HCV infection

Usually, an acute HCV infection episode has a subclinical evolution, jaundice being present in only 10% of the cases. The aspect of acute fulminant hepatitis is rarely found, but the disease takes a severe acute form when infection is superimposed on an unknown chronic hepatic disease, when a HBV-HCV co-infection occurs, or in liver transplant receivers. Evolution is marked by a high proportion of chronicization of liver disease (70-80%) and by the development of cirrhosis (20%) after a mean time period of three decades. Hepatocellular carcinoma (3-4%) and cirrhosis explain the great majority of deaths in patients with posttransfusion hepatitis of this etiology. The slow development of progressive liver disease with a severe outcome is characteristic,

and an important number of subjects with non-progressive infection or slightly progressive chronic hepatic disease remain unknown.

Negative prognostic factors regarding the rapid progression of the disease are: genotype Ib, a high level of viremia and the degree of genetic diversity of the virus (quasispecies), transfusion transmission of HCV, immunodeficiency, HBV or HIV co-infection, alcohol abuse.

In Romania, the prevalence of genotype 1 is about 99% (approx. 95% genotype 1b and 4% genotype 1a, respectively).

The development of cirrhosis is favored by: age over 40 years, daily alcohol consumption of at least 50 g, male sex, transfusion-associated infection, HBV and HIV co-infection. If in compensated cirrhosis, the 5-year survival rate is 90%, the proportion decreases to 50% at 5 years from decompensation.

The clinical picture of chronic C virus hepatitis is most frequently absent or effaced. A quite characteristic sign is persistent asthenia unjustified by the amount of physical or intellectual effort performed, fatigability, inappetence, myalgia, pain in the right hypochondrium. Sometimes, a non-systemic dyspeptic syndrome can be present. All these manifestations indicate a certain severity of the disease, specific hepatic manifestations (jaundice, hepatosplenomegaly) occurring at an advanced stage of the disease.

Sometimes, ***extrahepatic manifestations*** can be present in this chronic hepatitis, which are considered to be the expression of immune disorders: thrombocytopenic purpura, arthralgia, nodular polyarteritis, mixed cryoglobulinemia, Sjogren syndrome, autoimmune thyroiditis, membrane glomerulonephritis, autoimmune hepatitis and various cutaneous manifestations such as lichen planus, sialadenitis, corneal ulcerations.

Other associations of HCV with: hepatocellular carcinoma (50-75% of hepatocellular carcinomas are HCV positive), HBV co-infection (5-10%).

The biological evaluation required in the presence of a suspicion of chronic hepatitis is represented by biological hepatic investigation (targeted on the 4 syndromes described for hepatitis B) and the determination of etiology. It should be noted that in hepatitis C, transaminase values can vary in time (which does not necessarily indicate a change in the disease evolution), and that there are many cases of chronic hepatitis C with normal or quasi-normal transaminase values (GOT, GPT).

To establish etiology, anti-HCV antibodies are routinely used (third generation ELISA techniques with a sensitivity ~ 97%). Current tests allow to detect seroconversion, with the occurrence of these antibodies at two weeks from the time of infection. Current techniques do not allow for anti-HCV detection within two weeks from this time moment (serological window), hence the risk of false negative reactions, including in immunosuppressed patients. Subjects suspected of HCV infection initially require third generation ELISA

testing. The presence of anti-HCV antibodies signifies hepatitis C disease, without being indicative of healing. But the presence of anti-HCV antibodies along with changed transaminase values usually signifies an active infection. In case of doubt, it is recommended to determine viremia.

The determination of viremia is performed by HCV RNA PCR. This will also quantify the level of viremia, which is generally required for therapy. For the evaluation of extrahepatic lesions, the following will be determined: cryoglobulins (for the diagnosis of cryoglobulinemia), proteinuria, the Addis sediment, creatinine clearance (for glomerulonephritis).

The association between chronic hepatitis C and autoimmune hepatitis is not rare, which is why ANA, LKM1 and SMA will also be determined.

The morphological evaluation of chronic hepatitis is performed by LBP, allowing for disease staging and therapeutic decision. The presence of lobular lesions, as well as the presence of steatosis (even in the absence of alcoholism) is somewhat typical for C virus hepatitis.

Chronic hepatic involvement is characterized by the presence of lymphoid follicles in the portal space, the involvement of bile ducts, the development of steatotic lesions of Mallory bodies, along with a necroinflammatory portal, periportal or lobular process and the immunohistochemical detection of HCV RNA in the infected hepatocytes. The degree of fibrosis indicates the severity of this involvement and cirrhogenic evolution.

Non-invasive evaluation by FibroTest or FibroScan (or ARFI) can be chosen.

HCV genotyping can provide information about the severity of liver disease and the potential response to antiviral treatment (genotype 1 – the most difficult to treat). In Romania, almost all patients are infected with genotype 1, about 99%.

Diagnosis is made based on the clinical picture (when available), on biological and particularly etiological examination, on histological grading. The association with B virus infection as well as with autoimmune hepatitis is possible.

The evolution of the disease is long lasting, the average time period from infection to cirrhosis is about 15-20 years, frequently even longer.

Possible ***complications*** are evolution towards liver cirrhosis (quite frequent) and hepatocarcinoma (most frequently on the background of cirrhosis), as well as the presence of purpura, glomerulonephritis evolving towards chronic renal failure, or other autoimmune diseases (thyroid, cutaneous, etc.).

The ***treatment*** of chronic C virus hepatitis includes general measures and medication.

General measures are similar to those for hepatitis B.

Drug therapy: Currently, there are 2 types of treatment against HCV hepatitis. The oldest one, used for more than 15 years is *Interferon based*, and the other one is an all-oral treatment, without Interferon: "*Interferon free*".

Interferon based therapy, the classic treatment, has been used for more than 15 years and associates **peginterferon** (subcutaneously) **and ribavirin** (orally). The aim of treatment is to eradicate HCV, which is expressed by sustained virological response, SVR (12 weeks after the cessation of treatment): normalization of aminotransferase values and HCV RNA negative (negative PCR), with the improvement of the histological picture. Classically, this therapy is indicated in active disease, with fibrosis greater than or equal to 1, with increased or normal transaminase values, in the absence of decompensated cirrhosis and in cases with present viremia (positive HCV RNA by PCR).

There are several parameters that predict a good response to IFN therapy: young age, female sex, recent disease onset, low viremia level, absence of cirrhosis, absence of severe histological lesions, absence of cholestasis, infection with a different genotype than Ib, low iron concentration in the liver, absence of obesity, and more recently, genetic structure of IL28B (interleukin IL). In this algorithm, the greater the number of "good" parameters, the better the chance of a good therapeutic response is.

Peginterferon is a pegylated interferon, which enables its slow degradation and elimination and consequently, the maintenance of high plasma levels even under the conditions of its weekly administration. *The treatment scheme is peginterferon + ribavirin for 48 weeks in genotype 1b.*

The available peginterferon preparations are PegIntron 1.5 micrograms/kg body weight/week and Pegasys 180 micrograms/week (regardless of body weight). Virological response can be evaluated at 3 months, when viremia decreases in responsive subjects to undetectable levels or more than 100 times compared to initial values. In the case of no virological response at 3 months, therapy is stopped.

Ribavirin is administered orally, in a dose of 1000-1200 mg/day (5 or 6 tablets/day): 1000 mg/day in patients with a weight of less than 70 kg, and 1200 mg/day in those weighing more than 70 kg.

Adverse effects of IFN have been described in hepatitis B, and ribavirin can induce moderate hemolytic anemia (the hemogram and reticulocytes will be monitored monthly).

Response rates following PegInterferon and Ribavirin are approximately 50%. Therapeutic efficiency increases if a second generation protease inhibitor (Simeprevir) is added to the treatment.

Interferon free treatment has been introduced in the international market for approximately 2 years. There are several antiviral drugs (protease inhibitors, polymerase inhibitors, etc) with synergic action, preventing viral replication, acquiring a sustained virologic treatment after only ***12 weeks of treatment***. Among the first such drugs are Sofosbuvir, Ledispavir, Simeprevir etc. The number of these direct antiviral drugs is increasing while their exorbitant price is decreasing.

Due to the increased efficacy of interferon-free therapy (sustained response rates above 95%), lack of side effects, HCV chronic hepatitis interferon treatment was almost abandoned.

Starting with 2015, in Romania, the National Health Insurance System fully covers the cost of treatment for HCV with Viekirax / Exviera in the form of tablets (combination of Ombitasvir, Partiaprevir, Ritonavir and Dasabuvir - 4 tb/day), and from 2018 with two more regimens, Harvoni (combination of Sofosbuvir and Ledipasvir - 1 tb/day) and Zepatier (combination of Elbasvir and Grazoprevir - 1tb/day). The rate of sustained virological response (SVR) to interferon free therapy is very high, over 95% (slightly less possibly in case of liver cirrhosis).

In addition to these three medications, the next generation of pangenotypic antiviral medication is also available. This is represented by the combination of Sofosbuvir + Veltapasvir + Voxilaprevir, and Glecaprevir + Pibrentasvir. They are recommended in cases of hepatitis HCV genotype non 1, currently rare in our country.

2. AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is an immune disease that predominantly occurs in the female gender and is characterized by chronic liver injury and immune systemic manifestations.

Autoimmune hepatitis (AIH) is a relatively rare disease; the fact that it is not sufficiently investigated and that diagnostic methods (determination of antibodies) are relatively expensive also contributes to its rare nature.

In general, AIH is detected in a patient with chronic hepatic disease, usually with marked hypergammaglobulinemia, fever, arthralgia, in whom viral markers are negative. In these cases, immunological markers (ANA, LKM 1 and SMA) are positive.

Etiopathogenesis

Due to a genetic predisposition or to an exogenous factor, a loss of immune tolerance to liver tissue occurs, which transforms it from self to non-self. Of exogenous factors, hepatitis C virus frequently triggers autoimmune hepatitis, while hepatitis B is more rarely the cause.

Some drugs can transform self to non-self (oxyphenisatine, alpha-methyldopa). The target of immune response is a liver-specific membrane protein (LSP) which, through a certain mechanism (viral, drug toxic mechanism), undergoes denaturation, becomes non-self, generates antibodies and antibody-dependent cytotoxicity develops.

The clinical picture is generally richer than in chronic viral hepatitis, but symptoms can sometimes be almost absent. Onset usually occurs in young women, or after the age of 40 years, with asthenia, fatigability, fever, arthralgia. Immune manifestations can be varied, including: thyroiditis, amenorrhea, autoimmune hemolytic anemia, chronic glomerulonephritis, rheumatoid polyarthritis, thrombocytopenic purpura, etc.

Biological picture

Altered liver biology translates into an increase of transaminases (GOT, GPT), usually to values 3-50 x the normal values (the highest transaminase values in chronic hepatitis, which are frequently indicative of autoimmune hepatitis). The other liver tests: QI, serum bilirubin, albumin are variably

changed. Marked hypergammaglobulinemia will be almost always present, as an expression of immune manifestations (usually higher than 30-35%).

Immune changes specific for AIH are the presence of some autoantibodies.

The following will be most frequently determined:
- ANA (antinuclear antibodies) in a titer higher than 1/40
- SMA (smooth muscle antibodies)
- anti-LKM 1 (anti-liver kidney microsomal antibodies)
- anti-LSP (anti-liver-specific protein antibodies).

Histological examination, obtained by liver biopsy, reveals severe piecemeal and bridging necrosis. Interface hepatitis is typical for autoimmune hepatitis.

Positive diagnosis is made based on the clinical signs of chronic hepatitis, with immune systemic manifestations (other autoimmune diseases), based on a biological picture with obviously increased cytolysis, with hypergammaglobulinemia, without the presence of hepatic viral markers, but with the presence of autoantibodies (ANA, SMA, anti-LKM1).

Autoimmune hepatitis is subdivided into several types, depending on the present autoantibodies:
- **AIH type 1**: characterized by the presence of ANA and SMA; it represents the great majority of AIH (approx.70%). It usually develops in women aged around 40 years. It is frequently associated with other autoimmune disorders. It often evolves towards cirrhosis (about 50% of the cases, if left untreated).
- **AIH type 2**: characterized by the presence of anti-LKM1 in the serum. It occurs in both sexes, frequently during childhood. Hypergammaglobulinemia is extremely high. This type is frequently associated with C virus infection, and evolution towards cirrhosis may occur in up to 80% of the cases.
- **AIH type 3**: extremely rare. It is characterized by the presence of anti-LSP.

As it can be seen, the diagnostic classification (both as AIH and AIH type) requires an accurate, complex, as well as expensive biological evaluation. At the same time, failure to determine all these immune markers can lead to non-diagnosis and in time, to evolution towards cirrhosis.

The differential diagnosis of AIH should be made with:
- *chronic viral hepatitis* (where viral markers are positive); attention should be paid to the coexistence of C virus hepatitis infection and AIH.

- *chronic drug hepatitis* – where anamnesis may not always be relevant; the most frequently incriminated can be isoniazid – in patients with TB, alpha-methyldopa, oxyphenisatine – in some laxatives (but currently no longer in use).
- *Wilson's disease* – ceruloplasmin deficiency, frequently discovered only in the cirrhotic phase, where the Kayser-Fleischer corneal ring and neurological signs also occur. The determination of serum ceruloplasmin, cupremia and cupruria will make diagnosis.
- *alpha-1 antitrypsin deficiency* can lead to chronic hepatopathy. Diagnosis is made by the measurement of alpha-1 antitrypsin, which will be low or absent.
- *chronic alcoholic liver disease* – is relatively frequent and has a wide histological spectrum ranging from acute alcoholic hepatitis to steatosis, steatofibrosis and liver cirrhosis. A history of alcohol consumption, increased gamma-glutamyl transpeptidase values can be useful for diagnosis. Alcohol consumption is not always recognized by the patient, which makes etiological diagnosis difficult.
- *primary biliary cirrhosis (PBC)* is clinically characterized by chronic intense pruritus; biologically, marked cholestasis is present, with an expressed increase of gamma-glutamyl transpeptidase, alkaline phosphatase and bilirubin, as well as the appearance of antimitochondrial antibodies (AMA). In the initial phases of the disease, diagnosis can be difficult. In the presence of chronic cholestasis, primary biliary cirrhosis should be differentiated from
- *sclerosing cholangitis,* with the presence of fever, absence of AMA, where cholangio-MRI or ERCP evidences a marked poverty of the intrahepatic biliary tree (or a moniliform appearance of the biliary tree, with biliary stenoses and dilations).

The treatment of AIH is based on **immunosuppressive** medication.

The main medication is **corticotherapy** (which is associated with azathioprine – Imuran). Initially, prednisone 30-40 mg/day plus azathioprine 2-3 mg/kg body weight are administered, until remission is obtained. An alternative to prednisone therapy is budesonide. Subsequently, the prednisone dose can be removed, while maintaining the same azathioprine dose for a long time (years or the entire life).

Prednisone monotherapy is preferred in the case of cytopenia, thiopurine methyl transferase deficiency.

The presence of recurrences after the cessation of treatment requires the resumption of therapy. Many patients with AIH must be treated throughout their life, because only a small proportion of patients remain in remission in the absence of therapy.

For patients with an insufficient response, the use of cyclosporin, ursodeoxycholic acid, 6-mercaptopurine, methotrexate, cyclophosphamide or mycophenolate mofetil can be indicated.

Side effects of prednisone – osteoporosis, aseptic bone necrosis, type 2 diabetes mellitus, cataract, arterial hypertension, infections, psychosis, Cushing like facies, acne, obesity.

Side effects of azathioprine – cholestatic hepatitis, veno-occlusive disease, acute pancreatitis, severe emetic syndrome, rash, bone marrow suppression.

3. NON-ALCOHOLIC STEATOHEPATITIS

Non-alcoholic steatohepatitis (NASH) is a condition characterized by the presence of an ***association of steatosis with inflammation and fibrosis***, which occurs in subjects who do not use alcohol.

Histological lesions are very similar to those of **alcoholic steatohepatitis (ASH)**.

Etiological factors of NASH

The etiological factors incriminated in NASH are:

- ***obesity***;
- ***diabetes mellitus;***
- ***hypertriglyceridemia;***
- jejunoileal bypass for morbid obesity;
- prolonged total parenteral nutrition;
- some drugs (amiodarone, diltiazem, tamoxifen);
- occupational exposure to solvents.

In daily practice, the factors frequently associated with NASH are obesity, diabetes mellitus, and hypertriglyceridemia.

Obesity is one of the main disorders of the modern world; in some countries such as USA, up to 25% of the population is obese. A BMI (body mass index) >30 kg/m2 predisposes to the development of NASH. The greater the obesity, the higher the frequency of NASH is. At the same time, not all patients with NASH are obese; some of them are normal weight and have other steatohepatitis-inducing causes (such as dyslipidemia, diabetes mellitus, etc). In the Banat region, about 25% of adults are overweight.

Non-insulin-dependent diabetes mellitus is frequently associated with obesity and hypertriglyceridemia, which are NASH-generating causes.

Pathogenesis of non-alcoholic steatohepatitis

The first stage is that of an increased fatty acid uptake in hepatocytes (due to the causes described in the etiology section), associated with an increase of insulin resistance (even in non-diabetic patients). As a consequence of this increased fat uptake, hepatic steatosis develops in hepatocytes (fatty liver disease) and mitochondrial beta-oxidation increases, with the appearance of free radicals. These free radicals in hepatocytes induce cell membrane injury and cell death, along with inflammatory lesions and fibrosis (steatohepatitis)

Histological aspect

Histological lesions in NASH are very similar to those of ASH (alcoholic steatohepatitis or alcoholic liver disease) and are represented by *macrovesicular steatosis*, along with inflammatory phenomena (*steatohepatitis*), with the presence of Mallory bodies, predominantly lobular inflammation and perisinusoidal fibrosis. In advanced disease forms, *bridging necrosis* develops and finally, liver cirrhosis occurs.

Clinical picture

Patients with NASH are most frequently asymptomatic, and the disease is detected incidentally, on the occasion of a medical examination. In some cases, patients with NASH can have asthenia, pain (discomfort) in the right hypochondrium, and in case of advanced disease with the development of liver cirrhosis, typical signs of cirrhosis such as jaundice or ascites.

However, it should be mentioned that most frequently, patients with NASH are completely asymptomatic, and the disease is discovered incidentally (increased aminotransferases discovered during an occasional testing).

Clinical examination often reveals an obese patient, sometimes with known diabetes mellitus or dyslipidemia, with an enlarged liver of a higher consistency on palpation. The spleen is more rarely enlarged, generally in the case of advanced disease.

Paraclinical examinations

Laboratory exams that can be changed are, besides glycemia relevant for diabetes mellitus or hypertriglyceridemia, *increased transaminase* levels. Transaminases, as an expression of a hepatocytic disorder, are slightly to moderately increased (1.5 to 3 times the normal values). In general, GPT (ALT) increase is higher than GOT (AST) increase. Sometimes, a slight increase of alkaline phosphatase may occur. The absence of gamma-glutamyl transpeptidase differentiates NASH from ASH (alcoholic steatohepatitis).

Liver ultrasound is the easiest imaging method that can diagnose fatty liver loading, with a quite good reliability (approximately 70-80%). The typical ultrasonographic appearance of steatotic liver is hyperechogenic (“bright liver”), with posterior attenuation. In the case of advanced NASH with the development of liver cirrhosis, ultrasound can demonstrate the presence of typical signs of this disease such as: ascites, hepatic heterogeneity, splenomegaly, signs of portal hypertension, caudate lobe hypertrophy.

Computed tomography can semi-quantitatively estimate liver fat content, but it is a relatively expensive method for this estimation, so that ultrasound remains the most widely used method in clinical practice.

Liver biopsy is the gold standard method that allows the accurate staging of a patient with NASH. However, the routine use of liver biopsy in patients with NASH is debatable, because of the high frequency of this disease, of the relatively good prognosis of these patients, and of the fact that the biopsy result does not change therapy. It can be useful for the exact staging of the disease and prognosis (absence or presence of fibrosis and particularly, of cirrhosis).

A serologic test - ***FibroMax*** can assess steatosis, activity, and fibrosis. It also evaluates the alcoholic and nonalcoholic components of the disease, but it is expensive and performed only in dedicated laboratories.

FibroScan (Transient Elastography) is useful for fibrosis assessment and thus for prognosis assessment in NASH and is routinely used for this purpose. If the FibroScan device also has the CAP (controlled attenuation parameter) module, an objective quantification of steatosis can be made.

The treatment of non-alcoholic steatohepatitis includes a diet and a drug component.

Diet in patients with obesity will be compulsory, weight loss being the objective in this first stage of therapy. Weight loss should be progressive, and physical exercise is indispensable (both improve insulin resistance). In obese patients, reaching an ideal weight will frequently solve liver disease. In diabetic patients, a long-term strict glycemic control is extremely important. In the case of hypertriglyceridemia (with or without hypercholesterolemia), a diet poor in saturated fats is compulsory.

Drug treatment includes several drugs that can be used:

- metformin (Meguan) decreases insulin resistance (it is administered even in non-diabetic patients);
- vitamin E (as an antioxidant), 800 mg/day
- ursodeoxycholic acid (Ursofalk) is administered in a dose of 10-15 mg/kg body weight/day;
- glitazones (pioglitazone, rosiglitazone).

None of the drugs described above has clearly proved its efficiency in NASH (with the possible exception of vitamin E). Drug treatment alone for NASH, in the absence of treatment for the causal factor (obesity, dyslipidemia), will not lead to the improvement of hepatic function, so diet is indispensable.

The prognosis of NASH is good in the case of hepatic steatosis or mild steatohepatitis lesions, while in the case of hepatic fibrosis or particularly, hepatic cirrhosis, this is more reserved. Progressive weight loss (up to the ideal weight), along with physical exercise, control of diabetes and hypertriglyceridemia, are the solutions required for the improvement of this hepatic disease.

The evolution of non-alcoholic steatohepatitis depends in the first place on its generating factors, on their importance (severity of obesity), as well as on the treatment of the generating causes (weight loss, control of diabetes or hypertriglyceridemia). The development of fibrotic lesions makes hepatic histology more difficult to reverse.

4. ALCOHOLIC LIVER DISEASE

Definition

Alcoholic liver disease is represented by all non-specific pathomorphological lesions associated with clinico-paraclinical manifestations, of which some are characteristic, being induced by alcohol abuse.

The prevalence of alcoholic liver disease varies significantly depending on the country, being influenced by specific traditions, religion, and especially by the ratio between the price of alcoholic beverages and the population's income (the cheaper the beverages, the lower the affected social levels are). The current tendency is an increase in the prevalence of the disease, which is lower in France and USA, where the government's anti-alcohol use campaigns have been successful.

Etiology

Excessive alcohol consumption has varied effects on the organism. For reasons that are not yet known, 1/3 of chronic alcohol users have no hepatic consequences. The others develop fatty liver, alcoholic hepatitis or cirrhosis, as well as chronic pancreatitis, dilated cardiomyopathy or neuropsychiatric disorders. There are several **risk factors** for liver involvement in alcoholics:

1. ***Duration and alcohol dose.*** An alcohol dose of 60-80 ml absolute alcohol/day for men and 40-50 ml/day for women is considered as toxic. The duration of consumption is also important, which should be longer than 5 years for a risk to exist. Continuous consumption is more dangerous than intermittent consumption. Also, liver damage does not depend on the type of beverage, but on its alcohol content.

Women are much more susceptible than men.

2. ***Gender.*** For the same ingested alcohol amount, higher blood concentrations are reached in women, gastric metabolization is lower and cytochrome P450 is less effective in women.

3. ***Genetic factors.*** Although a unique genetic marker clearly associated with susceptibility to alcoholism has not been evidenced, it seems that alcohol-related behavioral models are inherited.

4. ***Hepatitis (B or C) virus coinfection***. The coexistence of B or C virus infection increases the severity of alcoholic liver disease.

5. ***Nutritional factor***. Protein-calorie malnutrition precedes alcoholism in patients with a low socio-economic level, accelerating the development of alcoholic liver disease. It has been demonstrated that a balanced diet can protect alcohol users, at least for a time period.

Pathogenesis of alcoholic liver disease

Alcohol is metabolized in the liver by three pathways, the result being the same, acetaldehyde – a metabolite with a high hepatotoxicity. The three pathways are:

1. The alcohol dehydrogenase (ADH) pathway, the main alcohol metabolization pathway
2. The microsomal oxidation system pathway – cytochrome P450 plays a role in alcohol oxidation when alcohol concentration increases to more than 50 mg/dl.
3. The catalase pathway, which plays a secondary role.

Acetaldehyde is subsequently oxidized to acetate, but in alcoholics, there is a progressive reduction in the capacity of mitochondria to oxidize acetaldehyde, whose accumulation leads to the promotion of lipid peroxidation and to the formation of protein complexes. In addition to the toxic effects of acetaldehyde, the cirrhogenic role of alcohol should not be neglected. It has been demonstrated that Ito cells (adipocytes) involved in fibrogenesis are activated after chronic alcohol consumption.

Pathomorphological aspects in alcoholic liver disease

There are three forms of hepatic histological lesions in alcohol consumers, which are major histological stages:

1. Alcoholic fatty liver is a reversible benign form induced by the accumulation of large lipid droplets in hepatocytes.

2. Alcoholic hepatitis includes vacuolization degeneration and hepatocytic necrosis, acute neutrophilic infiltrates, sometimes pericellular fibrosis, sinusoidal line and venular line, as well as characteristic Mallory bodies (alcoholic hyaline). Alcoholic hepatitis can be reversible, but it is a much more severe lesion, being the most important precursor of cirrhosis.

3. Alcoholic cirrhosis comprises fibrosis throughout the liver tissue, from the portal space to the centrolobular veins, and regeneration nodules.

In what follows, the three clinico-histological forms of alcoholic liver disease will be described, of which cirrhosis will be discussed in a separate chapter.

1. Alcoholic fatty liver (alcoholic liver steatosis) ALS

The lipids that accumulate in alcoholic fatty liver can be derived from several sources: diet, adipose tissue, de novo hepatic synthesis in carbohydrates.

The predominant source depends on chronic or acute alcohol consumption, the lipid content of diet. In alcoholics, the majority of lipids in the liver are derived from diet and from the altered oxidation of fatty acids. The accumulation of lipids during chronic alcohol consumption is not an endless process, redox state changes throughout the liver diminish during the course of chronic alcohol consumption.

Pathomorphologically, steatosis is the presence of lipids in more than 5% of hepatocytes. Macroscopically, the liver is enlarged, firm, of a yellowish color. Microscopically, increased lipid storage is seen, and intrahepatic cholestasis can subsequently appear.

Clinically, there is asymptomatic hepatomegaly and sometimes chronic liver disease stigmata such as: Dupuytren contracture, testicular atrophy, palmar erythema, vascular stars and gynecomastia. Subsequently, the following may occur: physical asthenia, cachexia, fever, anorexia, nausea, vomiting, jaundice, painful hepatomegaly, splenomegaly and ascites. Alcoholic hepatitis is associated with the majority of these. Another complication of alcoholic fatty liver is **Zieve syndrome**, which consists of hyperlipemia, hemolytic anemia, jaundice and abdominal pain.

Paraclinically, there is an increase in transaminases, with an AST/ALT ratio higher than or equal to 2 in more than 80% of the cases, an increase of gamma-GPT. Positive diagnosis is histological, steatosis being evidenced by ultrasound.

A particular form is focal steatosis, which raises problems of differential diagnosis with a tumor formation.

Evolution and prognosis are benign if alcohol consumption is stopped. The complications that may occur in patients with ethanol steatosis are sudden death by fat embolism, alcohol withdrawal or hypoglycemia.

Treatment involves stopping ethanol consumption in the first place, the correction of possible malnutrition, and the so-called hepatoprotective drugs (mainly silymarin and vitamin B complexes), whose efficiency is questionable.

2. Alcoholic hepatitis

Unlike alcoholic steatosis, in alcoholic hepatitis (AH), necrosis, inflammation and fibrosis are present. The most important aspect is the predominance of damage in the perivenular area. Hepatocyte ballooning, oxidative stress on the liver by an increase in the rate of generation of oxygen free radicals, and consecutive lipid peroxidation occur. Free radicals are toxic through their reactions on lipids. Another effect of chronic alcohol consumption is microsomal enzyme induction that can amplify the hepatic toxicity of other

agents such as drugs but also, of carbon tetrachloride, anesthetics, cocaine and nitrosamines.

Lesions are pathomorphologically more severe than in steatosis, AH being a precursor of cirrhosis, but not all alcoholic cirrhoses pass through the stage of AH. The most important lesions in AH are ballooning (vacuolization) degeneration, neutrophilic inflammatory infiltrate and Mallory bodies (alcoholic hyaline), Pas-negative eosinophilic material formed by amorphous material, having altered intermediate filaments as a substrate.

The histological diagnosis criteria for AH are: hepatocellular necrosis, alcoholic hyaline and neutrophilic inflammatory infiltrate.

Patients can be clinically asymptomatic, they may have usual manifestations (anorexia, nausea, physical asthenia, fatigability, abdominal pain, jaundice, weight loss, fever), or manifestations due to complications (encephalopathy, UGB, ascites) which rapidly progress towards death.

Clinical examination evidences hepatomegaly, hepatic sensitivity, signs of portal hypertension (splenomegaly, visible umbilical veins, ascites), signs of alcoholism (palmar erythema, ecchymoses, vascular stars, gynecomastia).

Paraclinically, anemia (due to the marrow-toxic effect of alcohol, folic acid and iron deficiencies, altered vitamin B6 metabolism), leukocytosis or leukopenia with thrombocytopenia may be present. Transaminases, gamma-GTP and alkaline phosphatase, are always increased, sometimes bilirubin and the prothrombin time also increase and albumin decreases. Usually, transaminase values do not exceed 300 U/L, and the AST/ALT ratio is approximately 2:1.

The main differential diagnosis is made with NASH (non-alcoholic steatohepatitis), which occurs in diabetes mellitus, obesity, massive small bowel resections, hyperlipidemia or after the consumption of certain drugs.

The evolution of AH can be complicated by some consequences of liver failure such as portal hypertension, which can be reversible after the cessation of alcohol consumption or irreversible when fibrosis evolving into cirrhosis develops.

Ascites is another complication, being massive and difficult to control, and paracentesis is compulsory as part of treatment.

Hepatic encephalopathy is another complication in severe AH forms.

Early mortality in alcoholic hepatitis varies between 20-80%, with a mean of 50%; thus, acute AH is a severe condition. The worst prognosis is that of patients with severe jaundice, encephalopathy, renal failure or gastrointestinal bleeding.

A *useful* ***prognostic score*** is ***Maddrey's formula***, a simple equation used in severe AH. It uses bilirubin (mg%) and the prothrombin time (sec):

[4.6 x (prothrombin time – control)] + serum bilirubin

A score higher than 30 indicates severe AH with a poor prognosis.

Treatment consists of the cessation of alcohol consumption, which is compulsory. Nutritional deficiencies are corrected, parenteral amino acid treatment being highly effective.

The degree of malnutrition is directly correlated with short-term mortality (1 month) and long-term mortality (1 year). Patients without malnutrition have a mortality rate of 15% versus patients with severe malnutrition – 75%. Enteral nutrition supplements (Fresubin Hepa) with branched-chain amino acids are indicated for patients whose diet cannot ensure the necessary caloric intake.

Corticosteroids were used for a long time in the treatment of acute AH, due to their immunosuppressive, antiinflammatory and antifibrotic role. In the acute phase, hydrocortisone hemisuccinate 250-500 mg/day can be administered, followed by prednisone or prednisolone 30-60 mg/day for 4 weeks.

Despite medication, the mortality rate of acute alcoholic hepatitis remains high. In case of a contraindication to corticotherapy, pentoxyphylline can be used, due to its anti-TNF effect.

5. LIVER CIRRHOSIS

Definition

Liver cirrhosis is the final stage of chronic liver disease, which is characterized by extensive fibrosis and remodeling of liver architecture, associated with hepatocytic necrosis and the appearance of regeneration nodules. The name of cirrhosis was given by Laennec, after the Greek word "kirrhos" (the yellow-brown reddish color of cirrhotic liver).

The evolution of the cirrhotic process is long, lasting years or tens of years (generally, from 5 to 30 years), and during the evolutive process, the passage from acute hepatitis to chronic hepatitis and cirrhosis takes place. The presence of necrotic and inflammatory lesions is followed by the progressive development of fibrosis, in the form of collagen bands that disrupt the normal liver architecture, with a tendency to the formation of regeneration nodules (which have no centrolobular vein).

The two fundamental processes, fibrosis and regeneration in the form of nodules, are compulsory. The *histological activity* of cirrhosis is assessed by the presence or the absence of lymphoplasmacytic inflammatory infiltrate in the connective fibrous tissue.

Etiology

The etiology of liver cirrhosis (LC) is multiple. The most important causes of liver cirrhosis are the following (we mention the most common particular names of LC):

1. viral causes: B, C and D (postnecrotic LC)
2. alcoholic cause (Laennec cirrhosis)
3. cholestatic cause:
    a) primary biliary cirrhosis (intrahepatic cholestatic cirrhosis)
    b) secondary biliary cirrhosis (after prolonged biliary obstruction, from extrahepatic cholestasis)
4. metabolic cause:
    a) Wilson disease (ceruloplasmin deficiency, copper deposition)
    b) hemochromatosis (iron deposition)
    c) cirrhosis induced by alpha-1 antitrypsin deficiency
    d) glycogenosis (glycogen deposition)
5. vascular cause:
    a) cardiac cirrhosis (in severe and prolonged heart failure)

b) cirrhosis in the Budd-Chiari syndrome (hepatic vein thrombosis, veno-occlusive disease)
6. drug cause – drug cirrhosis (oxyphenisatine, metothrexate, amiodarone, carbon tetrachloride, isoniazid, etc.)
7. autoimmune cirrhosis (secondary to autoimmune hepatitis)
8. nutritional cause – nutritional cirrhosis (denutrition, bypass)
9. cryptogenic cirrhosis (of undetermined cause).

The macroscopic classification *of cirrhosis* is made depending on:
a) Liver size:
- hypertrophic
- atrophic
b) Liver morphology:
- Micronodular (usually alcoholic). Many regeneration nodules of small sizes, 2-3 mm, extending to all lobules, are seen.
- Macronodular (usually postviral, but also toxic, autoimmune).
Uneven regeneration nodules, larger than 3 mm in size.
- Micro-macronodular (found in biliary cirrhosis).

Pathogenesis

All liver cirrhosis have the following elements in common, which are compulsory:

1. Cell death: this differs depending on etiology. Most frequently, cell necrosis develops, a real violent death, following the direct aggression of pathogenic agents. Sometimes, necrosis follows an inflammatory process and is the consequence of immune mechanisms. Cell death can also occur through the exacerbation of apoptosis (naturally programmed death of hepatocytes), as it happens in alcohol aggression.

For cirrhosis to be initiated, necrosis must develop in time and not be massive, otherwise fulminant liver failure occurs.

Cell necrosis may be focal or can follow certain tracts similarly to the inflammatory process (portal-portal, portal-central or central-central necrosis).
Following cell destruction, parenchymal collapse, a real lobular collapse, occurs. Hepatocytes are framed by a collagen support tissue and, following collapse, these collagen frames become superimposed and confluent, forming the fibrous matrix of future cirrhosis.

2. Consequently, the second element is the development of ***fibrosis***. Along the tract of matrix condensations, after lobular collapse, fibrosis develops, which follows the tract of necrosis.

Pathogenesis differs depending on the etiological agent of LC. Thus, there is a direct proportional relationship in *alcoholic cirrhosis* between alcohol consumption and liver involvement. Anatomo-clinical studies have shown that

the frequency of liver cirrhosis is 7 times higher in heavy drinkers compared to non-drinkers.

The development of cirrhosis requires a certain dose and time period.

In men, an amount of 160 g alcohol/day for 15 years is considered to be necessary, while in women, the amount is smaller (60 g alcohol) and the duration is shorter (10 years). Sex differences are due, at least in part, to the reduced alcohol metabolizing capacity in the stomach, because of the deficient enzymatic equipment. Alcohol dehydrogenase, which ensures alcohol oxidation in the gastric mucosa, is lower in the stomach of women compared to men, and higher amounts of unchanged alcohol enter portal circulation. However, within the same sex, susceptibility to alcohol is different. The minimum threshold required for the induction of liver lesions is considered to be 60 g in men and 30 g in women.

The sequence of lesions in alcoholic liver disease is as follows:
- fatty loading - predominantly centrolobular necrosis - appearance of Mallory bodies - fibrosis - cirrhosis.

In *viral cirrhosis*, cell death occurs through necrosis directly caused by the virus or through the triggering of immune cellular or humoral mechanisms. The supporting liver tissue is formed by collagen, structural glycoproteins, proteoglycans and elastin. All these four components are increased in cirrhosis. Fibrosis is the consequence of an intense fibrogenesis process, which is mainly achieved on account of collagen. The fibrogenesis process involves portal space fibroblasts, Ito cells, which are myofibroblast precursors, and Disse space myofibroblasts.

3. Cell regeneration is the third element of the cirrhogenic process. The regeneration process is determined by cell death, but there is no balance between destruction and regeneration.

As a rule, regeneration is in excess and forms nodules that exert compressions on the surrounding fibrous tissue. These cause a compression on the vascular system in the connective tissue, and an increase in portal pressure. Through the process of destruction, regeneration and fibrosis, intrahepatic shunts are formed between the hepatic artery and the central vein, between the arterial and the portal system, with consequences on the liver function.

Clinical picture

The clinical picture of cirrhosis depends on the stage of the disease:
- In early stages, symptoms can be absent, or physical and mental asthenia may be present.
- Later, gingival and nasal bleeding, sub-jaundice or scleral and skin jaundice occur.
- In late stages, the appearance is typical of an icteric patient, with enlarged abdomen from ascites, with gynecomastia (in men). Limb-girdle muscular

dystrophies, along with a swollen abdomen from ascites, are typical of advanced cirrhosis.

The etiology of the disease can also have specific manifestations:
- alcoholism – dyspeptic manifestations, paresthesia, polyneuritis, diarrhea
- autoimmune manifestations (in hepatitis C and autoimmune hepatitis) – arthralgia, cryopathy
- thesaurismoses generate specific cutaneous manifestations (hemochromatosis).

Liver cirrhosis can be:
- ***compensated*** (when ascites and jaundice are absent)
- ***decompensated***:
  - *vascular* (ascites and edema present)
  - *parenchymal* (jaundice present).

The clinical symptomatology of liver cirrhosis is caused by the two main consequences of morphological restructuring:
a) reduction of liver parenchyma
b) presence of portal hypertension.

a) Parenchymal dysfunction, the so-called functional hepatic insufficiency, develops in time, through the persistence of aggression (alcoholism or the presence of the virus). These signs can occur earlier in viral cirrhosis or even during adolescence in Wilson disease.

Parenchymal dysfunction translates into general phenomena: anorexia, asthenia, fatigability, weight loss. This last symptom can be absent in alcoholics in whom ethanol consumption compensates nutritional deficiencies. Subsequently, effort hepatalgia occurs, and during acute periods, fever and pruritus. Fever appears as a result of intense cytolysis and is a sign of activity. Epistaxis and gingivorrhagia reflect coagulation disorders, due to defective coagulation factor synthesis.

b) Portal hypertension involves discomfort and postprandial bloating, gaseous syndrome as minor clinical manifestations. Then, ascites follows.

The clinical examination of a cirrhotic patient shows *on inspection* the presence of:
- spider naevi on the anterosuperior thorax (an extremely important sign because these naevi are typical of LC);
- scleral and skin jaundice or sub-jaundice (best visualized in the sclerae). Jaundice is present since early stages in primary biliary cirrhosis and in the final or acute stages of viral or alcoholic cirrhosis. It is accompanied by the elimination of colored urine and pruritus, in primary biliary cirrhosis (with the presence of scratching traces);
- palmar rubeosis;

- presence of collateral circulation on the abdomen, either periumbilically, with a jelly fish head appearance, or on the flanks;
- presence of ascites with a swollen abdomen; leg edema may also occur;
- muscular dystrophy, particularly of limbs, is characteristic, in the presence of ascites, with a spider-shaped pattern;
- a number of endocrinological changes occur: hypertrophic parotid glands, atrophic testes, gynoid distribution of pilosity in men.

In women, menstrual disorders up to amenorrhea are found. Gynecomastia is frequently found, but it can be iatrogenic (after diuretic treatment with spironolactone).

Liver *palpation* will show in the case of hypertrophic cirrhosis an enlarged liver, with a sharp edge, of increased consistency. Sometimes, only the right or left lobe can be palpated. In the case of atrophic cirrhosis or severe ascites, it is possible that the liver cannot be palpated, and thus, an important diagnostic element is lost.

Splenomegaly in cirrhosis is almost the rule, which is why spleen palpation can be a diagnostic element for liver disease.

In the presence of an enlarged abdomen, dullness on percussion (fluid) allows for the suspicion of peritoneal effusion (this suspicion should be confirmed by ultrasound, before paracentesis).

A clinical examination of a sub-icteric or icteric patient with vascular stars, with firm hepatomegaly and splenomegaly is highly suggestive of a diagnosis of liver cirrhosis.

Zieve syndrome occurs in alcoholics, and particularly in alcoholic cirrhosis. This is a particular and complex clinical form, characterized by hyperlipidemia and hemolytic anemia. The fatty loading of the liver is compulsory, regardless of the type of the liver disease. Fever, jaundice, abdominal pain and hepatomegaly clinically occur.

In liver cirrhosis, the involvement of other organs and systems is seen:

A. Digestive:

- Esophageal varices and fundal varices (in half of the patients with cirrhosis).
- Gastritis frequently occurs in cirrhosis, most frequently as gastric vascular manifestations in portal hypertension (portal hypertensive gastropathy): congestion, marble, mosaic or water-melon appearance.
- Gastric or duodenal ulcer is more common in liver cirrhosis, which could be explained by the presence of gastrin metabolizing disorders, as well as by a reduction of mucosal resistance. In the presence of UGB in a cirrhotic patient, the possibility of an ulcer should be considered.
- Biliary lithiasis is more frequent in cirrhosis (20% in men and 30% in women). Decreased bile salt secretion is discussed in its pathogenesis. It is frequently asymptomatic.

B. Extradigestive - The systems that can be affected are:
- Nervous: Hepatic encephalopathy occurs through brain impairment, as a result of severe liver function impairment; peripheral neuropathy is present in alcoholics.
- Other neurological manifestations: Babinski's sign, muscle rigidity, exaggerated osteotendinous reflexes.
- Osteoarticular: osteoporosis and osteodystrophy.
- Cardiovascular: pericardial collections, hemodynamic changes such as hypotension, toxic (alcoholic) cardiomyopathy can be present.
- Hematologic:
  - coagulation disorders – all coagulation factors are synthesized in the liver, except for factor VIII, which explains the presence of coagulopathies.
  - Thrombocytopenia frequently occurs in hypersplenism. It manifests through epistaxis, gingivorrhagia, petechiae or ecchymoses. Functional disorders with platelet aggregation disorders may also occur.
  - Anemia can be microcytic hypochromic, as a result of small repeated hemorrhages or large hemorrhages from esophageal varices rupture; it can also be hemolytic in the case of hypersplenism.
- Pulmonary. Several aspects are described:
  - Pleural collections (hydrothorax) occur in 10% of cirrhotic patients, the majority to the right.
  - Hepatopulmonary syndrome. It develops through the increase of plasma vasodilator levels or through the non-destruction or non-inhibition of circulating vasoconstrictors. Platypnea (improvement of dyspnea in decubitus position) and orthodeoxia (decrease of SPO2 in orthostatism with an improvement in clinostatism) clinically occur.
  - Primary pulmonary hypertension
- Renal. Hepatorenal syndrome (discussed in the section on complications).

Paraclinical investigations

The paraclinical investigations required for the diagnosis of liver cirrhosis are:
A. Biological investigations
B. Abdominal ultrasound
C. Upper digestive endoscopy
D. Morphological evaluation (laparoscopy or liver biopsy sometimes) and FibroScan evaluation.

A. The biological picture of liver cirrhosis is usually deeply altered. Thus, changes in the four hepatic syndromes occur:

1. inflammatory syndrome, with a moderate or marked increase in gammaglobulins (over 28-30% in active cirrhosis) and polyclonal

immunoglobulins (particularly IgG in primary biliary cirrhosis or IgA in alcoholic cirrhosis);

2. hepatocytolytic syndrome, translating into an increase in transaminases (GOT, GPT), is more reduced in cirrhosis unlike in chronic hepatitis, because of an important cell destruction (low cell reserve). Cirrhosis with normal or quasi-normal transaminases is quite frequent.

3. impaired liver synthesis syndrome is generally obviously altered in cirrhosis; because of hepatocellular insufficiency, a decrease in QI occurs (with the prolongation of the prothrombin time), there is a reduction of urinary urobilinogen, a decrease in albuminemia (from reduced liver synthesis), and a decrease in cholinesterase (this last investigation may frequently differentiate chronic hepatitis from cirrhosis, because in hepatitis, cholinesterase values are normal).

4. *biliary excretory syndrome* with the increase of total bilirubin, possibly of alkaline phosphatase and gamma-glutamyl transpeptidase, when cholestasis is present.

The biological picture can also include anemia, with leukopenia and thrombocytopenia, in case of *hypersplenism*.

In addition to a changed hepatic picture, the biological parameters allowing for the etiological categorization of liver cirrhosis will be investigated. These parameters are:

- for viral etiology: HBsAg, anti-HCV or anti-D (delta);
- for alcoholic etiology, anamnesis is useful as it is known that a daily dose of at least 60-70 ml absolute alcohol for a period of more than 10 years in men, and 30-40 ml absolute alcohol/day in women is toxic. The difficulty of anamnesis for alcoholism is known, and its biological markers are insufficient (gamma-glutamyl transpeptidase shows alcohol consumption over the last weeks);
- for Wilson disease, the measurement of ceruloplasmin reveals low or no values, cupremia and cupruria are elevated;
- for hemochromatosis, along with a possible pancreatic (diabetes) or cardiac involvement, high sideremia, high serum ferritin (more than 200 ng/ml) and an increased transferrin saturation coefficient (over 50%) will occur;
- for primary biliary cirrhosis, cholestasis enzymes (gamma-glutamyl transpeptidase, alkaline phosphatase, bilirubin) will be measured, along with antimitochondrial antibodies (AMA);
- in cardiac cirrhosis and Budd-Chiari syndrome, the diagnostic element is the underlying disease; in cirrhosis from alpha-1 antitrypsin deficiency, its measurement shows low or no values;
- in cirrhosis following autoimmune hepatitis, high gammaglobulin values will be found, as well as autoantibodies: ANA, SMA and anti-LKM1.

B. The ultrasound diagnosis of cirrhosis is relatively easy in advanced forms. Ultrasound will determine ascites and its approximative amount, the size of the spleen, the presence of liver heterogeneity (as an expression of cirrhotic

remodeling), caudate lobe hypertrophy (relatively typical of cirrhosis), thickening and layering of the gallbladder wall (from hypoalbuminemia, portal hypertension and lymphatic stasis), as well as ultrasonographic signs of portal hypertension (dilated splenoportal axis, collateral circulation).

C. Endoscopic diagnosis consists of assessing portal hypertension, by evidencing esophageal varices or portal hypertensive gastropathy. The presence of *esophageal varices* is a major sign of portal hypertension and, in the absence of other rare causes (portal thrombosis, schistosomiasis), is a sign of liver cirrhosis. This is why a case with a suspicion of cirrhosis will be investigated by esophagoscopy, to demonstrate the presence of esophageal varices. There are several endoscopic classifications of esophageal varices, but the easiest seems to be that of the Japanese Society for Gastroenterological Endoscopy, including three grades:

- esophageal varices grade I: small varices that disappear on endoscopic insufflation;
- esophageal varices grade II: varices that do not disappear on endoscopic insufflation;
- esophageal varices grade III: large varices that partially obstruct the esophageal lumen.

It should be mentioned that there are also *fundal varices* (diagnosable by visualization in retrovision), *esogastric varices* and, more rarely, duodenal varices.

Portal hypertensive gastropathy translates into antral changes determined by portal hypertension, which may have a water melon, mosaic or diffuse bleeding appearance. Mild forms and severe forms are described. The mild form has three endoscopic appearances: a mosaic ("snake skin") appearance, a hyperemic (water melon) appearance, and a scarlatiniform rash appearance. The severe form has two appearances: diffuse hemorrhagic spots and diffuse gastric bleeding. Lesions can be located anywhere in the stomach.

D. The morphological diagnosis of cirrhosis is required only in certain situations, i.e. in early cirrhosis, when typical clinical signs are absent. The presence of clinical signs typical of cirrhosis, such as cirrhogenic ascites or esophageal varices on endoscopy, makes the diagnosis of cirrhosis and no longer requires morphological examination. In other cases, when there is only a clinical or biological suspicion of liver cirrhosis, two morphological explorations can be performed:

- *diagnostic laparoscopy*, which allows to visualize the liver surface and to assess cirrhogenic regeneration nodules, makes the macroscopic diagnosis of liver cirrhosis;
- *liver biopsy* evidences in the histological fragment the fibrous hepatic remodeling process. The microscopic appearance of the cirrhotic liver shows a distortion of the normal lobular architecture by fibrous scars. Cell necrosis can be present particularly near fibrous scars; there may be no inflammatory process.

The fatty loading of hepatocytes is present particularly in alcoholic cirrhosis. In general, in the case of a suspicion of compensated cirrhosis, diagnostic laparoscopy is preferred, because it allows the easy and rapid evaluation of the liver surface (blind liver biopsy can miss the histological diagnosis of cirrhosis in about 10-20% of the cases because of the small size of the fragment, which does not evidence liver regeneration nodules).

Lately, in most cases fibrosis assessment is made using ultrasound based elastographic techniques. The oldest method is ***transient elastography (FibroScan)*** and is recommended as a reliable fibrosis assessment tool by most international guidelines. The method uses the transmission and reception of vibrations in liver tissue, with a probe, and results are expressed in kPa (kilopascals). The method has a sensitivity and a specificity of about 95% in the diagnosis of liver cirrhosis. The evaluation cannot be performed in the presence of perihepatic ascites. FibroScan values in cirrhosis range between 14 and 75 kPa, and with the increase of values, the risk for cirrhosis complications also increases. Recently, new elastographic methods that can also be used in the presence of ascites have been introduced (VTQ, Elast PQ or 2DSWE) (see the diagnosis of chronic hepatitis).

Evolution of liver cirrhosis

The evolution of liver cirrhosis is generally long. First, there is a ***compensated*** phase (without ascites or jaundice, when cirrhosis is often detected incidentally, on the occasion of surgery or necropsy), followed by a ***vascular decompensation*** phase (ascites, edema) or ***parenchymal*** phase (jaundice).

The functional hepatic reserve in these patients can be assessed based on some parameters that are grouped into the ***Child-Pugh classification***, which uses the following elements: albuminemia, ascites, bilirubin, Quick index and encephalopathy (parameters that are relatively easy to quantify). The different parameters are assigned a score and the classification is made based on the sum of these parameters, according to the following table:

Parameter	**1 point**	**2 points**	**3 points**
Serum albumin (g%)	> 3.5	2.8-3.5	< 2.8
Ascites	absent	moderate	severe
Encephalopathy	absent	mild (gr.I, II)	severe (gr.III, IV)
Bilirubin (mg%)	< 2	2-3	> 3
Quick index	> 70%	40-70%	< 40%

Child-Pugh classes are assigned as follows:
Child A: 5-6 points;
Child B: 7-9 points;
Child C: 10-15 points.

This Child Pugh classification is a prognostic index for survival, considering that cirrhosis is more advanced as the class evolves from A to C and as the number of points increases.

A possible criticism of this classification is that it does not take into account the presence and the degree of esophageal varices, which has a major influence on the prognosis of liver cirrhosis, through the complications generated by the rupture of esophageal varices.

In compensated cirrhosis, the clinical picture can be completely asymptomatic or minor clinical signs may be present (asthenia, decrease of appetite, flatulent dyspepsia, palmar erythema). The biological tests in all these situations are frequently unchanged.

The clinical **decompensation** of cirrhosis is differentiated into **vascular** (ascites, edema) and **parenchymal** (jaundice), although the two forms of decompensation are frequently concomitant. When biochemical tests are normal, inactive liver cirrhosis is present.

During the evolution of cirrhosis, acute episodes may occur as a result of intempestive alcohol consumption or of a new viral infection, which represent real acute hepatitis superimposing on the existing cirrhosis. Fever, jaundice, marked asthenia, loss of appetite, various degrees of hepatic encephalopathy are clinically present. Biologically, on the background of the ordinary picture, important increases of transaminases and sometimes, of cholestasis parameters are found.

Complications of liver cirrhosis

The complications of liver cirrhosis are numerous and will eventually lead to death.

The main complications that can occur in a cirrhotic patient are:

1. UGH (upper gastrointestinal hemorrhage);
2. hepatic encephalopathy;
3. ascites (vascular decompensation);
4. spontaneous bacterial peritonitis (SBP);
5. hepatocarcinoma;
6. hepatorenal syndrome.

1. Upper gastrointestinal bleeding

A) UGB is most frequently induced in cirrhotic patients by the *rupture of esophageal varices*. Rupture is usually related to the presence of large varices (grades II or III) and of specific endoscopic signs (“cherry red spots” – as an expression of severe portal hypertension). The appearance of esophageal varices rupture is determined by a sudden increase of portal hypertension: related to a weight lifting effort or defecation, sneezing, coughing, rapid increase of ascites, it can also occur following hot food consumption.

Other predictive factors of hemorrhage are: skin collateral circulation, presence of ascites, deep alteration of coagulation and "cherry red spots" on the variceal wall.

Sometimes, UGB can be induced by *fundal varices rupture* (usually, after esophageal varices ligation, portal hypertension generates fundal varices) or by portal hypertensive gastropathy or diffuse gastric bleeding.

The patient with liver cirrhosis will be evaluated for the presence of esophageal varices only endoscopically (not radiologically), and evaluation endoscopy will be performed once/year (possibly every 2 years). The absence or the presence of varices grade I at the first examination will require an annual reexamination.

Varices grade II and III benefit from treatment with propranolol for the primary prophylaxis of bleeding and do not require endoscopic monitoring.

UGB from variceal rupture is one of the main causes of death in cirrhotic patients; it is estimated that one year after the first hemorrhage, about 30% of cirrhotic patients die.

The therapy of UGB from esophageal varices rupture includes several stages:

- equilibration of the patient: by treating hemorrhagic shock with blood or plasma expander (water electrolyte balancing). The Hb value will be maintained around 8 g%. Volemic overload through excessive transfusion increases the risk of rebleeding.
- arterial vasoconstrictor medication for decreasing pressure in esophageal varices (vasopressin or terlipressin is administered in i.v. perfusion, usually in a bolus dose, followed by perfusion for 48-72 hours). Studies have demonstrated a similar efficiency of vasoactive drugs, but only terlipressin has been proved to decrease the mortality of patients with variceal UGB.
- endoscopic procedures. The endoscopic detection of ruptured varices requires the **elastic band ligation of esophageal varices** (**with rubber rings**) – the therapy of choice, or endoscopic sclerotherapy (a sclerosing solution – aethoxysklerol, hystoacryl, etc. will be injected with the sclerotherapy needle through the endoscope channel). The bleeding variceal group will be treated in the first place; then, other variceal groups are treated (between 5 and 20 rings/session).

Ligation sessions are repeated every 2 months, until the complete eradication of the varices.

- if endoscopic hemostasis is not possible and bleeding is massive, hemostasis by ***Sengstaken-Blackmore balloon catheter compression*** can be used. This method can be used for hemostasis in 70-80% of the cases, but rebleeding after the removal of the balloon catheter is 50%.
- ***the treatment of ruptured fundal varices*** is more difficult, because sclera-therapy or elastic ligation is more difficult to use. A sclerosing substance such as histoacryl (or aethoxysklerol) is injected through the endoscope in retrovision.

The prophylaxis of esophageal varices rupture is carried out in patients with non-bleeding varices grades II and III (primary prophylaxis), as well as in those who already had a hemorrhagic episode, from variceal rupture (secondary prophylaxis).

This is performed with:

- beta-blockers, which decrease venous return – propranolol 40-120 mg/day (a dose allowing to reduce rest heart rate by >25%).
- in patients with a contraindication of beta-blockers (hypertension, atrioventricular block, asthma), prophylactic variceal band ligation is performed.

In patients who already had a UGB episode from variceal rupture, several sessions of elastic esophageal variceal ligation (or endoscopic sclerotherapy) can be initiated, until the complete eradication of esophageal varices.

There are some situations when special techniques can be used (in case of fundal varices, when ligation has not eradicated the varices and there is repeated bleeding, in case of refractory ascites); portal hypertension decompression can be performed through:

- ***TIPS (transjugular intrahepatic portosystemic shunt)***
- surgical anastomosis (portacaval or splenorenal shunt).

B) It should be noted that up to one third of UGB cases in cirrhotic patients can be generated by bleeding from *hemorrhagic gastroduodenal ulcer*. This is why the presence of any type of UGB requires emergency endoscopy to evidence the cause of bleeding and, at the same time, to provide the therapeutic endoscopic solution (elastic esophageal variceal ligation, variceal sclerotherapy or endoscopic ulcer hemostasis). In *hemorrhagic ulcer*, endoscopic hemostasis is carried out using one of the following techniques:

- injection of a 1/10000 adrenaline solution in the ulcer base;
- thermal hemostasis with bipolar probes;
- endoscopic placement of a hemoclip on the bleeding source.

Then, antisecretory medication such as proton pump inhibitors (omeprazole, pantoprazole) will be administered intravenously. If endoscopic treatment is unsuccessful, radiologic embolization should be tried for hemostasis. Surgery is used only for cases in which these methods have failed to provide hemostasis, given the high operative risk in cirrhotic patients (marked intraoperative bleeding, postoperative development of hepatocellular insufficiency).

C) In *portal hypertensive gastropathy*, argon-beamer coagulation (APC) treatment or beta-blockers for the reduction of portal hypertension can be administered.

2. Hepatic encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome that occurs in cirrhotic patients. *Clinically*, there are behavioral disorders (agitation), slowness, somnolence, difficulties in answering questions, intellectual disorders

with difficulties in performing easy arithmetic, and finally, superficial or deep coma may occur.

Objectively, there are neurological signs such as flapping tremor (asterixis), which is the major neurological sign, characterized by spontaneous or provoked asymmetric upper limb movements of great amplitude, with a low frequency.

The etiopathogenesis of HE is generally complex, involving several triggering factors:

- *hyperammoniemia* – generated in the intestine by the ammonia-forming flora, starting from a protein substrate: the ammonia formed in the stomach from urea by ureasis produced by Helicobacter pylori; this ammonia easily reaches systemic circulation through portal-systemic shunts; the hematoencephalic barrier is permeable, and ammonia has a neurotoxic action.
- *increase of false neurotransmitters* (tyramine, octopamine) and decreased synthesis of true neurotransmitters (dopamine, norepinephrine).
- *increase in the serum concentration of aromatic amino acids* - (tryptophan, tyrosine, phenylalanine).
- *decrease of branched-chain amino acids* (leucine, isoleucine, valine).

The triggering causes of HE can be multiple:

- a hyperproteic diet
- UGB (through blood proteins, hypoxia that induces cytolysis)
- administration of sedatives or hypnotics
- various infections (particularly spontaneous bacterial peritonitis)
- superimposed acute alcoholic or viral hepatitis
- postdiuretic water electrolyte imbalances
- constipation
- surgery.

HE staging:

- stage I – apathetic, confused patient, loss of concentration capacity, altered sleep-wake rhythm
- stage II - somnolent, confused patient, difficulties in answering questions
- stage III – marked somnolence, temporal-spatial disorientation, response only to strong stimuli
- stage IV - coma, no response to stimuli.

There are certain psychometric tests or graphical tests that can evidence latent HE phenomena, which are particularly important in professionally active persons with liver cirrhosis.

The treatment of HE consists of:

- Avoiding the triggering causes described above (hyperproteic diet, UGB, constipation, water electrolyte imbalances from diuretics, infections).

- Diet will be normoproteic in cirrhotic patients without HE, but will be hypoproteic in patients with encephalopathy. At the onset of encephalopathy, proteins can be removed or reduced for several days (20-30 g/day), but after the disappearance of encephalopathy, the patients will be maintained on 50-60 g proteins/day. Meat proteins are more toxic than dairy product proteins, the best tolerated being proteins of plant origin (containing a lower amount of methionine and aromatic amino acids).
- Obtaining a regular intestinal transit will ensure the intestinal reabsorption of a small amount of ammonia. For this, **lactulose** (an osmotic laxative that acidifies the intestinal environment), in a dose of 30-60 g/day, or lactitol will be used. Enemas can be useful for emergency situations, allowing the evacuation of the colon content.
- The activity of the ammonia forming flora is inhibited by the administration of **rifaximin (Normix)** 3 x 1-2 tb/day.
- L-dopa and bromocriptine have been used for the restoration of neurotransmitters, with questionable effects.
- The administration of benzodiazepine antagonists (flumazenil) has brought spectacular effects in some cases, but the results are inconsistent. Flumazenil is administered i.v., in fractioned doses of 0.2 mg every 60 seconds up to a total dose of 1 mg.

In patients with episodic encephalopathy, a hypoproteic diet along with normal intestinal transit (possibly corrected with lactulose) are sufficient measures. The addition of Normix 3x2 tb/zi can be useful, possibly as discontinuous treatment. The search and correction of the triggering cause of HE are indispensable for success.

3. Ascites (vascular decompensation)

Ascites is a frequent situation in the evolution of liver cirrhosis. It is due to hypoalbuminemia, portal hypertension and lymphatic stasis. The diagnosis of ascites is clinically suspected, but is confirmed by ultrasound. Ultrasound also allows the semiquantitative assessment of ascites volume.

Exploratory paracentesis allows to evaluate ascites and to differentiate transudate ascites (<3 g% proteins) from exudate ascites (>3 g% proteins, usually in old duration ascites). On the same occasion, the elements in the fluid (erythrocytes, leukocytes) can be assessed, and the fluid can be seeded to detect potential spontaneous bacterial peritonitis (SBP). It should be noted that because of the high opsonization index, sometimes even in infected ascites, the culture is sterile; this is why the count of leukocytes/ml is extremely useful. Thus, more than 500 leukocytes/ml (or more than 250 polymorphonuclear cells/ml) signify fluid infection, even in the absence of a positive culture.

In a patient who initially has no ascites, periodic weighing is recommended, and in case of weight gain or increased abdominal volume, abdominal ultrasound will be indicated to confirm ascites.

The therapy of ascites syndrome will include the following measures:

A. Hygienic-dietary: prolonged *bed rest*

- *low sodium diet*. The patient will be warned about certain foods that contain salt in a disguised manner: mineral water, etc. Regarding bread without salt, this can be recommended in cases with severe ascites.

B. Drugs:

Diuretic therapy is usually associated with diet:

- Spironolactone (an antialdosteronic drug), a potassium-sparing diuretic, is the basic product, which is administered in doses of 50-400 mg/day (mean dose 100-200 mg/day). Spironolactone is administered daily. The effect of spironolactone occurs 2-3 days after administration and is weak. It will not be administered in case of hyperpotassemia or in case of renal insufficiency (creatinine over 2 mg%). Prolonged administration may cause gynecomastia.
- Furosemide (a strong loop diuretic) acts rapidly and is usually associated with potassium-sparing diuretics. The daily dose is 40-160 mg/day (1-4 tb/day); one or two tablets are generally sufficient. In other cases, spironolactone is administered daily, and furosemide is administered every 2 days.

Daily diuresis (which should be at least 1500 ml to be effective) and body weight will be monitored, and urinary sodium and potassium will be measured every two days (during hospitalization). Thus, a daily sodium excretion of more than 100 mEq is a good sign, particularly with a low potassium excretion (less than half of the excreted sodium amount). The diuretic dose can be adapted to the ascites volume, daily diuresis and daily weight loss.

C. Paracentesis

An alternative to diuretic therapy is *therapeutic paracentesis*. It is generally intended for cases with severe ascites (where the "drying" of the patient would require a long time) or with therapy-refractory ascites (diuresis less than 1000 ml/day despite sustained diuretic therapy). Therapeutic paracentesis consists of the removal of 5 liters of ascites daily or every 2 days. Other authors recommend the complete removal of ascites in a single session.

In order to avoid hypovolemia, with hypotension and renal ischemia, which may occur following paracentesis, it is recommended to administer sodium-free human albumin (8 g for 1 liter of removed ascites) or plasma expanders (dextran 70-500 ml). Therapeutic paracentesis is inexpensive and can be an effective solution, if used appropriately.

D. Surgical or non-surgical shunts:

In the case of refractory ascites (when despite maximum doses of spironolactone 400 mg /day + furosemide 160 mg/day, diuresis is very low), shunts can be used in addition to evacuation paracentesis:

- LeVeen *peritoneovenous shunts* (little used because of the risk of disseminated intravascular coagulation).

- *TIPS* (transjugular intrahepatic portosystemic shunt). This modern interventional technique ensures the resolution of therapy-refractory ascites or pleurisy.

4. Infection of ascites and spontaneous bacterial peritonitis (SBP)

These two complications occur in up to 10% of patients with vascular decompensated cirrhosis.

The clinical picture is not rich but can frequently induce encephalopathy or the sudden aggravation of the disease. SBP usually has an intestinal origin; gram-negative bacteria, most frequently E. coli, Klebsiella, traverse the intestinal wall. SBP is a complication that occurs in patients with ascites and represents ascitic fluid infection in the absence of a triggering cause (paracentesis, surgery).

Diagnosis is made by positive culture or increased leukocyte count (>500/ml) or more than 250 polymorphonuclear cells/ml. Ascites culture is very frequently negative, diagnosis being made based on the increased cellularity of the ascitic fluid.

Fever, chills, an alteration of the general status may clinically occur, but they can also be completely absent, particularly in severely impaired individuals. Spontaneous bacterial peritonitis (SBP) is a disease with a high mortality (if untreated). Treatment must be initiated as soon as possible following diagnosis.

Treatment

Injectable third generation cephalosporins are preferred: cefotaxime 2 g every 6-8 hours, or ceftriaxone 1 g every 12 hours, i.v. In case of positive culture from the ascitic fluid, treatment will be conducted according to the antibiogram. Therapy generally lasts 7-14 days. Despite correct treatment, mortality can reach 50%. Within a year of SBP treatment, in up to half of the cases, recurrences may appear. Given that recurrence is related to a low protein level in the ascitic fluid and to the degree of hepatocellular insufficiency, in cases with a predisposition for reinfection, the prophylaxis of reinfection can be done with norfloxacin 400 mg/day or ciprofloxacin for a long time.

5. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a common complication in cirrhotic patients; about 1/3 of these will die of liver cancer. In their turn, liver neoplasms occur in 80-90% of the cases on the background of liver cirrhosis. Viral B and C cirrhosis, as well as hemochromatosis, particularly favor the development of HCC.

HCC occurs in the liver regeneration process, generally requiring a hepatic disease with a long-lasting evolution. It is usually a unicentric form, but the multicentric or diffuse form has also been described.

It is recommended to monitor the following categories of patients for the early detection of a HCC:

- viral B and C liver cirrhosis;
- chronic hepatitis C and B (in the latter, the risk of HCC depends on the severity of fibrosis, inflammation and the level of viral DNA);
- alcoholic liver cirrhosis;
- genetic hemochromatosis;
- primary biliary cirrhosis.

Clinical picture

Classical: weight loss, rapidly increasing or diuretic-refractory ascites, fever or subfebrility, pain in the right hypochondrium. In contrast, there are completely asymptomatic cases, detected incidentally on the occasion of an ultrasound examination. Clinical examination evidences a hard tumoral liver (but in the case of small tumors, these signs can be absent).

The diagnosis of HCC is made using two methods: serological, by the measurement of alpha-fetoprotein, and imaging (ultrasound, including contrast enhanced ultrasound – CEUS, computed tomography and magnetic resonance imaging).

Alpha-fetoprotein (AFP) (normal values: 10-20 ng /ml) has a sensitivity below 60-70%. Values higher than 200 ng/ml are considered pathognomonic for HCC in patients at risk. However, 2/3 of HCC less than 4 cm in size may have AFP values lower than 200 ng/ml and about 20% of HCC do not produce AFP even if they have large sizes.

Ultrasound performed by an experienced examiner with high performance equipment easily evidences the lesions. Ultrasound can detect lesions between 3-5 cm in a proportion of 85-95%. Usually, in a non-homogeneous cirrhotic liver, a nodule of about 1 cm (hypo-, hyper-, isoechogenic or with mixed echogenicity) can be more difficult to evidence. Once detected, it will undergo complementary examinations. The method has a 60-80% sensitivity in detecting small lesions (1-2 cm). Contrast enhanced ultrasound (CEUS) using SonoVue increases performance in characterizing the detected nodules and allows a correct diagnosis in 80% of newlly detected nodules in cirrhotic liver.

Computed tomography and magnetic resonance imaging (MRI) with contrast are used as auxiliary methods for the characterization of liver nodules.

RECOMMENDATIONS:

-ultrasound is recommended as a screening test for HCC in cirrhotic patients;
-the optimal, but not ideal time interval for repeating ultrasound in 6 months.

In the suspicion of HCC, nodule biopsy will be performed only when the classical criteria (imaging +/- AFP) have failed to make diagnosis. Ultrasound (or CT) guided biopsy will be carried out with a fine biopsy needle (needles with an outer diameter larger than 1 mm). In general, CEUS or CT or MRI with contrast clarifies the great majority of the lesions detected in a cirrhotic liver.

Therapy of HCC:

-The first option, when possible, is *resection surgery* (if the functional hepatic reserve allows it) or *liver transplantation* (which is a solution for both cirrhosis and HCC).

-If surgery is not possible, in large tumors, *transarterial chemoembolization* (TACE) with doxorubicin and lipiodol (or gelaspon) through the hepatic artery, in the vascular branch corresponding to the tumor, can be chosen.

-In small tumors (less than 3 cm), ultrasound-guided *percutaneous ethanol injection therapy* (PEIT). Through this technique, absolute alcohol is introduced directly into the tumor with a fine needle, by percutaneous route, under ultrasound guidance, in several therapeutic sessions. An alternative to this is *radiofrequency ablation* (RFA), with better results compared to PEIT (but also with higher costs).

-In cases when none of the mentioned techniques can be used (large, metastatic or portal thrombosis tumors), *antiangiogenic therapy with Sorafenib* (Nexavar) 800 mg/day can be indicated, during the entire course of life.

-In small liver tumors, in the context of liver cirrhosis, *liver transplantation* can be the ideal therapeutic option.

6. Hepatorenal syndrome

Hepatorenal syndrome (HRS) is a functional renal insufficiency (the kidney is morphologically normal), which occurs in cases with advanced cirrhosis, with ascites and severe liver failure. The kidneys transplanted from a patient with HRS function normally in the recipient, demonstrating the functional aspect of the disease.

The cause seems to be renal ischemia, with the reduction of glomerular filtration. HRS can be triggered by the sudden reduction of volemia through paracentesis, digestive hemorrhage, diarrhea, infection.

Biologically, there will be a progressive increase of nitrogen retention, hyponatremia. Urine examination is normal, without proteinuria. Urinary sodium is extremely low, frequently less than 5 mEq/day.

Differential diagnosis should be made with glomerulopathy concomitant with cirrhosis (there is also proteinuria), hypovolemia following paracentesis or diuretics, pathological situations generated by nonsteroidal anti-inflammatory drugs or aminoglycosides administered in the cirrhotic patient.

Treatment is generally discouraging.

-In initial phases, the correction of water electrolyte disorders, the administration of plasma expander are attempted. Vasoactive medication – terlipressin associated with albumin, may improve the renal flow. TIPS can sometimes be useful.

-The only definitely effective therapy of HRS is liver transplantation. In its absence, mortality is the rule (over 90%). After reviewing the complications of liver cirrhosis and their therapy, it can be seen that this disease is marked by

many complications, which results in a generally reserved prognosis. Prognosis is better in compensated cirrhosis and it becomes reserved in decompensated cirrhosis with esophageal varices, HCC or SBP, complications which worsen even more the prognosis of these patients.

Treatment of liver cirrhosis

The evolution of liver cirrhosis is progressive, and structural disorganization is irreversible, which is why therapeutic measures cannot allow the healing of the patient, except by replacing the diseased liver.

The objectives of treatment are:

- Removing the etiological agent (alcohol, virus);
- Stopping evolution;
- Maintaining the state of compensation and inactivity of cirrhosis;
- Preventing decompensation and complications;
- Treating complications when they occur.

Thus, the treatment of liver cirrhosis can be divided into five groups:

A. General measures (hygienic-dietary) – applicable to all cirrhoses regardless of etiology.

-Rest is necessary in decompensated cirrhosis and in the case of complications. Patients with compensated cirrhosis may carry out their activity, avoiding exaggerated efforts. Postprandial rest in supine position can be indicated after the main meal.

-Diet is generally normal, it must be normocaloric (to avoid denutrition).

There are restrictions regarding the consumption of alcohol, proteins, fluids and salt:

- Alcohol is forbidden in any form of cirrhosis.
- Protein consumption in cirrhotic patients without encephalopathy is 1g/kg body weight/day; in patients with denutrition without encephalopathy the amount can be increased, in case of mild or moderate encephalopathy it is reduced to 20-40 g/day, and in severe encephalopathy it is excluded. In malnutrition cases, supplementation with enteral nutrition preparations is indicated.
- Fluid consumption will not exceed 1.5–2 liters/day.
- Salt consumption will be reduced to 2-4 g/day, particularly in patients with ascites.

Thus, in compensated cirrhosis, patients can live a quasi-normal life, with the avoidance of prolonged effort, with longer physical rest periods. Alcohol is totally contraindicated. Diet will be quasi-normal, with normal protein, carbohydrate, lipid and vitamin intake.

The treatment of decompensated cirrhosis requires prolonged physical rest. Potential complications will be treated according to the schemes described above.

B. Etiological treatment. The treatment of liver cirrhosis can be etiological, when the cause is known:

- In perfectly compensated cirrhosis of viral etiology, antiviral treatment can be attempted (lamivudine, adefovir, entecavir or peginterferon for viral B etiology, and combination of drugs with direct antiviral action -DAA for viral C etiology). In decompensated viral cirrhosis, peginterferon cannot be used. In decompensated viral B liver cirrhosis, lamivudine, adefovir or entecavir (preferably entecavir, because it very rarely induces resistance) can be administered.
- PBC therapy with ursodeoxycholic acid.
- In autoimmune cirrhosis – corticotherapy or/and azathioprine (Imuran).

C. Pathogenic treatment

- Corticotherapy. In compensated autoimmune cirrhosis, the administration of prednisone 40-60 mg may lead to significant improvements. Then, therapy is continued with azathioprine. Corticoid treatment can also be efficient in alcoholic cirrhosis, particularly during activity periods, or in superimposed acute alcoholic hepatitis.
- Bile acids (10-15 mg/body weight/day) are indicated in primary biliary cirrhosis, but can also induce improvements in alcoholic and viral cirrhosis, particularly in cholestatic forms (ursodeoxycholic acid 3x250 mg/day).
- Hepatoprotective medication or hepatotropic drugs do not change the disease evolution.
- Vitamin supplementations are justified in the case of deficiencies. Thus, vitamin K is little effective; in contrast, vitamins B6, B12 are useful in patients with neuropathy. In megaloblastic anemia, folic acid can be administered.

D. Treatment of complications (previously discussed)

E. Liver transplantation

6. LIVER DISEASES BY IMMUNE MECHANISMS

I. PRIMARY BILIARY CHOLANGITIS

Definition

Primary biliary cholangitis (the old name - primary biliary cirrhosis) (PBC) has an unknown etiology, it evolves with chronic cholestasis, progressive destruction of intrahepatic bile ducts, portal inflammation, and finally results in cirrhosis and liver failure. Inflammation affects the intrahepatic bile ducts, being also termed non-suppurative destructive cholangitis. For the first time, Walker reports the association of PBC and antimitochondrial antibodies (AMA), which will be subsequently used as diagnostic markers.

Epidemiology

The disease is found particularly in the white population, representing up to 2% of cirrhosis death cases. It is more frequent in women, the female/male ratio being 6/1.

Etiopathogenesis

The etiology of PBC is unknown. The initial factor that triggers the cascade of immunological events could not be evidenced.

Hepatic lesions are the result of two phenomena:

1. The non-suppurative destruction of bile ducts (mediated by lymphocytes). In PBC, ductopenia occurs, which is a reduction in the number of interlobular biliary canaliculi, up to their complete disappearance.

2. Hepatocyte lesions induced by primary and secondary bile acids, which in high concentrations are hepatotoxic.

PBC is associated with a number of autoimmune diseases such as: dermatomyositis, lupus erythematosus, scleroderma, autoimmune thyroiditis, rheumatoid polyarthritis.

Immune abnormalities involve both types of immunity:

A. *Humoral*. Serum IgM is significantly increased; in the serum of patients with PBC, a large number of antibodies appear. Thus, AMA (antimitochondrial antibodies) are present in 95-100% of the cases.

B. *Cellular*. Granulomas and lymphocytic infiltrate in the liver, as well as anergy to cutaneous tests are present.

All these immunological reactions lead in time to the destruction of interlobular and septal bile ducts. With their destruction, cholestasis, fibrosis and

finally cirrhosis occur. The destroyed biliary canaliculi have no regeneration capacity, unlike hepatocytes, which have an infinite regeneration capacity. Proximally to the destroyed bile canaliculi, bile retention develops. As a result of the toxic action of bile salts, piece meal necrosis occurs.

Morphopathology

PBC has four histological stages, with a specific clinical picture for each of these:

- Stage I (portal, cholangitis).
- Stage II (periportal).
- Stage III (septal precirrhotic).
- Stage IV (cirrhotic).

Clinical picture

Half of the diagnosed patients are asymptomatic, but all have signs of cholestasis: increased alkaline phosphatase and gamma-glutamyl transpeptidase.

In symptomatic forms, onset is insidious. Subsequently, the following occur: pruritus, jaundice, fatigue, melanin pigmentation of the skin, xanthelasma, steatorrhea, hepatosplenomegaly and malabsorption of vitamins K, A and D (hemorrhagiparous syndrome, vision disorders, bone pain, spontaneous fractures, osteoporosis). Intense pruritus may be a typical sign of disease.

Diagnosis

Cholestatic syndrome: increase of alkaline phosphatase, gamma-glutamyl transpeptidase, serum bilirubin in both components, serum bile acids (cholic acid) and serum lipids (particularly cholesterol).

Immunology: the increase of AMA (antimitochondrial antibodies) to a titer higher than 1/40, even in the asymptomatic stage, in 90-95% of the cases, is characteristic.

Imaging: ultrasound and tomography provide no specific data. FibroScan (transient elastography) may reveal the severity of liver fibrosis.

Evolution

PBC has a progressive evolution, the mean survival in asymptomatic stages is over 10 years, and in symptomatic stages, about 7 years. With the development of cirrhosis and esophageal varices, prognosis becomes more reserved.

A possible clinical staging of PBC is:
- asymptomatic
- symptomatic anicteric
- symptomatic icteric
- cirrhosis.

Treatment

Treatment of PBC is performed with ursodeoxycholic acid (UDCA) 10-15 mg/kg body weight/day. UDCA is administered throughout the course of life. Ursodeoxycholic acid is the drug of choice in the therapy of PBC. Lately, the prognosis of PBC has improved with the long-term use of UDCA.

II. SCLEROSING CHOLANGITIS

Definition

Primary sclerosing cholangitis (PSC) is a primary inflammatory fibrosing disease of both the intrahepatic and extrahepatic bile ducts, resulting in biliary cirrhosis and liver failure.

Classification

Sclerosing cholangitis is classified as follows:

A. Primary
- associated with autoimmune disorders or immunological disturbances
- non-associated with other disorders

B. Secondary. The cause is known: lithiasis of the main bile duct, cholangiocarcinoma, history of biliary surgery, chronic pancreatitis.

Etiopathogenesis

PSC is associated with a number of disorders, of which the most frequent are rectocolitis (50-75%), Crohn disease (5-10%), pancreatitis (5-20%), sarcoidosis.

The pathogenetic factors involved are only hypothetical, of infectious, toxic or immunological nature.

Pathomorphology

PSC is a chronic fibrosing and stenosing cholangitis, which progressively destroys the bile ducts, resulting in ductopenia and an insufficiency of biliary excretion.

There are four morphological stages:
- Stage I – portal hepatitis
- Stage II – periportal fibrosis
- Stage III – septal fibrosis and bridging necrosis
- Stage IV – biliary cirrhosis.

Clinical picture

Onset is insidious, in the form of chronic cholestatic liver disease, marked by biliary complications (pain, fever, angiocholitis). Jaundice, pain, pruritus, weight loss, asthenia, fever clinically occur. Some asymptomatic forms were diagnosed in patients with rectocolitis, in whom alkaline phosphatase levels were increased and endoscopic retrograde cholangiopancreatography (ERCP) evidenced characteristic changes of the biliary tree.

Diagnosis

Biologically, there are signs of chronic cholestasis, with the increase of alkaline phosphatase, transaminases, gammaglobulins (IgM) to 80-85%, and the presence of antineutrophil cytoplasmic antibodies (ANCA).

Imaging diagnosis is the diagnosis of choice. Examination can be initiated by **cholangio-MRI**, which evidences the changes of bile ducts by a non-invasive method.

Endoscopic retrograde cholangiopancreatography (ERCP) will demonstrate the following characteristic changes of the biliary tree:
- diffuse multifocal stenoses, separated by little dilated or non-dilated portions
- absence of dilation above an obstruction
- scarce intrahepatic biliary branches
- parietal irregularities, with a fringe appearance, particularly in the extrahepatic bile ducts
- a pseudodiverticular appearance of the main bile duct.

Morphological diagnosis is frequently irrelevant.

Evolution

The evolution of PSC is difficult to predict, being severe in symptomatic forms and difficult to define in asymptomatic forms.

PSC complications with a long evolution are: cirrhosis with all complications deriving from it, cholestatic syndrome (steatorrhea, malabsorption of liposoluble vitamins, osteoporosis). Other specific complications are: biliary lithiasis in 30% of the cases, and cholangiocarcinoma (a 4-10% risk).

Treatment

1. Treatment of cholestasis

(see PBC).

2. Treatment of complications

It refers to the treatment of:

- angiocholitis. Broad-spectrum antibiotics are administered, without the need for their prophylactic administration;
- severe stenoses. Their dilation is performed endoscopically, with balloon catheters and, possibly, stenting is applied endoscopically or percutaneously;
- formation of calculi. Treatment is surgical in symptomatic cases;
- cholangiocarcinoma. Treatment is surgical: either segmental resection or orthotopic liver transplantation (OLT).

3. Treatment of sclerosing cholangitis

A. Medical:

- Immunosuppressive agents: corticoids, azathioprine and cyclosporine have not proved to be effective in PSC. The only effective preparation seems to be methotrexate.
- Bile acids – ursodeoxycholic acid (UDCA) seems to be the most promising treatment, a dose of 15-20 mg/kg/day being necessary in the long term, even throughout the course of life.

B. Endoscopic:

This consists of dilation of stenoses with a balloon catheter and possibly, stenting.

C. Surgical:

It consists of biliary drainage in symptomatic PSC, which involves many complications and high risk. Cholangiocarcinoma is another indication for surgery.

Liver transplantation in PSC is a privileged indication, being recommended in the case of failed biliary drainage, with many angiocholitis episodes or cholangiocarcinoma.

7. HEREDITARY METABOLIC LIVER DISEASES

I. PRIMARY HEMOCHROMATOSIS

Definition

Primary hemochromatosis is a systemic ferruginous thesaurismosis characterized by iron storage in parenchymal organs (particularly the liver), and the development of liver cirrhosis, diabetes mellitus, skin pigmentation, arthropathy, cardiac impairment and hypogonadism. It is also termed "**bronze diabetes**", because it associates liver disease with diabetes mellitus and specific skin coloration.

Etiopathogenesis

The etiology of ***primary hemochromatosis*** is unknown.

A ***secondary form*** is also described, when iron overloading occurs: erythrocytic disorders (sideroblastic anemia, thalassemia major), oral iron ingestion, chronic liver diseases (alcoholic cirrhosis, late cutaneous porphyria). Parenteral iron overloading can also occur through transfusion, chronic hemodialysis.

Iron storage in the liver is correlated with age; hepatotoxicity depends on the duration of exposure and on the iron concentration in the liver. This iron hepatotoxicity is direct on collagen synthesis, with microsomal damage, leading to cell death, or it may affect the peroxidation of lipids in the lysosomal membrane, with its fragilization and cell death. The accumulation of iron in the liver is progressive, starting with the periportal area, and it can be microscopically evidenced by Pearls staining. Subsequently, fibrosis and later, cirrhosis develop.

Pathomorphology

Cirrhosis in hemochromatosis is micronodular. The stored iron is evidenced on biopsy by Pearls staining.

Clinical picture

Symptomatology most frequently occurs after 40-60 years of age in men (the male/female ratio is 5/1-8/1).

The classic triad of clinical symptomatology in hemochromatosis is the following:

1. Hepatomegaly. Hepatomegaly develops early, in the asymptomatic stage. In terminal stages, cirrhosis with splenomegaly, jaundice and ascites develops.

2. Diabetes mellitus. It is present in 50-60% of the cases, being the result of iron toxicity on beta-islet cells. 2/3 of patients are insulin dependent.

3. Skin pigmentation. It occurs in the advanced stages of the disease and particularly affects the exposed areas. It is due to melanin excess, not to iron storage in the skin.

Other manifestations associated with this triad are:

- Cardiac: congestive cardiac failure, as an expression of dilated cardiomyopathy.
- Symmetrical arthropathy, usually proximal metacarpophalangeal, interphalangeal, affecting the spine and knees.
- Endocrine: gonadal insufficiency, reduced libido and amenorrhea.

Diagnosis

The main investigations are aimed at assessing iron metabolism. Thus, the following occur in hemochromatosis:

- increase of the transferrin saturation coefficient over 45%;
- increase of serum ferritin to more than 200 ng/ml in men and more than 250 ng/ml in women;
- increase of sideremia over 175 mg%;
- iron excess in tissues. It can be evidenced by Pearls staining on biopsy fragments, or tomographically, by calculating the amount of iron in the liver, or ideally, by MRI. FibroScan can assess the severity of fibrosis. Other hepatic tests are non-specifically affected for hemochromatosis.

Evolution

The disease evolution is long, the mean survival being 5 years after diagnosis. Death occurs through liver or heart failure, diabetes mellitus complications and liver cancer (high risk). Prognosis is favorable in case of early diagnosis and treatment and becomes reserved in the liver cirrhosis stage.

Treatment

A. Diet

Iron-rich foods (spinach, liver) and alcohol are excluded; iron-containing drugs are contraindicated.

B. Phlebotomy is the most effective therapy; 1-2 sessions/week (350-500 ml blood/session), in order to remove 250 mg Fe/session, are conducted. In symptomatic patients, numerous phlebotomies are needed.

The criteria for assessing phlebotomy are: a decrease of the hematocrit by 5-10% below normal values, a decrease of the transferrin saturation coefficient to less than 45%, and a decrease of serum ferritin to less than 50 ng/ml. After these objectives have been reached, 2-3 maintenance phlebotomies/year will be performed.

C. Drugs: Iron chelating agents are indicated in patients with anemia syndromes or chronic renal insufficiency. Deferoxamine (Desferal) gives good results, being administered intravenously or subcutaneously in a dose of 1-2 g/day; it can be associated with 100-200 mg ascorbic acid.

D. Prophylactic treatment

- Primary prophylaxis includes genetic counseling and the identification of persons at risk based on HLA or on family history.
- Prophylaxis of complications is performed in the asymptomatic stage of the disease, by excluding alcohol, iron-rich foods and drugs, as well as by administering chelating agents, to prevent iron accumulation in tissues.

II. WILSON'S DISEASE

Definition

This is a thesaurismosis described by Wilson, which is characterized by copper storage in tissues and *hepatic, neuropsychiatric and ocular manifestations* (Kaiser-Fleischer ring), as well as other organ impairments (kidneys, bones, skin). The disease is genetic, with an autosomal recessive pattern of inheritance.

Etiopathogenesis

In Wilson disease, two important anomalies occur:

1. Decreased synthesis of ceruloplasmin, the serum copper-transporting protein.

2. Decreased biliary copper excretion.

In Wilson disease, there is no increased absorption of dietary copper, but a decrease of biliary copper excretion, which explains the positive balance. Copper is found in the plasma in two forms: bound to ceruloplasmin (90 microg%) and free (10 microg%). In Wilson disease, copper increases significantly above this concentration, reaching 100 microg%, and diffuses from the vascular space into tissues, where it induces cell lesions. The liver is the first organ in which it accumulates.

Morphopathology

Liver cirrhosis in Wilson disease is macronodular. Initially, hepatic steatosis occurs, followed by mononuclear infiltrates. Copper is concentrated in

lysosomes and can be evidenced by rubeanic acid staining. Lesions in the nervous system and kidneys are also found.

Clinical picture

In half of the patients the first symptoms occur in adolescence, only in 1% of the patients onset is after 50 years of age. A triad of clinical manifestations is also described in Wilson disease:

1. Hepatic – these are the first manifestations, but they are not specific; thus, hepatomegaly, splenomegaly, jaundice, vascular stars, ascites and other cirrhosis complications occur.

Acute fulminant hepatitis with hemolytic anemia represents another modality of onset. Progressive jaundice, ascites, hepatic and renal failure develop. The phenomenon is similar to acute copper poisoning, and prognosis is severe, with death occurring in days.

Clinical and laboratory findings are common to those of acute viral hepatitis. Chronic hepatitis develops at the age of 10-30 years and subsequently evolves towards cirrhosis.

2. Neuropsychiatric – they occur in the young adult and consist of choreiform movements, Parkinson syndrome, tremor worsening during intentional movements, walking disorders, dysarthria. Mental changes manifesting through non-adaptation to the group, impairment of intellectual abilities may suddenly occur. Anxiety, memory losses or even schizophrenic manifestations are less common.

3. Ocular – they are due to copper storage in Descemet's membrane at the periphery of the cornea and occur in the form of a gray-brown or greenish pathognomonic ring (Kaiser-Fleischer ring).

Other manifestations – copper excess in the skin and bones is accompanied by symptoms and signs due to the disorder of these organs: skin pigmentation, particularly in the legs, bone demineralization.

Diagnosis

Biological tests:

- Decrease of serum ceruloplasmin (normal values: 20-40 mg%)
- Increase of urinary copper excretion (normal values below 40 microg/24 hours, and in Wilson disease, values over 100 microg/24 hours);
- Increase of serum copper;
- Increase of copper levels in the liver (on biopsy);
- Non-specific alteration of hepatic tests.

Clinical forms

Three clinical forms are described depending on the dominant clinical manifestations:

1. Hepatic
2. Hepatoneurological
3. Neurological.

Acute fulminant hepatitis with hemolytic anemia is a potential onset of Wilson disease, or a potential evolution after the cessation of D-penicillamine treatment, leading to death in days.

Evolution

Untreated Wilson disease has a rapid evolution. Under treatment, hepatic and neurological impairments are obviously improved.

Complications are identical to those of liver cirrhosis.

In patients with untreated Wilson disease, death occurs after 15 years. The neurological form has the most severe prognosis. In patients with fulminant hepatitis, prognosis is severe even under treatment. Liver cirrhosis in Wilson disease also has a severe prognosis.

Treatment

1. Diet

It consists of a reduction of copper intake to 1.5 mg/day, by excluding copper-rich foods (shellfish, liver, nuts, cocoa, vegetables and water with a high copper content).

2. Drugs

D-penicillamine 1-2 g/day is a chelating agent, which reduces toxic free copper in blood and increases copper urinary excretion. It is associated with 250 mg/day vitamin B6. Zinc administration diminishes intestinal copper absorption (2x50 mg elemental zinc/day in the form of salts).

3. Liver transplantation

It is indicated in two situations: acute fulminant hepatitis associated with hemolysis, and decompensated liver cirrhosis, which does not respond to chelating agents.

4. Prophylaxis

It is difficult to perform, as the disease is hereditary. It includes genetic counseling and secondary prophylaxis in homo- and heterozygotes, in the asymptomatic stage, by chelating treatment.

8. LIVER TRANSPLANTATION

The aim of liver transplantation is to prolong the life duration and increase the quality of life of patients with end-stage liver diseases. Liver transplantation is intended for end-stage liver cirrhosis and acute liver failure cases.

Over the past 20 years, more than 20,000 liver transplants have been performed in USA, this figure being similar in Europe.

The number of liver (and other organ) transplant centers increases worldwide. In centers with a good experience in liver transplantation, 1-year survival after transplantation is over 85-90%, and 5-year survival is over 80%. The main type of liver transplantation is **OLT** (orthotopic liver transplantation). This consists of taking the liver from a clinically dead donor and transplanting it to the recipient (patient with an end-stage liver disease). The transplanted liver will replace the diseased liver, which is *removed*.

Lately, because of the lack of donors, the number of living related transplants has increased.

Indications of liver transplantation

The clinical conditions for which liver transplantation offers additional potential years of life represent a clear indication for liver transplantation. The main indications for liver transplantation used to be the following:

- primary biliary cirrhosis
- sclerosing cholangitis
- congenital extrahepatic bile duct atresia
- acute liver failure.

All these conditions offer long-term survival. At the same time, these disorders are not very frequent. Because of their high frequency, C and B viral liver cirrhosis, as well as alcoholic cirrhosis (after a compulsory withdrawal period of at least 6 months) have lately become the main indications for OLT.

According to the American United Network for Organ Sharing (UNOS), the main indications for liver transplantation in USA were as follows:

1. post-viral C liver cirrhosis
2. alcoholic liver cirrhosis
3. cryptogenic cirrhosis (without detected etiology)
4. primary biliary cirrhosis
5. acute liver failure
6. autoimmune liver cirrhosis
7. mixed alcoholic and post-viral cirrhosis
8. sclerosing cholangitis.

HCV viral liver cirrhosis currently represents the main indication of liver transplantation, given the large number of C virus infected persons.

After transplantation, the majority of the patients (90%) remain infected with the virus and about 45% have histological evidence of hepatitis 3-20 months after transplantation. Approximately 25% of patients will develop chronic hepatitis, but despite this high recurrence rate, the short- and long-term success of transplantation in patients with C virus is good.

HBV viral liver cirrhosis is extremely frequent in some regions (Asia). The post-transplantation infection of the graft is the rule in patients with pre-transplantation viral replication (HBeAg+ or HBV DNA+). The natural history of post-transplantation hepatitis B is rather poor, with the development of liver cirrhosis or even hepatocarcinoma in less than 2-3 years. Hence the necessity of post-transplantation treatment in patients with replicative B virus by various therapies (long-term anti-HBs immunoglobulins or their association with lamivudine or other nucleoside analogues). This post-transplantation therapy is very expensive (up to 10,000 USD in the first year), which makes the management of transplantation in patients with B virus very difficult. In cases treated in this way, post-transplantation survival is similar to that of other transplantation cases.

Timing of transplantation

The patients proposed for liver transplantation are on a waiting list that exists in each transplant center. Because the number of patients waiting for liver transplantation is continuously increasing, the identification of those with the best postoperative evolution is very important. Liver transplantation will be performed in patients with irreversible liver disease, before the deterioration of the patient's state reduces the chance of therapeutic success and increases the costs of transplantation.

In 1997, the American Transplant Association and the American Association for the Study of Liver Diseases established the following *minimum criteria for inclusion in the waiting list for liver transplantation*:

- Child-Pugh score > 7 points;
- Portal hypertension complications: upper gastrointestinal bleeding (UGB), spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), regardless of the Child-Pugh score;
- Estimated 1-year survival < 10%.

The contraindications for the inclusion of patients in the waiting list for LT are as follows:

- compensated liver cirrhosis;
- sepsis;
- advanced cardiopulmonary diseases;

- HIV seropositive patients;
- malignant extrahepatic disorders;
- active consumption of alcohol or drugs over the past 6 months;
- cholangiocarcinoma – recent studies reevaluate this contraindication, demonstrating a survival rate of 80% in carefully selected cases of cholangiocarcinoma complicating the evolution of primary sclerosing cholangitis, through the application of preoperative radio- and chemotherapy, followed by pre-transplantation exploratory laparotomy.

Situations requiring liver transplantation in patients with cirrhosis include: irreversible hepatic encephalopathy, ascites refractory to diuretics, spontaneous bacterial peritonitis, endoscopically uncontrollable repeated variceal bleeding, hepatorenal syndrome, severe coagulopathy, severe hypoalbuminemia and hyperbilirubinemia. Because the presence of these signs identifies patients with a high risk of low survival, emergency evaluation is required for liver transplantation and for putting the patient on a waiting list.

Hepatic encephalopathy refractory to lactulose and metronidazole is associated with a 1-year mortality of 15-40%.

Ascites refractory to diuretics has a 1-year mortality of 50-80%. In these cases, TIPS (transjugular intrahepatic portosystemic shunt) may prolong survival, but the life duration of the shunt is reduced by frequent occlusion and at the same time, costs are high.

Spontaneous bacterial peritonitis is relatively common in advanced cirrhosis and is frequently recurrent. Each episode incurs a mortality of up to 50%.

In general, patients *can be put* on a **waiting list for transplantation** when they have a Child-Pugh score over 7 (class B), but they *must be put* on the waiting list in the case of a Child-Pugh score higher than 10.

At the time of the decision for a patient to be put on a waiting list for OLT, a clinico-biological evaluation will be initiated, and potential contraindications for transplantation will be identified. The socio-economic living conditions of the patient as well as psychological factors will also be evaluated. The patient should be fully aware of the therapeutic decision and should give his/her *informed* consent for transplantation.

The patient proposed for liver transplantation will undergo cardiological examination (ECG, cardiac ultrasound, +/- coronarography), pulmonary radiography, biological tests: HBsAg, anti-HCV, anti-cytomegalovirus, anti-HIV antibodies, PPD, Doppler ultrasound of the liver and hepatic vessels, liver CT or MRI (for the determination of liver volume and the detection of potential hepatocarcinomas complicating liver cirrhosis). Psychological testing is also compulsory in order to verify patient compliance with permanent post-transplantation therapy.

The mean waiting time on the transplantation waiting list in USA and Europe is 4-8 months.

Patients on a waiting list will be seen by the hepatologist monthly. Patients on a waiting list will be transplanted in chronological order, while taking into consideration the severity of the disease. The final evaluation for transplantation will be performed hours before OLT. Modern liver preservation techniques allow the conservation of the liver for 12-16 hours after its removal. During the hours preceding transplantation, the recipient will be subjected to a detailed clinical and biological examination in order to evidence potential changes since the last evaluation.

Acute liver failure

Along with end-stage liver cirrhosis, acute liver failure is a transplantation indication.

Acute liver failure is a condition characterized by the rapid deterioration of hepatic parameters in a patient without a history of liver disease. It translates into hepatic encephalopathy, jaundice, profuse bleeding.

The main causes of acute liver failure are:

- acute viral hepatitis (A, B, D superimposed on B, non-A, non-B, E)
- postdrug: paracetamol, isoniazid, tetracycline, cocaine, etc.
- acute autoimmune hepatitis
- acute liver steatosis in pregnancy
- mushroom poisoning (Amanita phalloides)
- Reye syndrome
- etc.

The therapy of acute liver failure involves supportive measures. However, mortality in these cases is extremely high, which is why liver transplantation is the ideal therapeutic solution. Post-transplantation survival in these cases can exceed 90%. The only problem is the need to find a donor at the right moment, which is not always possible.

Liver transplantation for alcoholic cirrhosis

This is an important socio-economic problem. Considering the high number of alcoholic liver cirrhoses (particularly in countries such as France, for example), the moral problem of "consuming" a donated liver for an addictive patient (to the detriment of a patient with post-viral cirrhosis) is posed. However, if the patient has been *alcohol-abstinent for more than 6 months* and psychological testing proves the reliability of abstinence, the patient can be put on a waiting list for OLT.

While being on the waiting list, the patient with alcoholic cirrhosis will be verified at home by a social assistant and even unexpectedly, based on alcoholuria, for potential unrecognized alcohol consumption. If the patient is

found to consume alcohol, even occasionally, he/she will be removed from the waiting list for OLT.

The costs of liver transplantation are relatively high, but given that it saves lives and avoids additional costs for the treatment of complicated liver cirrhosis, liver transplantation is a necessary therapeutic option.

The costs of liver transplantation differ from one country to another and from one health care system to another.

The price of transplantation comprises the following:
- the price of pre-transplantation evaluation
- the price of tests during the hours preceding transplantation
- the price required for the procurement of the liver to be transplanted (support of the brain dead donor, special tests for the donor)
- the price of the liver transplantation surgery
- the cost of pre- and postoperative hospitalization
- the cost of post-transplantation medication (in the acute and chronic phase)
- the price of chronic post-transplantation follow-up.

In 1999, the first liver transplants were performed at the Fundeni Hospital in Bucharest (Prof. Irinel Popescu and the team). After a hesitant start and not very encouraging results, in 2001, the success rate of liver transplantation cases increased significantly, clearly opening the way to liver transplantation in Romania. The presence of only one liver transplant center in Romania (in Bucharest) is a handicap for the liver transplantation program in our country. On the other hand, the number of cadaver donors in Romania is relatively small, which is why the number of transplants at national level is also relatively small. Using part of the liver of a living donor (***living related transplantation***) can be a solution in the context of the lack of cadaver donors in Romania.

In order to cope with the lack of donors, new surgical techniques have been developed. The resources used for extending the pool of donors are: "marginal" donors (aged > 50 years, patients with hepatic steatosis, positive markers for hepatitis B or C virus); split liver transplantation technique; living related transplantation; hepatocyte transplantation.

In split liver transplantation, a liver from a cadaver is split into two functional grafts, the right lobe being used for an adult recipient, and the left lobe (segments 2, 3 and 4) or the left lateral segment (segments 2 and 3) for a small stature adult or a child.

Xenotransplantation is the grafting of organs obtained from a species in other species. The majority of the investigators consider the pig as a potential donor for humans, given the adequate size, the unlimited availability, as well as the ability to produce the graft by genetic engineering. The clinical use of xenografts does not seem to be feasible at present, although gene therapy has been able to solve hyperacute rejection.

Hepatocyte transplantation is aimed at treating genetic metabolic diseases (e.g. Crigler-Najjar syndrome), acute liver failure, and chronic complications of liver failure, such as HE. Hepatocytes can be isolated from a number of species (including humans), then they can be cultured or cryopreserved. Hepatocyte transplantation is currently considered a bridge until orthotopic LT is performed.

Identification of potential donors

Organ donors can be *brain dead* persons. These are usually cases of brain trauma from road traffic accidents, severe cerebrovascular accidents. Brain death is established based on complex neurological tests and on the repeated lack of electrical activity on the EEG. The team making the diagnosis of brain death is different from the transplant team and includes a neurologist (neurosurgeon), a resuscitator, and possibly, a forensic specialist.

The Romanian legislation in force regarding organ transplantation stipulates that organ donation can only be performed with the written consent of the closest family members. Hence, in many cases, even if a potential organ donor exists, the consent of the family cannot be obtained.

The Intensive Care Unit where a potential donor is found will notify the Transplant Center, which will start the procedures for a possible organ transplant. After the diagnosis of brain death is made, the *transplant coordinator* (who is not a member of the surgical transplantation team) will attempt to obtain the consent of the family.

The allocation of a potential organ for transplantation will be performed in the following order:

- the local center in the first place
- then, the regional center
- subsequently, at national level.

Transplant priorities are as follows:

- acute liver failure;
- liver cirrhosis with severe, immediate life-threatening complications;
- Child-Pugh class C liver cirrhosis.

Decision of compatibility

If in the case of kidney transplantation, HLA compatibility is necessary, in the *case of liver transplantation, only ABO compatibility is required*.

Another requirement is that of the compatibility of the donor liver size with the size of the recipient. In the case of a large donor liver and a small size recipient, only a liver lobe can be transplanted (surgical adjustment of the transplanted liver).

A liver transplantation variant is **split liver transplantation**, which consists of splitting the liver into two parts and transplanting them to two recipients (frequently the right lobe to an adult and the left lobe to a child).

Lately, because of the decreasing number of cadaver donors and of the increasing number of recipients on the waiting list, a new type of transplantation has been used: **living related transplantation** (the left liver lobe from a living donor is usually transplanted; this is the case of donation from parent to child or between other relatives). The technique is widely used in Japan, where religious precepts prevent transplantation from a cadaver, but it also becomes increasingly used in Europe and USA.

Technique of transplantation

When a potential brain dead donor appears and the family's consent for donation has been obtained, the procurement team will go to the location of the donor and, under strict sterile surgical conditions, will remove the organs (for which the family's consent has been obtained). The removed liver is preserved with ice and preservation solutions (Wisconsin solution). Using an ordinary coolbox, it is transported to the location where transplantation will be carried out. Meanwhile, the transplant team summons the recipient, who will undergo a last evaluation.

What is the role of a **bank of organs** and how is it organized? This is an administrative structure that deals with the detection of potential donors (generally in Intensive Care Units), the obtaining of the family's consent and subsequently, the transportation of the donor organ. In the bank of organs there are no organs, as the preservation time of the liver, heart or kidneys is of the order of hours.

The liver can be preserved with preservation solutions (Wisconsin, Euro-Collins solutions) and ice for up to 12-16 hours. However, ideally, it should be transported as rapidly as possible to the transplantation location, in order to avoid its variable deterioration.

The transplant team will remove the recipient's liver, and there will be an anhepatic phase for several minutes, during which extracorporeal veno-venous pump driven circulation will be used. After the preparation (the possible adjustment of the size) of the donor liver, this will be placed in the location of the old diseased liver (OLT). We mention that in liver transplantation, the only compatibility required between the donor and the recipient is ABO compatibility, which makes the choice of compatibility relatively easy.

The surgical anastomosis of the inferior vena cava, portal vein and hepatic artery will be performed (the last is the most important, because a failed anastomosis will lead to ischemia and to the loss of the donated liver); biliary

anastomosis (termino-terminal or choledoco-jejunal anastomosis) is also performed.

The duration of liver transplantation surgery is 3-7 hours, depending on the local anatomical situation of the recipient, as well as on the experience of the surgical team.

After surgery, the transplanted patient is carried to the ICU, where rigorous antiseptic conditions must be maintained to avoid intrahospital infections in a patient who will be immunosuppressed from post-transplantation therapy.

The main problems that may occur after transplantation are *acute and chronic rejection, and infections* (in an immunosuppressed patient).

Post-transplantation medication

The administration of post-transplantation medication is aimed at avoiding the acute or chronic rejection of the transplanted liver. In general, standard medication consists of:

- prednisolone;
- cyclosporine, tacrolimus (or more recently, sirolimus);
- mycophenolate mofetil.

Prednisolone administration is initiated during anesthesia, then the dose will be progressively reduced, from 300 mg to 20 mg in the first 2 weeks. Transition from induction to maintenance immunosuppression starts immediately after LT and lasts for several months.

Cyclosporine is administered as early as the intraoperative period, then i.v. administration is continued, and after 3 days, oral administration is initiated (Neoral). The administered dose will be adjusted based on serum levels (determination of cyclosporinemia). Azathioprine will be administered orally starting with day 3, in a dose of 1-1.5 mg/kg body weight/day.

The chronic administration of this medication is initiated after the patient's discharge and generally consists of the administration of prednisolone (starting with 20 mg/day; after several months, the dose is progressively reduced, up to 5-10 mg/day), cyclosporine (in a dose determining cyclosporinemia of 100-250 ng/ml), and azathioprine (Imuran) 1-1.5 mg/kg body weight/day (azathioprine is stopped 9 months after transplantation).

Post-transplantation rejection can be **acute** or **chronic.**

The clinical signs of **acute rejection** are: asthenia, fever, pain in the right hypochondrium, jaundice, and biological signs are: increased transaminase levels, possibly cholestasis. Confirmation is made by liver biopsy.

Acute rejection is treated with high prednisolone doses i.v. (500 mg/day) and in the absence of response, with OKT3, antithymocyte globulin (ATGAM) or mycophenolate mofetil.

Some studies have shown that the post-transplantation treatment of patients with tacrolimus instead of cyclosporine reduces the number of rejection cases.

Chronic rejection is much more insidious and usually manifests after more than 6 months post-transplantation. The causes include inadequate dosage of immunosuppressive medication, hepatic ischemia through partial thrombosis of the hepatic artery, cytomegalovirus infection. Diagnostic confirmation is made by liver biopsy.

Patients must always be informed before transplantation that they will have to take immunosuppressive medication throughout the course of their lives.

Although azathioprine can be stopped after 9 months, and in some cases with a favorable evolution, prednisolone can also be stopped, cyclosporine (or tacrolimus) administration will be continued throughout the course of life.

Post-transplantation infections represent another serious problem, because they can compromise all the efforts of the transplant team. Bacterial or viral infections may develop in the highly immunosuppressed patient.

Severe hygienic measures will be taken against post-transplantation *bacterial infections*, and if these occur, they will be treated with adequate doses of antibiotics (preferably following the antibiogram).

In the absence of antiviral prophylaxis, a reactivation of the following may occur in the first weeks after transplantation: *herpes infection* (oral or genital), which is treated with oral acyclovir, *cytomegalovirus infection* (post-transplantation prophylaxis is usually performed), or *varicella zoster virus infection*.

Fungal infections may also occur in immunosuppressed patients and are quite difficult to treat with amphotericin B.

In patients transplanted for B virus liver disease (particularly the replicative HBeAg+ or HBV DNA+ forms), in the absence of adequate prophylaxis, the infection of the grafted liver is the rule. This infection is avoided by the administration of anti-HBs immunoglobulins (HBIG), starting with the anhepatic phase of transplantation and continuing in the long term. Lately, it has been attempted to combine these immunoglobulins with an antiviral agent (lamivudine), which is less expensive and more available, and will support therapy alone after the first month post-transplantation.

After transplantation, vaccination with live viruses (even attenuated) will be contraindicated. Other vaccinations can be administered. Annual anti-influenza vaccination is recommended for transplanted patients.

Other possible complications that may occur in transplanted patients are:

- vascular complications

- biliary complications.

Vascular complications are represented by hepatic ischemia, in case of inadequate vascular anastomosis or in case of hepatic artery thrombosis. These vascular complications, unless rapidly corrected (angioplasty or surgery), will lead to the loss of the graft, requiring retransplantation.

Biliary complications are represented by the stenosing of the termino-terminal biliary anastomosis and must be solved endoscopically (dilation of stenosis by ERCP) or surgically. The rate of post-transplantation biliary complications may vary from 5 to 30%, depending on the experience of the surgical team and on local anatomy at the time of transplantation.

To conclude, we mention that survival after liver transplantation in centers with good experience is approximately 90% at 1 year and 80-85% at 5 years, with a good quality of life and acceptable costs (considering the money saved by avoiding the treatment of the multiple severe complications of advanced cirrhosis).

Medical and civic education, aimed at increasing the number of donors and at developing new transplantation techniques (living related transplantation), will allow to save an increasing number of patients with end-stage cirrhosis.

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