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FUNCTIONAL DYSPEPSIA – A MODERN REVIEW

Miglena Stamboliyska, Kamen Ivanov
Clinic of Gastroenterology, UMHAT "St. Marina" – Varna

ФУНКЦИОНАЛНА ДИСПЕПСИЯ – СЪВРЕМЕНЕН ПРЕГЛЕД

Миглена Стамболийска, Камен Иванов
Клиника по гастроентерология, УМБАЛ „Св. Марина" Варна

РЕЗЮМЕ

Функционалната диспепсия, наричана в миналото неязвена диспепсия есериозен гастроентерологичен проблем, често срещан в ежеднедната клинична практика, смущаващ качеството на живот на пациентите, свързан с повишаване разходите за здраве. Функционалната диспепсия е понятие, според Рим III критериите, дефинирано като присъствие на диспептични симптоми, изхождащи от гастродуоденалната област, в отсъствието на каквито и да било органични, системни или метаболитни заболявания, които да обяснят симптомите. Възприети са две подгрупи на функционалната диспепсия, според преобладаващите симптоми :постпрандиален дистрес синдром, проявявящ се с пълнота и ранно засищане след нахранване и епигастрално-болков синдром с епигастрална болка или парене. Патогенезата е сложна и не добре изяснена.В основата на патогенезата са налични две големи патофизиологични отклонения: абнормен стомашен мотилитет и висцерална свръхчувствителност. Има и други фактори свързани с патофизиологията и патогенезата и това са факторите, които модифицират манифестацията на симптомите: абнорна стомашна киселинна секреция, HP-инфекция,психологични фактори, диета, начин

ABSTRACT

Functional dyspepsia, known also as "non-ulcer'' dyspepsia in the past, is a serious problem in Gastroenterology, very common in everyday clinical practice, disturbing the quality of life of the patients, with increasing health costs.

Functional dyspepsia is determinate, according to the Rome III criteria as the presence of gastrointestinal disorders, in the absence of any organic, systemic or metabolic disease, which could explain the symptoms. Categorized in 2 subgroups of functional dyspepsia, according to the predominant symptoms – postprandial distress syndrome: early satiation or postprandial fullness and postprandial epigastric pain syndrome-with epigastric pain or burning. The pathogenesis of FD is complicated and still remains unclear. The basis of pathogenesis are available two major pathophysiological abnormalities: abnormal gastric motility and visceral hypersensitivity. There are another factors related with pathophysiology and pathogenesis of FD, that also modify the manifestation of the symptoms – abnormal gastric acid secretion, infection with Helicobacter pylori, psychological factors, diet and lifestyle. The most common clinical symptoms of functional dyspepsia are: postprandial fullness, belching, early satiation, nausea, vomiting, retrosternal or epigastric burning, epigastric pain. There is an overlap of clinical symp-

на живот. Най-честите клинични симптоми на функционалната диспепсия са: пълнота, подуване в горния етаж, рано засищане, гадене, оригване, повръщане, епигастрална болка, парене и ретростернално парене. Наблюдава се оверлап на клинични симптоми при пациенти с функционална диспепсия, Поставянето на диагнозата става по пътя на изключването. Пациенти с типични симптоми и без алармени симптоми могат да не се подлагат на диагностично изследване и могат да бъдат лекувани емпирично. Лечението на функционалната диспепсия е предизвикателство за гастроентеролога в клиничната практика.Стратегията „Тествай и лекувай за HP“ е подходяща за неизследвана диспепсия, в популацията с висока честота на HP инфекция. При клиника на постпрандиален дистрес синдром, прилагането на прокинетици е средство на избор. Акотиамид е нов прокинетик, който показва потенциал да подобри функциониращите системи и качеството на живот при пациенти, чрез механизъм който включва подобряване на стомашната акомодация.

Ключови думи: Функционална диспепсия, инфекция с Helicobacter pylori, гастроинтестинални нарушения,патологичен мотилитет, прокинетик.

toms in patients with functional dyspepsia. The diagnosis is managed by way per exclusion. A patients with typical signs and symptoms of FD without any alarm symptoms may not be subjected to a diagnostic tests and can be treated empirically. The treatment of functional dyspepsia is a challenge for the gastroenterologist in the clinical practice. The strategy “test and treat for HP-infection” is preferred for a non-examined dyspepsia in the population with a high risk of HP infection. In clinic of postprandial distress syndrome, the use of prokinetic agents is the first choice of treatment. Acotiamide is a new kind of drug, demonstrating strong potential for optimize the treatment of FD and superior the quality of life in patients with FD, through a mechanism that involves increased gastric accommodation.

Key words: Functional dyspepsia, infection with Helicobacter pylori, gastrointestinal disorders, abnormal motility, prokinetic.

INTRODUCTION: THE TERM „DYSPEPSIA“ MEANS INDIGESTION.

Dyspeptic symptoms are very common in the general population and affects it in 20 – 40%, depending in different regions of the world.

There are many study results, shows different frequency and impact of dyspepsia in the primary population. These results are influenced by the criteria for definition of functional dyspepsia (FD).

Expert consensus (23, 26) has proposed to define FD as pain or discomfort centered in the upper abdomen. FD is represented as a heterogeneous group of symptoms, that are centered in epigastric region. Typical dyspeptic symptoms include postprandial fullness and/or discomfort, early satiation, epigastric pain, epigastric burning, and other gastrointestinal symptoms such as nausea, belching, or abdominal swelling, which also occur frequently.

DEFINITION OF FUNCTIONAL DYSPEPSIA

Functional dyspepsia is defined as a condition in which upper abdominal symptoms occur in the absence of any organic disease that explains them (9, 23, 26, 29).The term dyspepsia display a variety of digestive disorders, such as: delayed gastric emptying, accelerated gastric emptying and impaired gastric accommodation after meal, hypersensitivity to gastric distention, abnormal gastric sensory or motor function is infrequent.

The functional gastrointestinal disorders are a collection of conditions affecting every

part of the gastrointestinal that share most of the following features (5):

- the underlying pathophysiologic mechanisms are largely unknown
- no anatomic or traumatic defect that could cause the dysfunction;
- not related to a metabolic abnormality such as hypothyroidism;
- they cause symptoms that are often vague and difficult to localize;
- they are (dys)functional in that the normal neuromuscular function of the affected part of gastrointestinal tract is impaired and/or causes discomfort;
- psychosocial factors may affect the susceptibility to gastrointestinal tract (GIT) dysfunction and the ability to cope with symptoms.

In order to improve the diagnosis of these GI disorders, international experts of their meetings in Rome have developed and accept the Rome criteria for the diagnosis of FD. The existence of the Rome criteria are the result of international cooperation to improve the diagnosis and treatment of functional gastrointestinal disorders. Rome diagnostic criteria which are I, II and III, categorized functional gastrointestinal disorders and defined symptoms, classificated in different subgroups, based on the diagnostic categories (23).

The first definition for FD called and identified as "on-ulcer'' dyspepsia is given by Talley and et al. (28, 29). According to the Rome I criteria, the concept of FD includes: pain in the upper abdomen or retrosternal pain, discomfort, retrosternal burning(heartburn), nausea, vomiting or other symptoms, related to the upper digestive tract and lasting more than 4 weeks, not result to exercise, focal lesion or systemic disease, responsible for this.

"Non-ulcer'' dyspepsia is subdivided into three subgroups, dependending of predominance of the following symptoms:

- Gastroesophageal reflux – similar FD (with leading symptom burning -retrosternal and epigastric burning)
- Dysmotility – similar FD (bloating, early satiation and stretching)
- Ulcer- similar FD (with epigastric pain).

In chronological aspect is the identification and definition of a FD, according to the Rome II criteria (6, 26). This is the pain or discomfort centered in the upper abdomen, in the absence of anyorganic disease, that might explain these symptoms.

Following diagnostic criteria are used:

- duration of the symptoms – at least 12 weeks, which need not to be consecutive, in the previous 12 months.
- continious or repeated FD (pain or discomfort, centered in the upper abdomen)
- no evidence of organic disease by the endoscopy, to explain the symptoms.
- no evidence that FD passes after defecation, excludes irritable bowel syndrome (IBS).

The following 3 subgroups were identified, depending on the leading symptom:

- ulcer – similar FD (upper abdominal pain)
- dysmotility – similar FD (epigastric fullness)
- undefined, non-specific FD (mixed symptoms)

The third in historical aspect contribution of FD, according to the recent Rome III criteria (6, 23,26) is defined as a presence of the symptoms , that are believed to originate from the gastrointestinal tract (GIT), in the absence of any organic, systemic or metabolic diseases, which is likely to explain the symptoms.

Diagnostic criteria includes one or more of the following symptoms: postprandial fullness and/or discomfort, early satiation, epigastric pain, epigastric burning, in absence of any organic disease, to explain the symptoms. It should have been completed for the last 3 months with symptom onset, at least 6 months before the diagnosis is accept.

There are 2 subgroups according to the predominant symptoms (6, 23, 26):

- **Postprandial distress syndrome (PDS),** presenting with fullness and early satiation after meals
- **Epigastric pain syndrome (EPS)** – with epigastric pain or burning

FREQUENCY AND DISTRIBUTION OF FUNCTIONAL DYSPEPSIA. SOCIAL IMPORTANCE

Functional dyspepsia is one of the two most common functional gastrointestinal disorders and is estimated to account for 5% of primary carevisits, with aneconomic burden of at least US $1 billion per year in the USA (1).

PATHOGENESIS. PATHOPHYSIOLOGICAL MECHANISMS

Functional dyspepsia (FD) is a heterogeneous disorder in which different pathophysiological mechanisms are at based on the specific symptoms. Elucidating the pathogenesis of FD means answering the question, "Why do symptoms occur?". The factors contributing to symptom manifestation in FD probably should be divided into 3 categories:

- physiological abnormalities that directly induce symptoms,
- factors that modify those physiological abnormalities,
- factors that govern abnormal responses to stress.

The symptoms of FD are directly caused by two major physiological abnormalities:

- abnormal gastric motility
- visceral hypersensitivity

The pathogenesis of FD has focused on the functional deviation in the digestive tract. Many study tracks (18,19,21,26,31) determined how does the digestive tract in patients with FD diverges from that in healthy individuals. In the functioning of the stomach, abnormal gastric motility and visceral hypersensitivity are thought to be the phenomena that are most closely related to the manifestation of FD symptoms.

ABNORMAL GASTRIC MOTILITY

On regard to abnormal gastric motility, postprandial motility, in particular, is a major problem (14).It has been learned that postprandial gastric motility has two phases: a phase when an accommodation reflex occurs in the proximal stomach (fundus) after food consumption, and a subsequent phase when distal gastric distension occurs after delay. It is becoming clear that the proximal gastric distension that occurs in the first phase, correlates fairly well with dyspeptic symptoms. The accommodation reflex is regarded as an appropriate biological response by which food provided with areservoir in the stomach, but in FD patients, the reflex can be impaired, leading to early satiation seen in 40–50 % of FD patients.

Delayed gastric emptying after the indigestion of solid food is seen in approximately 40% of FD patients.

VISCERAL HYPERSENSITIVITY

Visceral hypersensitivity is considered as the physiological abnormality, most closely related to FD, has been shown to be involved in functional disorders throughout the gastrointestinal system, including non-erosive gastroesophageal reflux disease (NERD) in the esophagus, IBS and FD. When a balloon is distended in the stomach of an FD patient and a healthy control, the threshold at which pain is perceived is significantly lower in the FD patients than in the controls. In 35–50 % of FD patients are proved to be hypersensitivity to such gastric distension stimuli.

Excessive acquired response, that is often seen in FD is a result of the impact of:

- the environmental during early life
- genetic abnormalities
- residual inflammation after gastrointestinal infection

A gastric hypersensitivity is said to be related to symptoms including postprandial pain, belching and weight loss. In addition to hypersensitivity to gastric distension, FD patients also seem to have hypersensitivity in the stomach and duodenum to gastric acid, bile acid, and some nutrients. Besides the well known physiological abnormalities, such as gastric motility disorder and visceral hypersensitivity, there are other factors related to the pathophysiology and pathogenesis of FD (18, 31). These are

factors that modify the manifestation of symptoms:

- abnormal acid gastric secretion
- infection with Helicobacter pylori
- psychiological factors
- diet
- lifestyle

ABNORMAL GASTRIC SECRETION

Excessive increased gastric acid secretion, affects the pathogenesis of FD, leading to abnormal gastrointestinal function. It is occurs with hypersensitivity abnormal gastric and duodenal motility, by inflammation of duodenal mucosa, induced variations in the symptoms. In this sense, the acid can be positioned as an indirect factor, which modifies the manifestation of clinical symptoms.

INFECTION WITH HELICOBACTER PYLORI. THE RELATIONSHIP HP INFECTION – FD

Discussing the possibility about HP infection as a factor for onset of the symptoms of FD. H. pylori infection is another important factor in the manifestation of FD symptoms that is localized in the stomach (18).The most common approach to investigate the relationship between H. pylori and FD has been to examine improvements in FD symptoms resulting from the eradication of H. pylori. The results of research on the effect of H. pylori eradication therapy on improvement in FD symptoms are not consistent. Conclusions from these trials, are controversial. Meta-analysis (7, 12, 18, 24) shows that HP-eradication therapy improves the symptoms of patients with FD, but the effect is not large about the permanent elimination of the symptoms. It is hard to believe that HP-infection is an important factor in the pathogenesis of FD. HP-eradication in patients with FD should probably be considered primarily, because it prevents the development of ulcers and cancer. According to the Rome criteria, H. pylori infection status does not affect the diagnosis of FD and both H. pylori infection-positive and HP-negative types of FD exist. Recently, the idea that H. pylori infection should be regarded as gastritis, an organic disease and H. pylori associated dyspepsia should not be considered as a functional disorder has been proposed. Latest strategys that HP (+) positive patients with FD should be HP-eradicated first. A new definition, that requires the patient to be H. pylori-negative for a diagnosis of FD may gain wide acceptance.

PSYCHO-PHYSIOLOGICAL FACTORS

Psychological factors significantly present in individuals with FD symptoms and change the pathogenesis. (33). It has also been reported that often FD patients have also symptoms of depression and tend to show psychological abnormalities. It is proved that anxiety and anger can induce hypersensitivity and abnormal motility of the esophagus and stomach – a finding which supports the idea that psychological factors greatly modify pathogenesis. It is interesting the relationship between psychological factors and FD – usually it is in a two-way (1). In one hand depression entails the development of the symptoms of FD, and in another – FD leads to panic disorder and depression. In this sense, anxiety disorders and depression are often regarded as comorbidities of FD. The idea is not that psychological factors directly cause abdominal symptoms, but rather that persons who are susceptible to dyspepsia also tend to have mood disorders such as anxiety, and to show symptoms of depression.

ROLE OF DIET

A different studies have begun to pay attention to the role of diet in triggering gastrointestinal symptoms. FD symptoms have been associated with the indigestion of gluten and fat, and with the amount of indigested food. As for the positive effects, the addition of glutamate to a diet, high in energy and protein promoted gastric emptying and rice and spicy food (chili) may improve dyspeptic symptoms.

LIFESTYLE

Lifestyle may also affect the manifestation of FD symptoms (20, 21). FD has also been associated with insufficient sleep and disturbed eating habits, such as irregular meal times. It seems quite possible that a lifestyle, in which sleep or meals are irregular could induce autonomic dysfunction and thereby affect the manifestation of dyspeptic symptoms. Additional data are needed to elucidate the role of smoking, excessive caffeine consumption, social factors including poor socio-economic status and a poor living environment in FD**.** Other factors that induce an influence in patients with FD to stress are: influence of the environmental, genetic abnormalities, gastrointestinal infections.

Patients with functional gastrointestinal disorders do not have symptoms all the times. Their symptoms can disappear and reappear, as well as worsen and improve. Stress can trigger these symptoms. Functional abnormalities in the gastrointestinal tract are not seen constantly in patients with functional gastrointestinal disorders. The abnormalities occur as the digestive tract responds to external stimuli such as stress and environmental changes. It is possible that reaction to stress is genetically determined. That is way the attention should be directed over the study of genetic abnormalities in patients with FD. The manifestations of the symptoms of FD are associated with a single-nucleotide polymorphism (SNP) genotype at position 825 of the G protein beta-3 subunit gene (18, 31).

ROLE OF LOW–GRADE INFLAMMATION

The results of some studies (31, 32) determined the role of inflammatory mechanisms in the pathogenesis of FD. Some authors (10) reports, that the risk of developing FD is increased after gastrointestinal infections. This is so-called post-infectious FD.

That was first recognized as a possible clinical manifestations of FD from Tack et al. (25). So the conclusion that impaired gastric accommodation and abnormal motility and also the symptoms of early satiation, weight loss, nausea and vomiting are more frequently observed in patients with post-infectious FD. Tack et al. (25) found increased risk in the patients with PI-FD of impaired gastric accommodation after meal, associated with dysfunction of gastric neurons. As the proof of this concept is the fact that patients with Salmonella gastroenteritis of Lamblia intestinalis infection, suffering from visceral hypersensitivity and delayed gastric emptying. Some studies (10, 31, 32) found that infiltration of the duodenal mucosa by macrophages was significantly increased in post-infectious FD patients. Some relationship was detected between the level of intestinal inflammation and cellular infiltration in the PI-FD, and the persistence of the immune cells. Developing the hypothesis that the transit inflammation leads to permanent changes in the structure and function of GIT. Some authors (10, 31) reported that the signs of a low-grade inflammation, are no exception in PI –FD, characterized by elevated levels of tryptase in the biopsy. Others (10, 31, 32) defined PI -FD as a non-specific or inconclusive subgroup of FD and it was formed as a third subtype of FD.

In recent years there are a discussion about existing other mechanisms in the pathogenesis of FD.

ROLE AND IMPORTANCE OF THE IMMUNITY SYSTEM INFLAMMATION

Elevated levels of TNF, IL -1-B , L-10 and an increase in T-cells , compared to healthy controls are positively correlated with the intensity of symptoms such as pain, nausea, vomiting and delayed gastric emptying (32). According to the concept of duodenal-inflammatory component in FD, as well as the increased level of eosinophils into the duodenum, demonstrated the relationship between the increasing levels of eosinophils in the duodenum and anamnesis of allergy and postprandial distress syndrome (PDS). Some researches (31) determinate full activation of the immunity system in FD, not

only in the group of PI-FD. The basic mechanism in the pathogenesis needs to be found, but we may suggest that the reduced function of the mucosal barrier may facilitate an immune mediated response to the antigens in the lumen.

INCREASED PERMEABILITY OF THE DUODENUM IN FD

The presence of functional changes in the mucosa of the duodenum , determinate by the endoscopy and biopsies, confirmed by the significant decrease of adhesion molecules in the duodenal mucosa, increased number of eosinophils and mast cells. These observations (32) support the hypothesis of a mechanical relation between the mucosal integrity and low-grade activation of the immunity system. In celiac disease – dietary immunogenic proteins and gluten, reaching the lamina propria, due to increased intestinal permeability, which causes the response of T-cells in susceptible individuals. Impaired integrity of the intestinal wall and low inflammation is unifying finding in celiac disease and FD. The presence of celiac disease should be excluded in patients with dyspepsia.

CLINICAL SYMPTOMS

The most common clinical symptoms of FD are: postprandial fullness, swelling in the upper abdomen, early satiation, nausea, belching, vomiting, epigastric pain, burning and retrosternal burning. Some studies (14, 18, 31) indicate that the frequency of impaired gastric accommodation in patients with FD is in 40%. Tack et al. (14) show that early gastric satiation is one of the most frequently occurring symptom of FD and it is observed in more than 90% of patients with impaired accommodation, compared to 40% of those with normal function. In these cases more often affects the symptom – weight loss. The reduction of body weight in 70% compared to 40% in healthy. The following symptoms by the frequency in the population are: postprandial fullness and bloating of upper abdomen. The wide variety of symptoms, due to a several pathophysiological mechanisms, results in onset of the functional disorders. The FD is divided into two main groups (13, 25). By the epidemiological researches from the US and Europe also confirm the presence of two major subgroups:

- postprandial distress syndrome (PDS)
- epigastric pain syndrome (EPS)

PDS is characterized by an early satiation after meal, fullness and/or discomfort that is activated after the meal. Symptoms of nausea, rarely – vomiting and bloating, as well as belching, may be present in all patients with FD. By the patients in this subgroup was observed also a weight loss. The presence of some symptoms, associated with food intake are confirmed by researches, to support the Rome III criteria. Choung et al. (4) identified three subgroups of FD symptoms -pain, early satiation, nausea and vomiting. It is believed that psychosocial disorder or disease, as the main relating factor determinate the severity of the symptoms. Two-way relationship between the functional gastrointestinal disorders and psychological factors is the basis of FD (33).

In fact, depression causes FD and also in patient with FD, we observed an increased anxiety and depression. In the medical centers of General Practitioners in Europe and Asia was observed an overlap between EPS and PDS. So there is an overlap of clinical symptoms and also overlap between PDS and EPS in patients with FD (11).

Each subgroup is characterized by leading symptoms. According to the main overlap symptom, patients with FD were divided into three subgroups:

- patients with FD, overlap with gastrointestinal diseases, including the upper and lower GI tract;
- patients with FD and overlap with non-gastrointestinal diseases;
- patients with FD and overlap with symptoms inside the subgroups;

A. Overlapping symptoms in subgroups:

Overlapping ulcer-like symptoms with dysmotility-like symptoms and reflux-like symptoms have been reported in non-ulcer dyspepsia of Talley et al. (28, 29). In 43% of patients with FD can be classified into more than one group. According to Rome III criteria and their frequency is different – between 56% and 62%.

FD overlap with non -gastrointestinal diseases

Functional somatic syndrome include fibromyalgia syndrome, chronic fatigue syndrome, syndrome of hyperactive bladder. Very often they are associated with an irritable bowel syndrome (IBS) in the same individuals. Up to 50% of patients with fibromyalgia have a symptoms of FD. In 40% of the patients with FD there is a chronic fatigue syndrome. Up to 40% of patients with interstitial cystitis have symptoms of FD.

FD overlap with upper gastrointestinal diseases (retrosternal burning or GERD)

Overlap of FD with retrosternal burning was present in the half of the patients, so and the reflux symptoms. In 60% of patients with reflux symptoms have FD. Overlap of GERD is present in 30% to 40% of the patients with FD, according to Rome III criteria. Very often there is a combination between GERD and FD and non-erosive GERD with reflux disease /NERD/ and erosive reflux disease /ERD/. Patients with NERD have overlap with FD frequently, than those with ERD and GERD overlap with NERD.

FD overlap with diseases of the lower gastrointestinal tract

According an epidemiology researches about the overlap of FD and IBS indicate that the frequency of FD in IBS was 27%. There is a tendency to increase frequency of IBS and FD. FD and IBS often overlapping, especially in cases of constipation, as a main clinical symptom. The most common clinical symptoms of FD are: fullness, bloating, early satiation, nausea, belching, vomiting, epigastric pain, burning and retrosternal burning.

FD – diagnosis algorithm, diagnostic methods

Diagnosis of FD is achieved per exclusionem. Based on instrumental and functional studies through which excludes organic, structural disorders and metabolic diseases. Patients with typical symptoms of dyspepsia and no alarm symptoms do not need to undergo further investigation, and can be managed empirically. When risk factors, including NSAID use, age above a certain threshold (such as 45–55 years), or alarm symptoms (such as unintended weight loss, substantial or recurrent vomiting, progressive dysphagia, evidence of gastrointestinal bleeding, or family history of cancer) exist alongside new-onset dyspepsia, prompt endoscopy is recommended (13, 25, 26, 34). An upper endoscopy (FGS) is recommended for all patients up to 50 – 55 years of age, because of the GI- diseases diagnostic. At the same time, this procedure brings relief and satisfaction in the suffering patients. It is necessary to make HP- diagnostic in patients with FD. In this aspect the strategy – "Test for HP", appears to be effective in the diagnosis of FD, by reducing the use of diagnostic endoscopy.

METHODS TO CHARACTERIZE SUBTYPES OF FD

These are methods used for demonstrating hypersensitivity and impaired gastric accommodation. They are not standardized and are not used in the routine clinical practice.

- **nutrient drink test**
  After overnight fasting, participants ingest a nutrient drink containing 1–1.5 kcal/ml at a constant rate (for example, 30 kcal/min) until a volume ingested results in full satiation and inability to drink any more (termed the maximum tolerated volume).
- **gastric emptying by scintigraphy**

Scintigraphic measurement of gastric emptying has been standardized with the use of a relatively low-calorie and low-fat meal (for example, an Egg Beaters® meal of 23 kcal, or a two-egg meal.

- **gastric emptying by stable-isotope breath test**

  Stable-isotope breath tests are in the process of being standardized, so that a meal with a reasonably long shelf-life (for example, 6 months) with known caloric and nutrient characteristics can be used- 13CO2

- **gastric volume measurements**

  Barostat measurements of gastric sensation, compliance and accommodation, and single photon emission CT-measurements of gastric volumes during fasting and after meals Univariate associations exist between fullness/satiety or bloating and gastric discomfort volume, between preprandial gastric volume or gastric compliance and upper abdominal pain.

DIFFERENTIAL DIAGNOSIS OF FD

In the presence of any alarm symptoms should be done differential diagnosis between organic and functional dyspepsia (23). Gastric acid secretion associated diseases of the upper gastrointestinal tract are the most common reason for the symptoms. The differential diagnosis of FD includes diseases of hepatobiliary and pancreatic system.

We have to exclude the following diseases:

- Esophagitis
- Peptic ulcer disease
- Carcinoma of GIT
- Cholelithiasis
- Pancreatitis
- Carcinoma of the pancreas
- Celiac disease
- Myocardial ischemia

TREATMENT OF FD

Treatment of FD is a challenge for the gastroenterologist in a clinical practice. Eradication of HP-infection, the benefits of antisecretory drugs, using of prokinetic agents and antidepressants is recommended as a leading treatment strategy for a FD by consensus (1, 3, 16, 17, 19, 22)

- Compared to Europe and America, HP – eradication therapy in Asia, leading to a higher rate of symptom relief and a higher incidence of symptomatic response after a medication with prokinetic agents (3,8,12, 19).
- The variety of clinical manifestations of FD and uncertain pathomorfologica lmechanisms lead to difficulties for selecting a drug therapy to treat FD. (23, 22, 24)
- Although the updated guidelines for the treatment of FD and diagnostic criteria, the treatment **remains uncertain.**

Patients with different symptoms and mostly non-alarmic, could not undergo further diagnostics procedures and could be treated empirically, according to the management guidelines (1,28)

The strategy „test and treat for HP-infection“ is mostly acceptable for a non-diagnosted patients with FD in the population with a high frequency of HP- infection. This strategy is efficient and cost effective by reducing the use of endoscopy and proton pump inhibitors (PPI). The differences in the pathophysiology in the two major subgroups of FD, such as PDS and EPS, should be used for the development of target therapy in patients with FD. Primary empirical antisecretory therapy has the potential to eliminate the symptoms and treatment of mucosal lesions in most patients with organic FD, subject to GERD or Peptic ulcer disease (PUD). The same therapy is effective in 1/3 of the cases of FD. The HP-eradication and the treatment with prokinetic agents relief the clinical symptoms in 2/3 of patients with FD (1,2). Obviously the frequency of HP-infection in the population results about the first choice empirical therapy in patients with unexplained FD. That is way in a population with a high frequency of HP-infection -over 20%, testing and eradication of HP–infection, and also the therapy with PPI and prokinetics is an attractive approach for the young patients with FD (1, 7). In a populations with a low frequency of HP-infection, antisecretory therapy and especially with PPI for

1–2 months is a successful approach and is the recommended option, especially when there are symptoms of heartburn and burning (7). In cases with the EPS, the first choice treatment is a therapy with PPIs. In other symptoms such as fullness, early satiation, bloating – clinical manifestation of PDS, the prokinetic agents therapy is recommended (1,7).

Modification in lifestyle with exclusion of certain nutrients and risk factors improves symptoms of FD (18,20). Positive effect has avoiding caffeine, alcohol and NSAIDs, as well as make multiple dietary changes including eating more frequent, smaller meals and avoiding fatty or spicy food.

THERAPEUTIC OPTIONS OR BASIC GROUPS OF MEDICAMENTS, FOR THE TREATMENT OF FD

- Eradication of HP infection
- Prokinetic agents
- Antisecretory drugs (PPI, H2 blockers, antiacids)
- Digestive enzymes
- Probiotics
- Antidepressants
- Psychotherapy
- Phyto-extracts or placebo – therapy

HP-ERADICATION THERAPY:

HP –eradication may lead to effect in HP – positive patients with symptoms associated with HP – infection. Overall the effect of HP – eradication on FD remains limited (3, 12, 17). Meta-analysis suggest a better effect of HP – eradication among the population in China (18, 19). Almost the same results from the treatment of HP-positive patients with 2 different HP-eradication therapies-standard triple therapy and sequential (24).

ANTISECRETORY THERAPY:

Includes therapy with PPIs, H2RAs, antacids and agents protecting the mucosa. The treatment with PPIs is the most efficacy in patients with FD, in which there are a symptoms of GERD and less effective in those with epigastric pain. They reduce the acid related symptoms in FD. There aren't differences between the efficacy of PPI in two subgroups: EPS and PDS (1, 7, 21).

THERAPY WITH *PROKINETIC AGENTS*

Prokinetic agents considering as the most suitable for the treatment of FD. Cases of response to treatment with prokinetic agents is 42%, compared to placebo in 31% of cases (8). They accelerate gastric emptying, motility and has effect over PDS. Prokinetics seems to be the target therapy for the GI motility disorders (8). Compounds with upper gastrointestinal prokinetic action can be organized into distinct groups based on the receptors they act through (including dopamine, serotonin, motilin and ghrelin receptors) to enhance gastric motor activity. Domperidone (a dopamine-2 receptor antagonist) and cisapride (a 5-HT4 receptor agonist) stimulate gastric motility by facilitating the release of acetylcholine from the enteric nervous system. (3, 16) These are – Domperidon, Cisapride, Levosulperid, Itoprid and Tegaserod. A meta-analysis (34) shows the advantages of prokinetics over placebo in functional dyspepsia, with a relative risk reduction of 33%. Talley et al. (18) in 2007, reported a good results in treatment with Itoprid, which is a mixed dopamine – receptor agonist.

Acotiamide is a promising new prokinetic (27, 30) that enhances acetylcholine release via antagonism of M1and M2 muscarinic receptors and also functions as a cholinesterase inhibitor. Demonstrating strong potential for optimize the treatment of FD and superior the quality of life in patients with FD, through a mechanism that involves increased gastric accommodation (15, 18, 19, 27). It is suitable for the treatment of PD with leading PDS. Recommended dose is 3 x 100 mg for 4 weeks. Efficacy, leading to the elimination of the three symptoms related to nutrition: early satiation, fullness and bloating (15). A new studies about Acotiamide are in progress in Europe.

PSYCHOTROPIC AGENTS

Anxiolytics and antidepressants, especially tricyclic antidepressants, had some benefit in treating functional dyspepsia (1, 9, 16)

There are reports (3, 9, 17, 21) for a strange effects of anxiolytics and antidepressants in small doses on FD, especially over the refractory one.

These are antidepressants – Amitriptylin, Mianserin, Fluoxetine. Meta analysis (9) reported an improvement in the clinical symptoms of Amitriptyline in 70% of cases compared to 20% with placebo. In fact antidepressant is related to improved the sleep and is selective serotonin reuptake inhibitor (SSRI)– Paroxetine, enhanced gastric accommodation in healthy individuals. The 5-H1A agonist- Buspirone, seems to be the most promising psychoactive agent for functional dyspepsia (1).

The majority of patients with FD have relief of the symptoms and responded to treatment with antidepressants.

TARGETING VISCERAL HYPERSENSITIVITY

The principal drug classes under evaluation for visceral hypersensitivity are neurokinin receptor antagonists and peripherally acting κ-opioid receptor agonists. Fedotozine and Asimadoline are the medicaments from this group, efficacy for the treatment of FD.

PSYCHOLOGICAL AND BEHAVIORAL THERAPIES

For behavioral therapy are needed experienced psychotherapists and benefits is not clear. There are some cases reported that hypnotherapy is superior to both supportive and antisecretory therapies in improving symptoms and quality of life, both over the short term and the long term. (2,3). Hypnotherapy, might be an effective treatment for dyspepsia, capable of leading to substantial major economic advantages.

The most new drugs for the treatment of FD are Ghrelin (RM-131) and Kalmitcinal – motilin-agonist, as the last one is considered to be the first choice drug for gastroparesis – as a clinical manifestation of FD.

In conclusion – despite the intensive research in field of FD, the treatment is still unsatisfactory. Evolution is the understanding about the pathophysiology of this disease may enable the development of targeted treatment in the future.

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Адрес за кореспонденция:

Д-р Миглена Стамболийска

Клиника по хепатогастроентерология,
УМБАЛ Св. Марина
e-mail: m.stamboliyska@abv.bg

Address for Correspondence:

Miglena Stamboliyska, MD, PhD

Clinic of Gastroenterology,
UMHAT "St. Marina" Varna
e-mail: m.stamboliyska@abv.bg

РОЛЯ НА ИЗСЛЕДВАНЕТО НА ЧЕРНОДРОБНАТА ПЛЪТНОСТ ЧРЕЗ ПРОПАГИРАЩА УЛТРАЗВУКОВА ЕЛАСТОГРАФИЯ ПРИ ПАЦИЕНТИ С ХРОНИЧНИ ЧЕРНОДРОБНИ ЗАБОЛЯВАНИЯ: ПРОСПЕКТИВЕН, НАЧАЛЕН ОПИТ

Ирина Иванова, Диана Ганчева, Антония Атанасова,
Соня Банова, Деница Дукова, Миглена Стамболийска,
Иван Шалев, Милко Мирчев, Мария Атанасова, Искрен Коцев
Клиника по Гастроентерология, Университетска Болница „Св.Марина“ – Варна

THE ROLE OF LIVER STIFFNESS MEASUREMENT BY TRANSIENT ELASTOGRAPHY IN PATIENTS WITH CHRONIC LIVER DISEASE – PROSPECTIVE INITIAL EXPERIENCE

Irina Ivanova, Diana Gancheva, Antonia Atanassova,
Denitsa Dukova, Sonya Banova, Miglena Stamboliiska,
Ivan Shalev, Milko Mirchev, Maria Atanassova, Iskren Kotzev
Clinic of Gastroenterology, University Hospital “St.Marina” – Varna

РЕЗЮМЕ

ВЪВЕДЕНИЕ:

Цел: В проспективно проучване да се изследва клиничното значение на ултразвуковата пропагираща еластография при началното изследване и стадиране на пациенти с хронични чернодробни заболявания.

Пациенти и методи: 335 последователно хоспитализирани пациенти бяха изследвани с: физикален метод; рутинни лабораторни показатели за чернодробна функция; конвенционална абдоминална ехография, последвана от еластография чрез FibroScan 402; горна ендоскопия

ABSTRACT

Aim: A prospective study was performed to study the role of ultrasound elastography in initial evaluation of patients with chronic liver diseases.

Patients and methods: A total of 335 patients were assessed in a hospital-based settings using: physical exam; laboratory liver function tests; B-mode ultrasound followed by transient elastography (Fibroscan 402); upper endoscopy after clinical suspicion for presence of cirrhosis; liver biopsy for staging (in 85 patients).

Results: Studied population included 335 adults (mean age 48.5 years, 61% male) with different etiology of chronic liver diseases. In 327 patients (97.6%) liver stiffness (LS) can be assessed by Fi-

при клинично съмнение за цироза; чернодробна биопсия за стадиране (при 85 от случаите).

Резултати: От 335 включени болни с различна етиология на хроничното чернодробно заболяване (на средна възраст 48.5 години, 61% от тях мъже), еластографията бе успешно извършена в 327 (97.6%) от случаите при средна успеваемост 89.4% и интервал на вариабилност до 30%. Чернодробната плътност се асоциира силно с холинестеразната активност в серума, с протромбиновото време и тромбоцитния брой. При пациентите с начална фиброза (n=20) се установи средна чернодробна плътност 6.2 kPa; при септална фиброза (n=24) – 9.23 kPa; при мостова фиброза (n=28) – 10.86 kPa и при цироза (n=13): 18.72 kPa. Праг на чернодробната плътност от 7 кРа бе с добра специфичност 95.3%, но суб-оптимална чувствителност 55% в дефинирането на сигнификантна фиброза. Методът е с диагностична точност за цироза от 88.9% при праг 14.5 kPa.

Извод: Пропагиращата еластография е добър метод за първоначална оценка на пациентите с хронични чернодробни заболявания.

Ключови думи: чернодробна фиброза; цироза; пропагираща еластография; чернодробна плътност

broScan 402 with a median success rate of 89.4% and interquartile range of up to 30%. LS was found to be strongly associated with cholinesterase activity, prothrombin time and platelet count. The comparison with invasive staging revealed: 20 patients with mild fibrosis had median LS of 6.28 kPa; 24 patients with septal fibrosis had median LS 9.23 kPa; 28 patients with bridging fibrosis had LS 10.86 kPa and in 13 cirrhotic patients LS was 18.72 kPa. The cut-off of 7 kPa had good specificity of 95.3% but sub-optimal 55% sensitivity for diagnosis of significant liver fibrosis. The diagnostic accuracy of elastography for cirrhosis at threshold of 14.5 kPa was 88.9%.

Conclusion: Transient elastography is a valuable method for initial investigation of patients with chronic liver disease.

Key words: liver fibrosis; cirrhosis; transient elastography; liver stiffness.

INTRODUCTION

Extension of liver fibrosis defines the stage of chronic liver disease, reveals prognosis and appropriate clinical management in our patients. Liver biopsy, the reference method for staging of liver disease is invasive, in-patient procedure with several limitations due to sampling errors and observer variability. Finally, liver biopsy is contraindicated and carries significant risk in patients with coagulation disorders, recent jaundice, presence of low platelets and albumin concentration, and in some specific subgroups as cases with terminal renal failure and benign liver lesions. Also, repeated examinations for monitoring of disease course and effect of treatment isn't always feasible. There is an important need of rapid, reliable and non-invasive test for assessment the severity and stage of liver injury. Ultrasound transient elastography (TE) is a first and strong validated technique for measurement of tissue stiffness, integrated in FibroScan device (EchoSens, France). The method is mostly evaluated for staging of chronic hepatitis C viral (HCV) infection, including special population of co-infected with human immunedeficiency virus (HIV) and post-transplanted patients. There is growing evidence of importance of TE in diagnostic algorithms in chronic hepatitis B, alcoholic and non-alcoholic fatty liver disease (5, 9, 10). Measuring liver stiffness by TE can answer the two important questions regarding every day clinical practice: presence of hepatitis versus liver cirrhosis and may define clinical significant fibrosis (stage 2 or above, according to METAVIR, F≥2) (4, 11). The prognostic role of TE for cirrhosis progression

and development of hepatocellular carcinoma (HCC) should be further studied (3, 4).

The purpose of this prospective, one-center study was to evaluate the role of liver stiffness (LS) measurement, obtained with FibroScan in referred patients with different etiology of chronic liver disease and to compare the staging results of clinical and laboratory routine procedures, as well as the conventional ultrasound, upper endoscopy and finally liver biopsy analysis.

PATIENTS

Three hundred thirty-five consecutive patients with chronic compensated and decompensated liver diseases (n=335) underwent evaluation at the Gastroenterology Clinic of University Hospital St.Marina (Varna, Bulgaria) between March and May 2014 and were included in the trial. The patients with current antiviral therapy, presence of ascites, severe acute hepatic cytolysis and biliary obstruction were excluded from the study. The enrolled patients provide their written and informed consent regarding all clinically indicated procedures.

METHODS

The following parameters were collected at time of TE test: subject age, gender and BMI; routine laboratory parameters (platelet count, liver enzymes, albumin, bilirubin, prothrombin time, cholinesterase activity, fibrinogen, cholesterol) and data from conventional ultrasound examination (liver and spleen size, detection of steatosis, B-mode assessed presence or loss of liver elasticity by subjective evaluation of left lobe movement induced by right ventricule contraction). At the same day, the LS measurement was done with a FibroScan 402 device equipped with M-probe (EchoSens, Paris, France) based on routine examination protocol in fasting subjects. Operators are physicians from our Clinic, responsible for patient's diagnostic and therapeutic approach, experienced at least 50 TE procedures. The placement of the probe was assisted by percussion (intercostal space showing strong liver dullness sound), by A-mode window of the device and by B-mode ultrasound in some difficult cases in order to assess the most appropriate place of transducer to examine a portion of at least 6 cm liver span free of large vessel structures. At least 10 successful acquisitions of the propagating shear waves were done for each patient and results are documented as median LS expressed in kilopascal (kPa), IQR – interquartile range (in kPa and as %) and success rate (SR, %). Test is considered as reliable if the SR exceeds 60% and IQR ≤30%.

Percutaneous liver biopsy was performed within 12 months period of time of LS measurement by Menghini technique (14–16 g Hepafix needle, Braun). Only liver biopsy specimen with length above 1 cm are included into analysis, comparing histology grade to LS, so this subgroup were consisted of 85 patients. 42 of the 85 patients enrolled in that analysis had liver biopsy and LS measurement within the same week. Liver fibrosis and necro-inflammatory activity were evaluated semi-quantitatively according to the METAVIR and Ishak scoring system. Fibrosis was staged on a 0–4 scale: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Activity was graded according to modified histology activity index. Steatosis was assessed in 4 scale grade (0–3). Upper endoscopy (Exera, Olympus) was done in 70 patients: in cases of suspected cirrhosis to investigate signs of portal hypertension as well as to confirm presence of liver cirrhosis if relative contraindications for liver biopsy exist; in patients with "histological" cirrhosis.

STATISTICAL ANALYSIS

We used descriptive statistics for primary analysis. Results were given as the median and standard deviation or 95% confidence interval (CI) values. Also we compared the results of TE (LS measurement) with several parameters, the most important with the categories of the fibro-

sis stage, using the nonparametric analysis of variance and a correlation coefficient of Spearman (r) estimated the trend between the LS and the ordinate fibrosis stages and the other laboratory, ultrasound and histology parameters. One-way ANOVA tested analysis of difference. Diagnostic performances of TE were assessed by area under the receiver operating characteristic curve (AUROC) analyses. Evaluations were done by Prism GraphPad software v.5 (free trial version).

RESULTS

FibroScan elastography failed to establish LS in 2.4% of included patients: median age of this patient's small group was 56 years and all cases had BMI above 30. Thus, the statistical analyses were based on 327 patients: age 48.5 ± 14 years, 61% male, with mean BMI 26.1. Among them, 133 had HBV infection, 80 had HCV infection, 36 had Wilson disease, 23 had autoimmune hepatitis, 15 subjects had primary biliary cirrhosis, 28 had current significant alcohol intake and 12 patients had non-alcoholic fatty liver disease. Normal ALT was assessed in 45.2% of enrolled patients at time of TE, ALT was 1 to 5 times upper limit of normal (ULN) in 31.5% and above 5 times ULN in 23.3%, respectively.

TE measurements of LS were done with SR of 89.4% (minimum 61%, maximum 100%). According to principal criteria for validation of the test – IQR, the results could be categorized to: very reliable (IQR ≤10%) in 30.6% and reliable (IQR 11–30%) in 69.4% of investigated patients. The concordance of measurement of LS between 4 operators was tested on 2 subjects and was found to be 0.92. In addition, TE was performed in 15 subjects admitted for evaluation of gastro-intestinal tract disorders in which liver disease can be excluded. In this small control group assessed LS was 5.05 ± 0.66 kPa (variation from 2.7 kPa to 7.9 kPa).

Table 1 summarizes the results of LS measurement in patients with different etiology of liver disease.

Table 1: Liver stiffness (LS), according to etiology of chronic liver disease.

Diagnosis	N	Liver stiffness (kPa)		
		Mean	SD	Min – Max
Chronic hepatitis C	80	**17.40**	14.3	3 – 73.5
Chronic hepatitis B	133	**13.06**	12.63	3.2 – 75
Wilson's disease	36	**11.91**	15.98	2.3 – 75
Autoimmune hepatitis	23	**12.61**	12.1	3.4 – 61
Primary biliary cirrhosis	15	**23.82**	21.3	5.4 – 75
Steatosis / Steatohepatitis	40	**18.39**	18.1	3.41 – 69

According to physical exam, abdominal ultrasound, liver function tests plus platelet count and in part of patients based on data from invasive tests – liver biopsy and upper endoscopy, 262 patients were staged with chronic hepatitis and 65 patients (19.9%) with liver cirrhosis. Oesophageal varices were registered in 61.5% of patients with cirrhosis. TE was done in 17 new cases with hepatocellular carcinoma (HCC). Results from TE in patients with hepatitis, cirrhosis and HCC were shown in table 2.

Diagnosis	Liver stiffness (kPa)		
	Mean	Standard deviation (SD)	Min – Max
Chronic hepatitis (n=262)	**9.52**	7.2	2.3 – 36
Cirrhosis (n=65)	**36.5**	24.4	7.2 – 75
Hepatocellular carcinoma (n=17)	**27.7**	28.2	6.9 – 75
All studied patients (n=327)	**14.56**	15.50	2.3 – 75

A significant association between LS and decreased cholinesterase activity, pro-thrombin index, albumin level, platelet count, as well as AST/ALT ration, AST and GGT activity, cholesterol and bilirubin level were observed (Table 3). LS correlated with subjective evaluation of decrease of liver elasticity by B-mode US and increased spleen dimensions.

Calculated LS was compared to METAVIR fibrosis score of 85 patients with chronic viral hepatitis (Table 4). Significant association between LS and histology fibrosis stage was assessed ($r=0.67$, $p< 0.0001$). We couldn't find significant relationship between histology activity index and LS ($r=0.13$, $p=0.4$) and between LS and grade of steatosis ($r=0.11$, $p=0.5$), as shown in Table 3.

Table 3. Correlation between LS and parameters of laboratory analysis, abdominal ultrasound and liver morphology.

Parameter	Correlation coefficient, r	95%CI	P value
Platelet count	–0.492	-0.59 to –0.39	<0.0001
AST/ALT ratio	0.341	0.21 – 0.46	0.0001
AST	0.329	0.22 – 0.43	<0.0001
GGT	0.332	0.21 – 0.44	<0.0001
Cholinesterase	–0.675	–0.78 to –0.53	<0.0001
Bilirubin	0.341	0.18 – 0.48	<0.0001
Prothrombin index	–0.642	–0.75 to -0.50	<0.0001
Albumin	–0.529	–0.66 to –0.38	<0.0001
Cholesterol	–0.375	–0.54 to –0.18	<0.0001
US B-mode assessed loss of liver elasticity	0.543	0.45 – 0.62	<0.0001
US assessed splenomegaly	0.534	0.44 – 0.61	<0.0001
Fibrosis stage (METAVIR)	0.670	0.45 – 0.81	<0.0001
Modified histology activity score	0.139	–0.2 – 0.45	0.4 (ns)
Histological grade of steatosis	0.110	–0.22 – 0.42	0.5 (ns)

Table 4. Measured LS by FibroScan in patients with histology data for fibrosis stage (n=85).

Liver stiffness (kPa)	Histology stage (according to METAVIR)			
	F0-F1	**F2**	**F3**	**F4**
n	20	24	28	13
Median	**6.28**	**9.23**	**10.86**	**18.72**
95% CI	4.72 – 7.81	5.55 – 12.9	7.53 – 14.2	13.08 – 24.3

Patients with discrete fibrosis (F0-F1) had preserve liver elasticity – median value of 6.28 kPa. In the subgroup of patients with septal fibrosis (F2) median LS was 9.23 kPa, but comparing to results of FibroScan elastography in F0-F1 patients there is no significant difference. Also, LS in subjects with bridging fibrosis – 10.86 kPa is comparable to F2 patients. Significant difference was observed between measured LS in F0-F1 subgroup vs. F3/F4 subgroup as well as between patients with bridging fibrosis and cirrhosis (Figure 1).

A cut-off of 7 kPa predicted the presence of at least septal fibrosis (F2-F4) with 95% specificity and 55% sensitivity. A total of 30 patients were misclassified as having no significant fibrosis and if physicians relies only on TE these patients could not receive benefits of highly effective anti-viral treatment. Overall, only 61.2% were correctly diagnosed comparing to liver biopsy as a reference.

At cut-off of 14.5 kPa, cirrhosis could be predicted with certainty 90.8% and excluded with 93.3% certainty. A total of 18 (11.1%) patients were misclassified: 6 patients with cirrhosis and 12 patients without cirrhosis based on invasive staging with liver biopsy and endoscopy. So, the diagnostic accuracy of TE for cirrhosis at cut-off 14.5 kPa was assessed as 88.9%. Decreasing the cut-off level led to sub-optimal sensitivity of FibroScan measured LS for cirrhosis: for example threshold of 1 2kPa will incorrectly diagnosed 10 patients as having no cirrhosis.

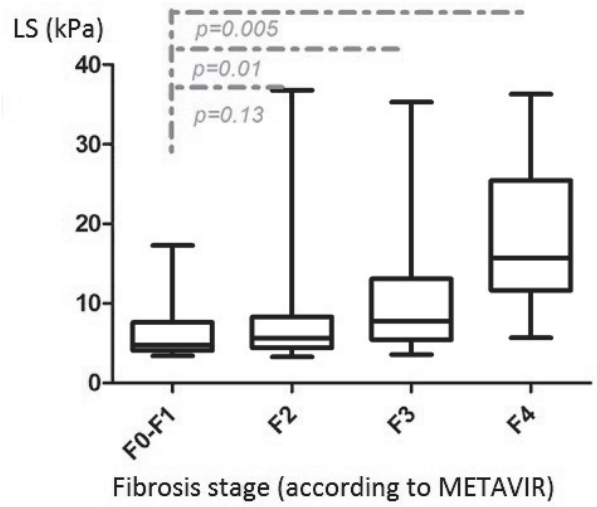

Figure 1. Comparison of LS vs. fibrosis METAVIR stage (results of one-way ANOVA analysis).

Measured LS in patients with detected oesophageal varices on upper endoscopy was 29.72 ± 3.1 kPa, vs. LS of 21.7 ± 4.5 kPa in patients with cirrhosis but without oesophageal varices but the difference isn't significant (p=0.18).

DISCUSSION

In the past 10 years, there has been growing interest on non-invasive alternatives of liver biopsy to stage patients with chronic liver diseases and to distinguish chronic hepatitis form compensated cirrhosis. Early diagnosis of liver cirrhosis is a major issue, because cirrhotic patients must be screened for oesophageal varices and monitored for liver cancer development but most importantly – they have the emerging need for effective treatment. Previous trials define TE as the most accurate non-invasive method for diagnosis of liver cirrhosis, especially in hepatitis C (3, 6). Optimal transient elastography (TE) cut-off for the diagnosis of cirrhosis depends on etiology of liver disease, ranges from 10.3 kPa in chronic hepatitis B and 12.5 kPa in chronic hepatitis C to 17.3 kPa in chronic cholestatic disease. Thus, a cut-off of 14.6 kPa is proposed to be used for chronic liver disease of various etiology (4, 5). Despite a good correlation between measured liver stiffness (LS) and histological fibrosis score (approximate r=0.70), studies are in agreement on existence of a "grey" area between 6 kPa and 9 kPa, that can't categorize accurately fibrosis F1-F3 stage (2, 10). For detection of significant fibrosis (≥ F2) the overall sensitivity is 0.71 to 0.78 and specificity is 0.82 to 0.84 for TE (1, 9). The best diagnostic accuracy of TE is for detection of cirrhosis (AUROCs of 0.94 – 0.97) (2, 3, 5–10).

We designed prospective pilot study to evaluate the role of LS measurement by FibroScan in complex prior-to-treatment management of patients with chronic liver diseases. Predominant etiologies were hepatitis B (40.6 %) and hepatitis C (24.5 %). LS measurement was unsuccessful in 8 patients (2.4%), mostly because of obesity. Fibrosis stage is significantly correlated with LS (r = 0.67). There was a significant difference in median LS value in patients with mild fibrosis (F0/F1) in comparison to patients having advanced fibrosis (F3) and cirrhosis (F4) (6.28 vs. 20.9 kPa, p = 0.001). However, the ability of TE to discriminate patients with discrete fibrosis (F0-F1) vs. moderate fibrosis (F2) was sub-optimal in our trial, and finding is in accordance with previous studies (10). It's generally accepted that ALT activity interferes with LS measurement and mean LS values may be increased with 1–2 points (kPa) in order to correctly categorize patients with high inflammatory activity. We couldn't perform analysis of LS according to ALT levels, due to the low number of patients in each stage-matched group. The role of LS measurement to predict liver cirrhosis (F4) was a primary point of our investigation. We defined the optimal threshold of 14.5 kPa for cirrhosis, findings similar to those from European and Asian cohorts (7–10). The diagnostic accuracy of TE for cirrhosis at that cut-off 14.5 kPa was assessed as 88.9%, slightly lower to previous published analyses. TE cannot replace endoscopy for esophageal varices screening (3). That conclusion is confirmed from our observation.

As there so no perfect single non-invasive tests for liver fibrosis assessment, further algorithms combining the laboratory and ultrasound methods should be evaluated as an initial screening tools.

Conclusion

FibroScan measured LS contributes to the diagnostic and treatment decisions. TE is fast, reliable method for non-invasive diagnosis of liver cirrhosis, particularly when the results are supported by clinical, laboratory and ultrasound data. At cut-off 14.5 kPa can be a tool for detection of cirrhosis in patients with chronic hepatitis.

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Адрес за кореспонденция:

Д-р Ирина Иванова Иванова,

Клиника по Гастроентерология,
УМБАЛ „Св. Марина“,
ул. Христо Смирненски 1, Варна 9010;
e-mail: irinaiivanova@abv.bg

Address for Correspondence:

Irina Ivanova, MD

Clinic of Gastroenterology,
UMHAT “St. Marina” Varna
e-mail: irinaiivanova@abv.bg

ВЪРХУ НЯКОИ СОЦИАЛНИ АСПЕКТИ НА САМОУБИЙСТВАТА В ОБЛАСТ ПЛОВДИВ НА Р. БЪЛГАРИЯ, ИЗВЪРШЕНИ ПРЕЗ ПЕРИОДА 2000 – 2009 г.

д-р Марин Балтов, д.м.
Медицински Университет – Пловдив, Катедра по Обща и клинична патология и Съдебна медицина, УМБАЛ "Св. Георги" ЕАД, Отделение по Съдебна медицина

CERTAIN SOCIAL ASPECTS OF SUICIDAL HANGING DEATHS IN THE REGION OF PLOVDIV, REPUBLIC OF BULGARIA, IN THE PERIOD 2000–2009

Marin Baltov, MD
Medical University Plovdiv, Department of General and Clinical Pathology and Forensic Medicine St. George University Multi-Profile Hospital for Active Treatment EAD Department of Forensic Medicine

РЕЗЮМЕ

Самоубийството е сериозен медицински и социален проблем на съвременното общество. Проблемът е актуален и за област Пловдив, която се нарежда на второ място по брой на самоубийствата в Р. България.

Цел на настоящото изследване е да се проследи динамиката на суицидният индекс в Пловдивска област през периода 2000 – 2009 год., разпределението на самоубийствата по пол, възраст, местоживеене, социално и семейно положение.

Установено е, че суицдиният индекс през годините, с известни колевания проявява тенденция към намаляване. Мъжките самоубийства надвишават около 2,3 пъти женските. Преобладават суицидите извършени от градски жители, но суицидният индекс в селските

ABSTRACT

Death by hanging is one of the most common suicide methods. This research studies some social aspects of suicidal hangings committed in the region of Plovdiv, Republic of Bulgaria, during the period 2000–2009.

Throughout that period, 944 suicides were committed in the region, of which 480 (51.56±1.66%) by hanging. Men committed 365 (76.04±1.95%) of the hangings, whereas women – 115 (23.96±1.95%). People living in the cities of the region committed 54.58±2.27% of the suicides, whereas rural residents – 45.42±2.27%. The smaller part of the population of the region of Plovdiv lives in the country, so suicide index with rural residents is 2.2 times higher than the suicide index of urban population. The average age of suicides who committed hanging is 56.13±0.82

райони е по-висок, поради миграцията на населението. Най-много суициди се извършват от лицета във възрастовата група 40 – 64 год. С повишен суициден риск са социалните групи на пенсионерите, безработните и семейните лица.

Ключови думи: самоубийства, пол, възраст, социално положение.

years, and the relative share of persons in mature age (45–64) is the largest.

Key words: suicides, hanging, suicide index.

Suicide is a phenomenon which accompanies the historic development of mankind. Today, it is a global humanitarian problem due to the growing number of people choosing to end their own lives. On a global scale, it is one of the three causes of mortality (12, 13).

One of the most frequently used suicidal methods is death by hanging (5, 7, 8, 9). In Europe, the highest rates of suicidal hangings are reported in the former socialist countries – Lithuania, Poland, Latvia, Estonia (13). Varying information is reported about the Balkan peninsula regarding the number of suicidal hangings committee, which is the largest in the region of Mures, Republic of Romania (9).

In the Republic of Bulgaria, the relative share of committed suicidal hangings has increased over the years. In the period 1929–1941, they make up 30.12% of all suicides and increase to 68.9% in the period 1989–2001 (3, 4).

AIM

The aim of this study is to examine some of the social aspects of suicidal hangings in the region of Plovdiv over the period 2000–2009.

MATERIAL AND METHOD

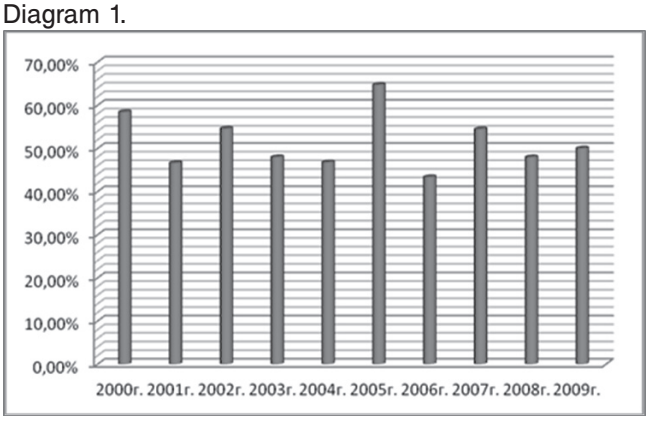
The object of study are the committed suicidal hangings which are registered at the Departments of Forensic Medicine of St. George University Multi-Profile Hospital for Active Treatment EAD and Plovdiv Multi-Profile Hospital for Active Treatment AD, Plovdiv, over the period 2000–2009. The information about the population in the region used is courtesy of the National Statistical Institute (NSI) (14). For the collection of input information has been used a historical method of choice. This is required by the need to perform a thorough and comprehensive investigation of the problem in time. Alternative, variation, non-parametric and graphical analysis has been used in the statistical processing of information (1, 2).

OWN RESEARCH DATA

Over the period 2000–2009, 944 cases of suicide were registered in the region of Plovdiv, of which 480 (51.56±1.64%) suicidal hangings. The dynamics of the relative shares of hangings in reference to the total number of suicides during the period under examination shows a vastly broken line (see diagram 1).

CHANGE IN THE RELATIVE SHARE OF HANGINGS IN REFERENCE TO THE TOTAL NUMBER OF SUICIDES DURING THE PERIOD UNDER EXAMINATION

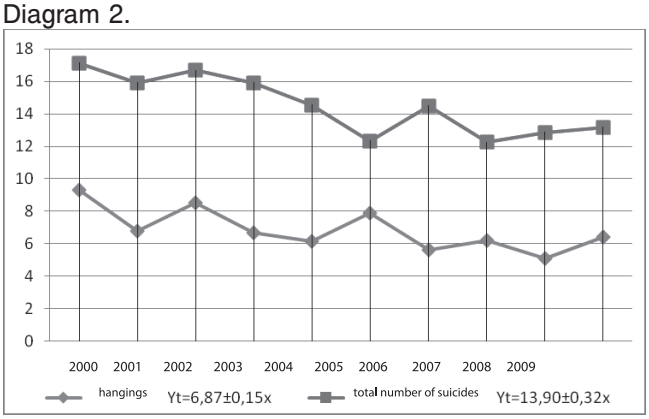
Diagram 1.



Based on the information available about the population in the region, the hanging suicide index has been calculated and compared to the total suicide index of the region (see diagram 2).

DYNAMICS OF THE SUICIDE INDEX OF HANGINGS AND THE TOTAL SUICIDE INDEX IN THE REGION OF PLOVDIV

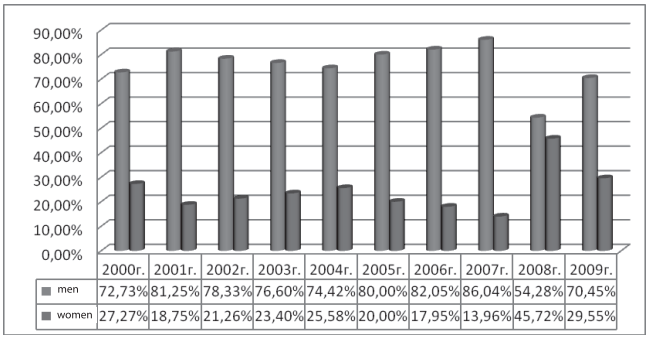
Diagram 2.



During the period 2000–2009, 365 men (76.04±1.95%) and 115 women (23.96±1.95%) committed suicide by hanging. The relative share of hangings committed by men and women changes over the years (see diagram 3).

GENDER STRUCTURE OF SUICIDAL HANGINGS DURING THE PERIOD UNDER EXAMINATION

Diagram 3.

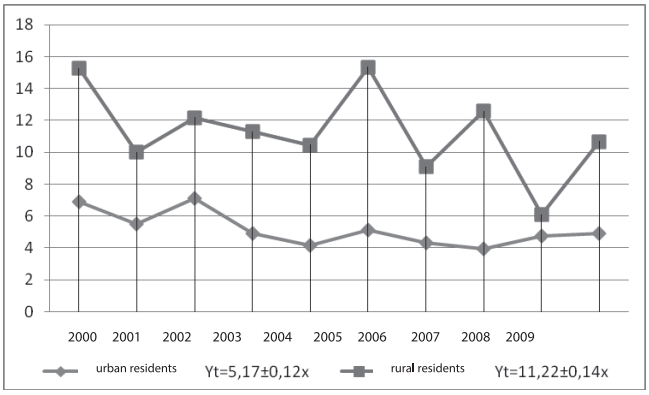


	2000г.	2001г.	2002г.	2003г.	2004г.	2005г.	2006г.	2007г.	2008г.	2009г.
men	72,73%	81,25%	78,33%	76,60%	74,42%	80,00%	82,05%	86,04%	54,28%	70,45%
women	27,27%	18,75%	21,26%	23,40%	25,58%	20,00%	17,95%	13,96%	45,72%	29,55%

Out of the 480 cases of suicidal hanging, 262 (54.58±2.27%) were committed by urban residents, whereas 218 cases (45.42±2.27%) were committed by rural residents. A better idea of the different suicidal behaviour of urban and rural residents is given by the suicide index (see diagram 4).

SUICIDE INDEX OF URBAN AND RURAL RESIDENTS WHO COMMITTED SUICIDAL HANGING DURING THE PERIOD 2000–2009

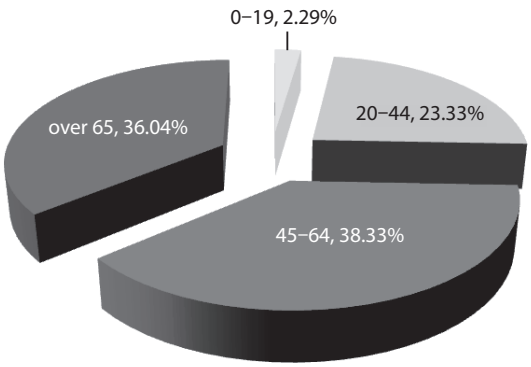
Diagram 4.



The average age of suicides for the entire period is 56.13±0.82 years (Sx=16.49). A distribution has been made of suicidal hangings by age groups of the period under examination (see diagram 5).

DISTRIBUTION OF THE TOTAL NUMBER OF SUICIDAL HANGINGS IN THE REGION OF PLOVDIV BY AGE GROUPS DURING THE PERIOD UNDER EXAMINATION

Diagram 5.



DISCUSSION OF THE RESULTS OBTAINED

The evidence found shows that death by hanging is the most common suicidal method used in the region of Plovdiv. The relative share of committed suicidal hangings to the total number of suicides varies over the years so their

dynamics is unstable, with a peak in 2005 and a dip in 2006. The data from the last year of the research is close to the mean rate for the period.

The suicidal hanging rates established by us are close to the rates reported for the region of the Balkan peninsula – Montenegro – 51.88%, Republic of Serbia – 57.00%, the region of Trakya in the Republic of Turkey – 41.8% (5, 6, 10, 11).

The suicide index (‰), which gives a better idea of the quantitative side of hangings also varies, but since 2006 its values have been decreasing and in 2008 was reported its lowest rate.

In all countries for which information is available, there is prevalence of men in hangings as suicides, but inter-gender ratio is variable. For the region of Plovdiv, the proportion between men and women suicides is 3.2 : 1.0, identical to the proportion in Montenegro, but lower than the rate reported for the Republic of Romania and the Republic of Turkey (5, 6, 8).

The distribution of suicidal hangings by gender over the entire period under examination shows predominance by men. The relative share of male suicides reaches its peak in 2007, and its lowest rate in 2008. In that same year, the relative rates of male and female suicides by hanging come close, with the difference being smaller than 10%. For the entire period under investigation, male suicidal hangings were 76.05±1.95%, and female – 23.96±1.95%. The distribution of the number of suicides by gender over the period is well outlined by the ratio index. Non-parametric analysis confirms the existence of statistically significant difference at level 95.00%, $P<0.05$ ($\chi^2=17.05$).

Place of residence is one of the risk factors for suicidal behaviour. Throughout the entire period under observation, residents of cities in the region of Plovdiv committed 54.58±2.27% of all cases of hanging, whereas rural residents committed 45.42±2.27%. Defining the suicide index by place of residence of the persons committing suicide has reveled much higher rates for people living in the country. One of the reasons for that is the population decline of villages on the one hand, and on the other, their deteriorating economic situation. All this is combined with the easy access to the means for committing suicide makes it the most common method of suicide in the country.

The distribution of suicidal hangings by age groups shows that their largest share is within the age group 45–64. This group is most seriously affected by economic crisis. The oldest people who committed suicide were a man and a woman at the age of 89.

CONCLUSIONS:

1. Committing suicidal hanging was chosen by 51.56±1.64% of all suicides in the region of Plovdiv.
2. Suicidal hanging dynamics over the period 2000–2009 was fluctuating with a tendency for reduction.
3. Men commit 3.2 times more suicides by hanging than women.
4. The suicide index of hangings committed by rural residents is e 2.2 higher than the suicide index of hangings committed by urban residents.
5. Most hangings are committed by people in mature age (45–64).

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Адрес за кореспонденция:

Д-Р МАРИН БАЛТОВ,

МУ Пловдив, УМБАЛ „Св. Георги“,
Катедра по съдебна медицина,
Пловдив 4000,
ул. В. Априлов 15-А
E-mail: dr.baltov@abv.bg

Address for Correspondence:

DR. MARIN BALTOV MD,

Medical University Plovdiv, Department of General and Clinical Pathology and Forensic Medicine, St. George University Multi-Profile Hospital for Active Treatment EAD, Department of Forensic Medicine,
15a Vasil Aprilov Blvd.,
4000 Plovdiv, Republic of Bulgaria,
E-mail: dr.baltov@abv.bg

Волвулус в областта на илео-цекалния ъгъл – наблюдение върху един клиничен случай с обзор на литературата

Емилия Тошева, Анна Тасева, Владимир Тасев, Петьо Токов, Валентин Попов
Клиника по Обща и чернодробно-панкреатична хирургия
УМБАЛ„Александровска" ЕАД, Медицински университет – София

Volvulus in the ileocoecal angle – observation of a clinical case and literature overview

Emilia Tosheva, Anna Taseva, Vladimir Tasev, Petio Tokov, Valentin Popov
Clinic of General and Liver-Pancreatic Surgery
UMHAT "Alexandrovska", Medical University – Sofia

РЕЗЮМЕ

Авторите представят клиничен случай на волвулус в областта на илео-цекалният ъгъл с нетипична клинична картина и хистологичен резултат. Представен е кратък обзор и дискусия по тази рядка форма на илеус.

Ключови думи: илеус, волвулус, цекум, хирургия.

ABSTRACT

The authors present a clinical case of volvulus in the ileocoecal angle with atypical clinical presentation and histology, as well as a brief literature overview and discussion on this rare form of ileus.

Key words: ileus, volvulus, caecum, surgery

INTRODUCTION

Intestinal volvulus is defined as a twisting of a loop of intestine around its mesenteric attachment site. It is more frequently related with malrotation, when the normal process of rotation and fixation of the midgut is disturbed. Complications that may occur with malrotation are mechanical obstruction or twisting of the intestines with subsequent ischaemia (with or without necrosis of the wall) of a part or all the midgut. Volvulus can occur at various sites of the gastrointestinal tract, including the stomach, small intestine, caecum, transverse colon and sigmoid colon (3,6). Its clinical presentation is determined by the twisting of the intestinal lumen versus the axis of the superior mesenteric artery and the extent of obstruction and impair-

Fig.1 and 2. Plain abdominal radiograms in caecal volvulus

ment of blood supply in the respective intestinal segment. Midgut volvulus secondary to intestinal malrotation is more common in infants and children, but it can occur in persons of all ages, as in the observed clinical case [1, 3 6, 8].

PRESENTATION OF THE CLINICAL CASE

An 80-year old woman, hosp. No. 26073, was admitted by emergency for complaints of abdominal pain accompanied by nausea, vomiting and loose bowel movements. The patient's complaints have been lasting for 2 weeks, with periodic, less pronounced characteristics. In the last 24 hours prior to hospitalisation, the patient's complaints intensified and became permanent, with fever of up to 38°C. Objective status: deteriorated general status, alert, afebrile. Tongue: dry and coated. Arrhythmic heart activity, pulse 84 beats/min, AP 130/80 mmHg. Abdomen: above the thoracic level, with visible peristalsis. Auscultatory evidence of gurgling and rumbling peristalsis. On deep palpation the abdomen was painful in all quadrants, but without positive / + / Blumberg's sign. There was a large, reponible left-sided inguinal hernia with diameter of about 10 cm. Rectal examination: empty rectal ampulla. The abnormal laboratory findings included only hypoalbuminaemia, impaired coagulation status (prothrombin time 20 sec., INR 1.70, fibrinogen 4.66 g/l, normal APTT), hypokalaemia. The rest laboratory parameters were within the normal ranges. Two plain abdominal radiographies were performed within a period of 4 hours, revealing hydro-aerated shadows of small intestinal origin, as in volvulus or internal incarceration [Fig.1 and 2].

Following admission to the surgical clinic, the patient was subjected to active resuscitation and rehydration therapy. Based on the preoperative diagnosis of mechanical ileus and left inguinal hernia, an emergency laparotomy was performed with the following intraoperative findings: clear exudate of 300 ml that was evacuated; malrotation of the caecum, determining "caecum mobille"; an intestinal segment, involving the initial ascending colon, caecum and distal ileum, twisted on a thick band with length of about 6–7 cm (Ladd's bands [1,7,9]), formed between the site in the Bauhin's valve region and the peritoneum of the right lateral canal. The twisted section of the colon was significantly distended, the serosa was pale, but without evidence of ischaemic necrosis. There were inflammatory changes in the intestinal wall and a dolichosigmoid section, adhered along a distance of about 1.5 cm. Proximally to the site of mechanical obstruction, the intestinal loops were significantly distended, filled with intestinal contents, with light purple intestinal walls, but preserved vitality. Right hemicolectomy, enteral insertion of a tube and decompression of the small intestines were performed, leading to normalisation of the intestinal colour. Left inguinal canal plasty was also performed (Fig. 3 and 4).

Fig. 3 and 4. Intraoperative findings in caecal volvulus

Fig. 5. Macroscopic appearance of an intraoperatively excised preparation after right-sided hemicolectomy

The permanent histological sample (By 2409) revealed acute and granulating transmural ulcerative defects in the ileocaecal valve and along 4 cm of the terminal ileum, with presented fibrin deposits on the serosa and evidence of fibrinous peritonitis. The microbiological study of the intraperitoneal exudate showed no bacterial growth and the cytological study revealed no abnormal cells.

In the early postoperative period, on the background of restored passage and scanty secretion without pathological processes from the abdominal contact drains, the following complications occurred: on the 4th postoperative day, AMI, left-sided pleuropneumonia with a right-sided encapsulated pleural effusion and postoperative acute pancreatitis with increased L-amylase levels of up to 260 U/l. The complications were managed with conservative therapy and the patient was dehospitalised dynamic and afebrile, with restored passage.

DISCUSSION

Volvulus of the caecum is a torsion of the intestine around its own mesenterium, observed in about 11% of all intestinal volvulus [1]. According to literature data, it affects more frequently young people, but is also seen in advance-aged people (50–60 years) [1,9]. Predisposing factors include malrotation with infringement in the development of peritoneal fixation (11–25% of the population) and twisting of the intestine on a point of fixation that may be an adhesion, tumour mass, calcified lymph nodes. In 1832, Reed was the first who described a location of the caecum in the upper left quadrant in two autopsies [6]. The process of normal intestinal rotation during embryonic development was described by Mall in 1898 [6]. Clear description of the anomalies in the rotation and fixation of the gastrointestinal tract was published by Dott in 1923 [3]. The specific reasons for the development of malrotation are unknown, but taking into account the fact that it occurs during foetal development, it can be assumed that any impact in the critical periods of development may cause it. A relationship between malrotation and the presence of other associated congenital anomalies was established (in 62% of cases) that increases the risk of death by 22 times [1,2,3,9]. Volvulus leads to obstruction and arrest of the passage. If not promptly diagnosed, it is life-threatening [6].

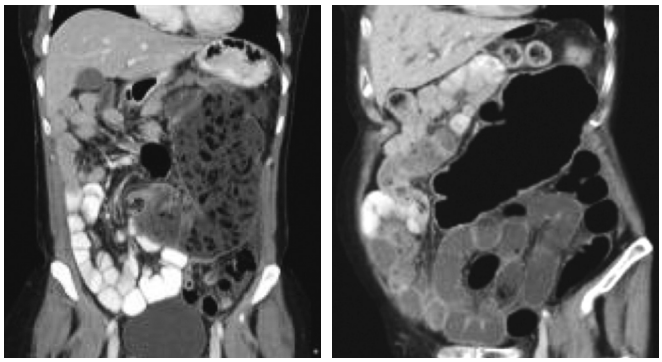

Fig. 6. Anterior and lateral CT scans of ileocaecal volvulus

Previous surgery, periods of cramping abdominal pain, intestinal discomfort, sometimes progressing to severe pain accompanied by repeated vomiting and palpable tumour mass in the lower abdomen are frequently reported in the anamnesis [4,6, 9].

In some patients, the caecum is rotated in the axial plane along its longitudinal axis, remaining in the lower right quadrant of the abdomen, as in the case reported here. Others present with the so-called caecal volvulus of the loop type, where the caecum is simultaneously twisted and inverted and enters the upper left quadrant of the abdomen. The terminal ileum is frequently twisted together with the caecum. The finding of an appendix filled with gas directs to the diagnosis. A rare variant is the so-called caecal bascule, where the caecum folds anteriorly without any torsion. Depending on the degree of rotation, the condition may interfere with the blood supply and lymphatic vessels. This leads to swelling of the bowel, increased vascular permeability, bleeding from the GI tract, the occurrence of mesenteric cysts and chylous ascites. Where there is involvement of the arteries and their complete obstruction, ischaemia, mucosal necrosis, bacterial translocation, Gr (–) sepsis and subsequent necrosis of the intestinal wall perforation and stercoral peritonitis may occur [1,4,9].

The diagnostic strategy focuses on plain abdominal radiographic data. A distended colonic loop is seen, with its longitudinal axis running from the lower right abdominal quadrant to the epigastrium and the upper left quadrant, depending on the initial position of the colon and the length of the mobile right colon. The haustration of the colon is preserved in contrast to the sigmoid volvulus, wherein such is missing [4, 9]. In advanced ileus, multiple small intestinal hydro-aerated levels can be visualised.

Barium enema, as a method of study, is sufficient for a conclusive diagnosis, and in partial obstruction, a portion of the contrast medium passes through the site of twisting and the volvulus is presented in more detail [2,4,5].

CAT rarely enters into consideration, but is able to provide a detailed and specific image, e.g. the symptom of „bird beak“ in sigmoid volvulus and the symptom of „turbulence“ in volvulus of the caecum, middle intestinal tract and sigmoid colon [2,5,4,9] (Fig. 6).

The treatment includes colonoscopic decompression in high surgical risk patients and surgical techniques, such as right hemicolectomy with a primary anastomose or stoma, caecostomy, untwisting and caecopexy, but at a high risk of relapses [5,8]. The choice of a surgical technique is determined mainly by local changes in the intestinal segment, peritonitis presence and dissemination, severity of ileus condition and comorbidities.

CONCLUSION

The presented case is a demonstration of protracted course of the disease in terms of clinical presentation, with a sharp deterioration in the general and local status, combined with the lack of evidence of peritoneal irritation. Meanwhile,

the histological result has shown evidence of fibrinous peritonitis, which does not correlate with the examined status of the abdomen and laboratory parameters. In this case, timely surgery and the correct choice of surgical method have led to a positive outcome of the diagnostic and treatment process.

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Адрес за кореспонденция:

ПРОФ. ПЕТЬО ТОКОВ

Клиника по Обща и чернодробно-панкреатична хирургия
УМБАЛ „Александровска“ ЕАД,
Медицински университет – София

Address for Correspondence:

PROF. PETIO TOKOV

Clinic of General and Liver-Pancreatic Surgery
UMHAT “Alexandrovska”,
Medical University – Sofia

СПОНТАННА ПЕРФОРЦИЯ НА ЕКСТРАХЕПАТАЛНИТЕ ЖЛЪЧНИ ПЪТИЩА – РЯДКА ПРИЧИНА ЗА ПЕРИТОНИТ

Евг. Аструков
Сити Клиник, София

SPONTANEOUS PERFORATION OF EXTRA HEPATIC BILE DUCT – A RARE CAUSE FOR PERITONITES

Evg. Astroukov
City Clinic, Sofia

РЕЗЮМЕ

Спонтанната перфорация на екстрахепатален жлъчен канал е рядка патология – в литературата намерих докладвани 50 случая при възрастни и 150 при деца. Имах шанса да лекувам пациент със спонтанна перфорация на холедоха. В статията се прави преглед на литературата. Дискутират се: решението което се взе на операционната маса, проблемите които имахме в следоперативния период както и начините за лечение на такива пациенти според литературата.

ABSTRACT

Spontaneous perforation of an extra hepatic bile duct is a rare pathology – in the literature I found reported 50 cases in adults and 150 in children. I had the chance to treat a patient with spontaneous perforation of the common bile duct. In the article a review of the literature is done. Discussed are: the decision we made during the operation, the problems we had in the postoperative period as well as the ways of treating such patients according to the literature.

According to my review the earliest publication concerning spontaneous perforation of an extra hepatic bile duct is in the references to the article of Hart D. E. (1). This article is published in Lancet in the year 1882 by Freeland (2) and is about a rupture of a hepatic duct. Later, in the year 1911, McWilliams (5) does a review of the perforations of the extra hepatic bile ducts. Out of 3180 operations on the biliary tree an acute spontaneous perforation was diagnosed in 29 or 0.9%. Most of them were perforations of the gall bladder due to stones, but 4 or 4.4% were

reported to be perforations of the common bile duct and 1 or 1.1% to the common hepatic duct. It still is a rare condition – Ticerhurst et al (6) in an article published in the year 2001 report of about 50 cases in adults in the world. A surgeon has a smaller chance to deal with spontaneous perforation of the left hepatic duct as the one described by Mizutani et al (7) or the same condition concerning the right hepatic duct as reported by Nguyen and Dasa (8). When you treat children you have much bigger chance to face spontaneous perforation of an extra hepatic bile duct – Xanthakos et al (6), Barnes et al (5) and Evans et al (13) report about 150 cases in children as far as the year 2010. Until the year 2001 were reported two case of perforation of a bile duct inside the liver parenchyma (6). Aydin et al (9) and Gundara et al (12) report each of them one such case outside the two mentioned above. In the article of Lee and Sun (10) one can find a case of infected biloma due to spontaneous biliary rupture.

CASE REPORT

PSB, an 80 years old man, was admitted in the hospital on the 12.VII.2012 with abdominal pain. The onset of pain is acute and began about midnight. With time the pain was getting stronger and stronger. The patient stopped taking food and water. Because of a stroke in the past he was not able to speak and was partially paralyzed in the right side of his body. For that reason the history of the illness is not full and, probably, not entirely correct. On physical examination were found distinct signs of peritoneal irritation – furred tongue, tenderness were present with both percussion and palpation, not voluntary rigidity of the rectus muscles and lateral abdominal muscles, rebound tenderness. Rectal examination proved he had an enlarged prostate. Routine laboratory data were not helpful in determining the etiology and duration of peritonitis. The patient was transferred to theatre for an emergency operative treatment. During the induction of anesthesia occurred an atrial fibrillation with uncontrolled high heart rate. Attempts to control this complication did not succeed. A cardiologist was consulted. The intervention was postponed for a few hours and cordaron treatment was applied until the condition of his heart improved. At laparotomy the peritoneal cavity was full of bile. A hemorrhagic pancreatitis was diagnosed predominantly on the head of the organ. There was fluid in the retro peritoneum and right lateral canal. On the common bile duct, close to the duodenum a perforation 3/3 mm was found. No gallstones neither in the gallbladder, no in the bile ducts. A T-tube was inserted at the site of perforation and the gallbladder was taken away. The peritoneal cavity was thoroughly washed and drained – a drain was inserted under the liver, in Douglas cavity and in the omental bursa. Contact with the patient in the postoperative period was very hard, almost impossible. On the second postoperative day he took out the T-tube and the drain placed in the omental bursa. About 850 cc of bile went out through the drain placed under the liver every 24 hours. On the 4–5 postoperative day gastrointestinal passage was restored so we started feeding him via a nose-gastric tube. One of the next days was diagnosed hypostatic pneumonia out of which he died on the 9-th postoperative day. Light microscopy examination B 289 from the 25 of July 2012 – gallbladder with chronic atrophic cholecystitis. Omentum with adipose necrosis and diffuse purulent inflammation – changes that are observed in acute pancreatitis.

DISCUSSION

Many reasons for that condition are under discussion. In adults occlusion of the bile ducts by stone is the most often reason accepted as a cause [70% according to Ticerhurst et al (6)]. Increased pressure inside the bile ducts is considered to lead to a perforation at the site where the wall of the canal is not strong enough. Necrosis of the wall at the site where a stone is traumatizing it is another possibility. Lakyova

et al (11) report a spontaneous perforation that occurred in a patient with acute pancreatitis. In our case we faced the same illness. Cholangitis associated with weakness of the wall of the biliary cannels and para pancreatic chances not much different from those observed in acute pancreatitis is another possibility. In children the surgeon most often faces a rupture of a cyst (congenital?) of the common hepatic duct. Excluding the perforations of the gall bladder the most often site of perforation is at the common bile duct or the place where the cystic duct is connected with the common hepatic duct. A perforation has been reported at every site of the biliary tree including congenital abnormalities as cysts of the common bile duct. The most common clinical manifestation of the disease is that of bile ascites or bile peritonitis. Ultrasound and/or CT will prove that there is a large amount of fluid inside the peritoneal cavity without, in most cases, been able to determine where it is coming from and what her structure is. Neither of this was done in our case because, on one side we had no doubt in the diagnose of peritonitis, the serious condition the patient was in, and on the other side no one thought of such a rare cause. In the past that diagnose was made either during an operation or at autopsy. Endoscopic Retrograde Cholangiopancreatography (ERCP) will find the perforation site and will disclose whether there is a distal obstruction of the common bile duct or not. In carefully selected patients Percutaneous Transhepatic Cholangiography (PTC) will determine the site of perforation and, if present, biliary obstruction. Both are done in patients with jaundice that was not present in our case. MRI is also capable of finding the site of perforation and the possible distal obstruction of the biliary tree. ERCP has the advantage of giving the possibility to extract stone(s), if present, performing a papililoshincterotomy and/or placing a stent at the site of perforation. That condition – "perforation of a biliary channel" as a rule is diagnosed late, on one side because of its rarity, on the other by reason of lack of typical sings. The delay leads to high percentage of death. There is not a conclusive decision how to treat such patients. Different surgeons apply different methods – external drainage, T-tube drain, endoscopic papililoshincterotomy and placing a stent, conservative treatment, suture of the perforation and drain, bile-digestive anastomose, laparoscopic treatment and so on. Conservative treatment, widely used in the past, was followed by high percentage of death. Operative treatment, accepted in our days, leads to much better results. In our patient we had to postpone it with a few hours by reason of heart problems. He died when peritonitis was overcome but his other illnesses were an obstacle to prevent the development of hypostatic pneumonia.

In our days perforation of a bile channel is still one of the rarest causes of peritonitis. For that reason neither doctors nor surgeons think about it. That leads to delay in diagnoses and treatment. The principles of treatment have not changed – closer of the hollow of the channel, secure drainage of bile distally and treatment of peritonitis and sepsis.

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Адрес за кореспонденция:

EVG. ASTROUKOV

City Clinic, Sofia

Address for Correspondence:

EVG. ASTROUKOV

City Clinic, Sofia

По случай 80 години от рождението на акад. Проф. Григор Велев, дмн, основател и първи главен редактор на списание „Българска медицина“

Председателят на БАНИ акад. проф. д-р Григор Велев е роден на 22 януари 1935 г. в гр. Хасково. Завършва основно и средно образование в родния си град и медицина в пловдиския Висш медицински институт. Първоначално работи в Хасковската окръжна болница. След това специализира за патолог и започва работа в ИСУЛ – София. Става завеждащ на Патолого-анатомичното отделение и асистент към Катедрата по патология на ИСУЛ.

През 1973 г. защитава дисертация на тема „Имунна стимулация на чернодробната регенерация“ и получава научното звание кандидат на медицинските науки (сега: доктор по медицина).

През 1984 г. е хабилитиран за доцент по патология и става ръководител на катедрата по Обща и клинична патология при ВМИ, Стара Загора. Една година по-късно защитава дисертация „Биопсична диагностика на хроничния хепатит“ за получаване на научното звание доктор на медицинските науки. През същата година е хабилитиран за професор.

Проф.Велев организира и редактира написването на първия двутомен учебник по патология за студенти и специализанти. Преиздаван и преработван няколко пъти този учебник и до сега е единствен в страната и се използва във всички медициски висши училища.

През 1989 г. акад. Велев е избран за ректор на Висшия медицински институт – Стара Загора. Специализира в Москва и Париж по проблемите на имунопатологията на черния дроб.

Акад. Григор Велев е автор е на 137 публикации в областта на стомашно-чревната, чернодробната, онко- и имунопатологията, сред които и пет монографии. Под редакцията му са написани „Ръководство за лекари патолози по Обща и клинична патология“ и четири

учебника за студенти по „Обща патология“ и „Клинична патология“. Съавтор е на четири „Ръководства за практически упражнения по патология“

След 1989 г. проф. д-р Григор Велев започва да пише активно политическа публицистика от позициите на модерния градивен национализъм. Публикувал е над 300 статии, анализи и коментари, посветени на актуални политически събития у нас и чужбина. Участвал е в десетки предавания на различни телевизии, посветени на политическите проблеми в България.

През 2003 г. Григор Велев откри в Скопие „Българска книжарница“ с 10 000 тома книги, която в продължение на няколко години бе средище на българската култура и дух във Вардарска Македония. От 2004 г. е председател на Комитета за защита на българите от Западните покрайнини. През същата година проф. Велев с група учени възстановява Българската академия на науките и изкуствата, която беше закрита по време на съветската окупация след Втората световна война и която е истинският приемник и наследник на българското книжовно дружество, създадено от нашите възрожденци още по време на турското робство.

Акад. Велев беше инициатор, мотор и организатор на Първия Световен събор на българите по света и първата сесия на Световния български парламент, които се проведоха през 2008 г. Със своите действия Асоциацията прояви внимание и съпричастност към живота на огромната, но позабравена българска диаспора и подсети държавните органи за необходимостта да се активизират при решаване на проблемите на българите, които живеят и работят зад граница.

Навръх рождения си ден, 22 март 2015 г., акад. Велев представи в аулата на Военномедицинска академия своята нова книга „История на българите от Македония**.** Древност. Средновековие и Българско Възраждане“ – том I. Предстои да излязат от печат втори и трети том: „Национално-революционните борби в Македония и разколът сред нейните организации“ и „Националното предателство на БКП – създаването на политическа нация „македонци“, македонски език и македонска история“. Премиерата на този дългогодишен изследователски труд мина при голям интерес.

Акад. Велев вече има зад гърба си много сериозни трудове в областта на историята. Той е автор на книгите „Национализмът“, „Диктатура.Терор. Геноцид. Шовинизъм (Фундаменти на комунизма, фашизма, националсоциализма)“; „Българският национализъм и неговото бъдеще“; „Българската национална кауза (1762–2012)“; и др.

Извън академичната си служебна ангажираност акад. Велев е прекрасен приятел, готов да помогне в тежки случаи с навременен съвет или конкретна незабавна помощ и съдействие за решаване на всякакви проблеми. С изключително богат житейски опит, със силно развито чувство за хумор, той е чудесен събеседник по различни теми на всекидневието.

ПОЗДРАВИТЕЛЕН АДРЕС

Уважаеми академик Велев,

Имаме честта и удоволствието да Ви поднесем нашите най-сърдечни поздравления по случай Вашата 80-годишнина, която отбелязахте на 22 март 2015 г. Вие сте инициатор и член на Редакционния съвет на сп. „Българска медицина“ и съдействате най-активно за поддържане на високо научно ниво на списанието и популяризиране на българските медицински научни постижения в нашата страна и зад граница.

Във Вашия дългогодишен живот Вие се проявявате като учен, високо компетентен лекар-патолог, блестящ преподавател, организатор на научни и граждански форуми, издател, изкусен оратор, автор на многобройни научни трудове в областта на медицината и на фундаментални исторически и политически книги.

Като председател на Българската академия на науките и изкуствата (БАНИ), която през ноември 2014 г. чества своята 10-годишнина от възстановяването си, Вие сте си поставил благородната цел да продължите традициите на Академията, ръководена от акад.Богдан Филов за обединение на националния научен и творчески потенциал в служба на Отечеството.

Екип на БАНИ изготви Българска национална доктрина, която бе изпратена до всички отговорни институции в страната и се очаква нейното разглеждане в Народното събрание.

С вашата енергия бе създадена и Асоциацията на българите по света и Световния български парламент.

Вие сте необикновена личност и достоен българин, посветил огромната си ерудиция, творчески заряд, воля и неизчерпаема енергия на науката , на националния идеал и националната кауза .

Вашето огромно дело е пример за вярност, преданост, синовна обич и безкористност, отдадени на Отечеството – за ново Възраждане на интелектуалната и творческа мощ на нашия народ и за духовно обединение на българите по света.

Приемете нашите най-искрени пожелания за щастливо и пълноценно дълголетие !

От екипа на сп. „Българска медицина“

The Bulgarian Medicine Journal, official edition of the Bulgarian Academy of Science and Arts, Science Division, Research Center for Medicine and Health Care is published in 4 issues per year. It accepts for publication reviews, original research articles, case reports, short communications, opinions on new medical books, letters to the editor and announcements for scientific events (congresses, symposia, etc) in all fields of fundamental and clinical medicine. The journal is published in English with exceptional reviews on significant topics in Bulgarian. The detailed abstracts and the titles of the articles, the names of the authors and institutions as well as the legends of the illustrations (figures and tables) are printed in Bulgarian and English. Bulgarian medicine is available online at the website of the Academy, publications section.

The manuscripts should be submitted in two printed copies, on standard A4 sheets (21/30 cm), double spaced, 60 characters per line, and 30 lines per standard page.

The size of each paper should not exceed 10 pages (up to 5 000 words) for original research articles, 12 pages for reviews (7 500 words), 3 pages for case reports, 2 pages for short communications, 4 pages for discussions or correspondence on scientific events on medical books or chronicles. The references or illustrations are included in this size (two 9x13 cm figures, photographs, tables or diagrams are considered as one standard page).

The abstracts are not included in the size of the paper and should be submitted on a separate page with 3 to 5 key words at the end of the abstract. They should reflect the most essential topics of the article, including the objectives and hypothesis of the research work, the procedures, the main findings and the principal conclusions. The abstracts should not exceed one standard typewritten page of 200 words.

Списание „Българска медицина", издание на Българската Академия на Науките и Изкуствата, Отделение за наука, Научен център по медицина и здравеопазване, излиза в четири книжки годишно. „Българска медицина" е достъпна онлайн на сайта на БАНИ, раздел издания.

В него се отпечатват оригинални научни статии, казуистични съобщения, обзори, рецензии и съобщения за проведени или предстоящи научни конгреси, симпозиуми и други материали в областа на клиничната и фундаменталната медицина. Списанието излиза на английски език с подробни резюмета на български и английски. Изключения се правят за обзорни статии по особено значими теми. Заглавията, авторските колективи, а също надписите и означенията на илюстрациите и в таблиците се отпечатват и на двата езика.

Материалите трябва да се предоставят в два еднакви екземпляра, напечатани на пишеща машина или на компютър, на хартия формат А4 (21 х 30 см), 60 знака на 30 реда при двоен интервал между редовете (стандартна машинописна страница). Освен това могат да бъдат изпратени като прикачени файлове по електронната поща на адресите, посочени по-долу.

Обемът на представените работи не трябва да превишава 10 стандартни страници за оригиналните статии (или 5000 думи според стандарта на англосаксонските издания) 12 страници (7 500 думи) за обзорните статии, 3–4 страници за казуистичните съобщения, 4 страници за информации относно научни прояви в България и в чужбина, както и за научни дискусии, 2 страници за рецензии на книги (монографии и учебници). В посочения обем се включват книгописът и всич-ки илюстрации и таблици. В същия не се включват резюметата на български и английски, чий-то обем трябва да бъде около 200 думи за всяко

The basic structure of the manuscripts should meet the following requirements:

TITLE PAGE

The title of the article, forename, middle initials (if any) and family name of each author; institutional affiliation; name of department(s) and institutions to which the work should be attributed, address and fax number of the corresponding author.

TEXT OF THE ARTICLE

Titles and subtitles should be standardized. The original research reports should have the following structure: introduction (states the aim, summarizer the rationale for the study), subjects and materials, methods (procedure and apparatus in sufficient detail, statistical methods), results, discussion, conclusions (should be linked with the aims of the study, but unqualified statements not completely supported by research data should be avoided). These requirements are not valid for the other types of manuscripts. Only officially recognized abbreviations should be used, all others should be explained in the text. Units should be used according to the International System of Units (S. I. units). Numbers to bibliographical references should be used according to their enumeration in the reference list.

ILLUSTRATIONS

Photographs should be presented both in the text body to indicate their location and in separate files as saved in jpeg, tif or bitmap formats.

The figures, diagrams, schemes, photos should be submitted in a separate file with: consecutive number (in Arabic figures); titles of the article and name of the first author. The explanatory text accompanying the figures should be presented along with the respective number of the figure in the main text body with space left for insertion of the figure.

(25–30 машинописни реда). Резюметата се представят на отделни страници.Те трябва да отразяват конкретно работнатахипотеза и целта на разработката, използваните методи, най-важните резултати и заключения. Ключовите думи (до 5), съобразени с „Medline“, трябва да се посочат в края на всяко резюме.

Структурата на статиите трябва да отговаря на следните изисквания:

ТИТУЛНА СТРАНИЦА

а) заглавие, имена на авторите (собствено име и фамилия), название на научната организация или лечебното заведение, в което те работят. При повече от едно за ведение имената на същите и на съответните автори се маркират с цифри или звездички;

б) същите данни на английски език се изписват под българския текст.

Забележка: при статии от чужди автори българският текст следва английския. Точният превод от английски на български се осигурява от редакцията. Това се отнася и за останалите текстове, включително резюметата на български.

Основен текст на статията. Заглавията и подзаглавията следва да бъдат уеднаквени и различими.

Оригиналните статии задължително трябва да имат следната структура: увод, материал и методи, собствени резултати, обсъждане, заключение или извод.

Методиките следва да бъдат подробно описани (включително видът и фирмата производител на използваните реактиви иапаратура). Същото се отнася и за статистическите методи.

Тези изисквания не важат за обзорите и другите видове публикации. В текста се допускат само официално приетите международни съкращения; при използване на други съкращения те трябва да бъдат изрично посочени в текста. За мерните единици е задължителна международната система SI. Цитатите вътре в текста е препоръчително да бъдат отбелязвани само с номерата им в книгописа.

References

The references should be presented on a separate page at the end of the manuscript. It is recommended that the number of references should not

Exceed 20 titles for the original articles and 40 titles for the reviews; 70 % of them should be published in the last 5 years. References should be listed in alphabetical order, English first, followed by the Bulgarian ones in the respective alphabetic order. The number of the reference should be followed by the family name of the first author and then his/her initials, names of the second and other authors should start with the initials followed by the family names. The full title of the cited article should be written, followed by the name of the journal where it has been published (or its generally accepted abbreviation), volume, year, issue, first and last page. Chapters of books should be cited in the same way, the full name off the chapter first, followed by"In:" full title of the book, editors, publisher, town, year, first and final page number of the cited chapter.

Examples:

Reference to a journal article:

1. McLachan, S. , M. F. Prumel, B. Rapoport. Cell Mediated or Humoral Immunity in Graves' Ophthalmopathy? J. Clin. Endocrinol. Metab., 78, 1994, 5, 1070–1074.

Reference to a book chapter:

2. Delange, F. Endemic Cretenism. In: The Thyroid (Eds. L. Braveman and R. Utiger). Lippincott Co, Philadelphia, 1991, 942–955.

Submission of manuscripts

The original and one copy of the complete manuscript are submitted together with a covering letter granting the consent of all authors for the publication of the article as well as a statement that it has not been published previously elsewhere and signed by the first author. The procedure should be complemented via electronic submission. Manuscripts of articles accepted

Илюстрации и таблици

Снимките – освен в Word, за да се знае местоположението им, следва да бъдат предоставени и като отделни файлове във формат jpg, tif или bitmap.

Илюстрациите към текста (фигури, графики, диаграми, схеми и др. черно-бели копия с необходимия добър контраст и качество) се представят на отделни листове (без обяснителен текст), в оригинал и две копия за всяка от тях. Текстът към фигурите със съответната им номерация (на български и на английски език) се отбелязва вътре в основното текстуално тяло на статията под съответния номер на мястото, където трябва да се разположи при предпечатната подготовка.Таблиците се представят с готово написани обяснителни текстове на български и на английски, които саразположени над тях; номерацията им е отделна (също с арабски цифри).

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Книгописът се представя на отделен лист. Броят на цитираните източници е препоръчително да не надхвърля 20 (за обзорите до 40), като 70 % от тях да бъдат от последните 5 години. Подреждането става по азбучен ред (първо на латиница, после на кирилица), като след поредния номер се отбелязва фамилното име на първия автор, след това инициалите му; всички останали автори се посочват с инициалите, последвани от фамилното име (в обратен ред) до третия автор, последвани от съкращшениетоет Al. Следва цялото заглавие на цитираната статия, след него названието на списанието (или общоприетото му съкращение), том, година, брой на книжката, началната и крайната страница. Глави (раздели) от книги се изписват по аналогичен начин, като след автора и заглавието на главата (раздела) се отбелязват пълното заглавие на книгата, имената на редакторите (в скоби), издателството, градът и годината на издаване, началната и крайната страница.

for publication will not be returned to the authors.

Peer-review process: following the international standards in the field, the Editorial board has adopted double-blind peer-review policy assigned to independent referees. The authors are encouraged to submit the names of three potential referees for editorial consideration

PUBLICATION ETHICS

Editors' obligations

The editor is responsible for deciding which of the articles submitted to the journal should be published.

The editor may be guided by the policies of the journal's editorial board and constrained by such legal requirements as shall then be in force regarding libel, copyright infringement and plagiarism. The editor may confer with other editors or reviewers in making this decision.

An editor at any time evaluate manuscripts for their intellectual content without regard to race, gender, sexual orientation, religious belief, ethnic origin, citizenship, or political philosophy of the authors.

The editor and any editorial staff must not disclose any information about a submitted manuscript to anyone other than the corresponding author, reviewers, potential reviewers, other editorial advisers, and the publisher, as appropriate.

Authors' obligations

The authors should ensure that they have written entirely original works, and if the authors have used the work and/or words of others that this has been appropriately cited or quoted.

An author should not in general publish manuscripts describing essentially the same research in more than one journal or primary publication. Submitting the same manuscript to more than one journal concurrently constitutes unethical publishing behaviour and is unacceptable.

ПРИМЕРИ:

Статия от списание:

1. McLachlan, S., M. F.Prumel, B. Rapoport. Cell Mediated or Humoral Immunity in Graves' Ophthalmopathy? J. Clin. Endocrinol. Metab., 78, 1994, 5, 1070–1074.

Глава (раздел) от книга:

2. Delange, F. Endemic Cretenism. In: The Thyroid (Eds. L. Braveman and R. Utiger). Lippincott Co, Philadelphia, 1991, 942–955.

Адрес за кореспонденция с авторите

Той се дава в края на всяка статия и съдържа всички необходими данни (вкл. електронна поща) на български език за един от авторите, който отговаря за кореспонденцията.

Всички ръкописи трябва да се изпращат с придружително писмо, подписани от авторите, с което потвърждават съгласието си за отпечатване в сп. „Българска медицина". В писмото трябва да бъде отбелязано, че материалът не е бил отпечатван в други научни списания у нас и в чужбина. Ръкописи не се връщат.

ПРОЦЕДУРА ПО РЕЦЕНЗИРАНЕ:

С оглед спазване на международните стандарти, редакционната колегия е приела процедура по 'двойно сляпа' рецензия от независимио референти. На авторите се предоставя възможноста да предложат на вниманието на редакционния екип три имена на специалисти в тяхната област като потенциални рецензенти.

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При това редакторът се съобразява със законови ограничения, свързани с въздържане от дискредитиране, нарушаване на авторски права или плагиатство.

Редакторът оценява интелектуалната стойност на един труд без оглед на възраст,

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Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. Where there are others who have participated in certain substantive aspects of the research project, they should be acknowledged or listed as contributors.

The corresponding author should ensure that all appropriate co-authors and no inappropriate co-authors are included on the paper, and that all co-authors have seen and approved the final version of the paper and have agreed to its submission for publication.

Obligations of the reviewers

Peer review assists the editor in making editorial decisions and through the editorial communications with the author may also assist the author in improving the paper.

Any manuscripts received for review must be treated as confidential documents. They must not be shown to or discussed with others except as authorized by the editor.

Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

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Unpublished materials disclosed in a submitted manuscript must not be used in an editor‘s own research without the express written consent of the author.

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Рецензентите подпомагат редкатора при вземане на решение. Посредством редакционната комуникация те могат да подпомогнат автора в повишаване а качеството на статията

Всички ръкописи, получени за рецензиране следва да се считат за поверителни материали и тяхното съдържание на следва да се разкрива пред никого, освен с разрешението на редактора.

Ethical regulations: reports with experiments on human subjects should specify whether the procedures were conducted in accordance with the ethical norms if the responsible committee on Human experimentation (local or regional) and/or with the Helsinki Declaration, as revised in 2000. Respective guidelines for animal experimentation should be considered.

PROCESSING CHARGES

Following acceptance for publication the authors are charged 5 euros per page for language editing and corrections.

Address for sending of manuscripts and other editorial correspondence

Prof. Dr Philip Kumanov
1431 Sofia, Zdrave str. 2, University Hospital for Endicrinology

And the next electronic addresses:

Prof. Dr Philip Kumanov, Editor-in-chief:
phkumanov@lycos.com

With copy for the scientific secretary –

Prof. Drozdstoj Stoyanov:
stojanovpisevski@gmail.com

Рецензиите следва да се придържат към обективни стандарти на оценка. Лични нападки срещу авторите са неприемливи. Критичните забележки следва да бъдат подкрепени с аргументи.

КОНФЛИКТ НА ИНТЕРЕСИ

Непубликувани материали не могат да бъдат използвани в собствени изследвания на редактора без изричното писмено съгласие на авторите.

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След положителна рецензия и одобрение на редколегията, авторите на статията дължат заплащане в размер на 10 лв. за всяка стандартна машинописна страница, с оглед на покриване разноските по ангийска езикова редкация на текста и коректури

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1431 София, ул. Здраве 2, УСБАЛЕ

Или на следния електронен адрес:

Проф. Д-р Филип Куманов, главен редактор:
phkumanov@lycos.com

С копие до научния секретар –

Проф. д-р Дроздстой Стоянов:
stojanovpisevski@gmail.com

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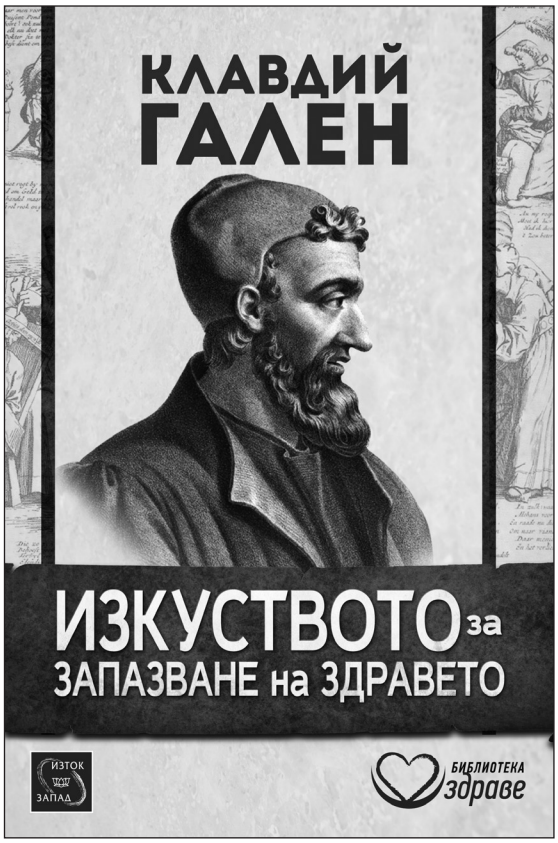
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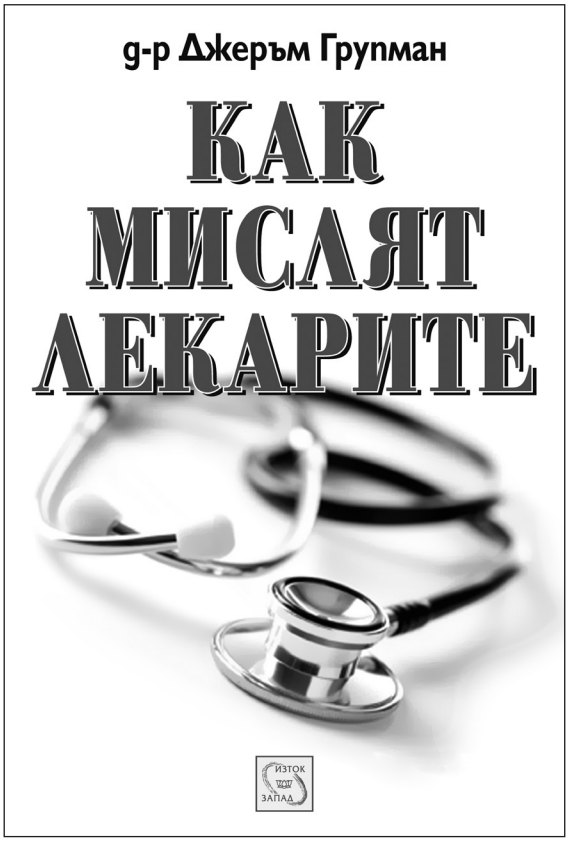
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МЕЛАНИ ТЪРНСТРОМ
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