Diaphragmatic hernia: formation mechanisms, clinical picture, treatment tactics

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An esophageal hernia (HH) is a chronic recurrent disease in which the cardiac esophagus, fundus of the stomach, and sometimes other organs of the abdominal cavity (intestinal loops, stuffing box, etc.) periodically move through the esophageal opening of the diaphragm to the chest cavity (posterior mediastinum) [18, 26].

The main mechanisms for the development of HH are considered [15, 18]:

- failure of connective tissue structures involved in the formation of the esophago-gastric junction;
- significant increase in intra-abdominal pressure;
- increased motor activity of the esophagus (hypermotor dyskinesia).

There are 3 types of HH [4]:

1. axial (axial) hernia is characterized by the fact that the abdominal part of the esophagus, cardial and fundus of the stomach with an increase in intra-abdominal pressure can freely penetrate ("slide") into the chest cavity. Such hernias are often called sliding. They are due to the weak attachment of the esophago-gastric junction to the diaphragm. Sliding hernias are usually not infringed, and small-sized hernias can be asymptomatic and can only be detected by X-ray or fibrogastroduodenoscopy [18, 25] (Fig. 1, 2);

2. paraesophageal (esophageal) hernias differ from axial hernias in that the abdominal (cardiac) part of the esophagus remains in the abdominal cavity, being fixed in the region of the esophageal opening of the diaphragm, while the fundus and/or antral sections of the stomach, and sometimes other abdominal organs (loops of the small or large intestine, epiploon, etc.) can penetrate into the chest cavity, located near the esophagus (i.e., paraesophageal). Thus, paraesophageal hernias are

formed during normal fixation of the esophago-gastric junction to the diaphragm, but with a significant expansion of the orifice of the diaphragm into which the abdominal organs can penetrate. Paraesophageal hernia is less common than axial, may be accompanied by infringement of the displaced organ [18] (Fig. 3, 4);

3. mixed hernias are characterized by a combination of signs of axial and paraesophageal hernias (Fig. 5) [18].

Each of the listed types of HH can be temporary, transient, occurring only with an increase in intra-abdominal pressure (non-fixed hernia) and a constant (fixed) protrusion of one or another esophagus or stomach into the chest cavity [18].

The pathogenesis of pain with HH, of course, consists of a number of components. Its development involves the distortion component (due to stretching of the esophagus walls during reflux of the stomach contents), inflammation (ulceration) of the esophageal mucosa, spastic component (hypermotor esophageal dyskinesia), ischemic component (compression of the hernia protrusion in the esophageal opening of the diaphragm). The last component is especially pronounced in the event of the impairment of the VOD [4].

When HH may develop as a pseudo-coronary, and coronary pain, arrhythmias [25]. Ya. G. Kolkin et al. (1996) [8], when examining more than a thousand patients with HH, 29% of patients with pain similar to angina were identified. Among these patients, a normal ECG was recorded only in 18% of cases, ECG signs of coronary heart disease were detected in 15%, diffuse myocardial changes — in 13%, deviation of the electrical axis of the heart to the left — in 19%, to the right — in 2%, sinus tachycardia — in 1%, sinus bradycardia — in 19%, ventricular premature beats — in 8%, impaired atrioventricular conductivity — in 2%, atrial fibrillation — in 3% of cases.

The following mechanism of pain in the HH is likely: the right vagus nerve, branching, directs part of its branches to the back wall of the stomach, part to the solar plexus. The displacement of the stomach upwards during the formation of a hernia is accompanied by the tension of the branches of the vagus nerve leading to

the solar plexus, as a result of which pain occurs. Such irritation of the vagus nerve can also lead to a reduction in the longitudinal muscles of the esophagus and a further increase in the hernia, that is, to the formation of a "vicious circle" [15, 27].

The ratio of gastroesophageal reflux disease (GERD) and HH may be twofold: GERD may contribute to the formation of HHD and vice versa [1, 7, 26]. According to V. Kh. Vasilenko (1971) [3], half of the patients with GERD have HHD. In contrast to GERD without HH, when heartburn is the dominant manifestation, pain prevails with GERD combined with HHD [19]. Pain with HH, according to various authors, concerns 25–85% of patients [8, 19]. Due to the prevalence of pain syndrome over dyspepsia in HHV, in this article we pay more attention to pain.

When HHL pain has distinct features. More often, pain is localized in the epigastric region, it has a very different nature and diverse irradiation. Constant pains lasting from several days to several months are usually observed, sometimes the pains disappear, but soon they resume again. Sometimes the pain shifts closer to the navel, often radiating to the back and hypochondrium. Periodically, pains are exacerbated in the form of short-term attacks, take shingles, and irradiation may be stronger than local pain. The latter is diffuse, deep, sharply increasing in the period of exacerbations, sometimes accompanied by fainting. The pain has the most varied shade: boring, burning, sharp, dull. Lying on your back and standing on your feet increase pain. The patient instinctively looks for a position that reduces pain, often "freezing" on the left side. A painful attack, as a rule, is sharply colored emotionally, accompanied by vasomotor reactions, the fear of death. Often the attack of pain is accompanied by vomiting at the beginning of food, and then with mucus and bile. Sometimes vomit contains blood. Vomiting is replaced by nausea and a sharp increase in commonly available belching. This may be accompanied by a drop in temperature, increased urination, cooling of the extremities. Pulse frequent, weak, soft. The attack can end as suddenly as it began. Most often, however, after a break, it is repeated, and a long chain of relapses begins, sometimes gradually subsiding. After an attack — weakness, depression, weakness [8, 26].

The pain is characteristic of the “cardiac mask” of the HH, especially since the attacks of pain can be accompanied by changes on the ECG (see above). Many of the patients with HH are treated for angina for years, and only the constant lack of appropriate changes on repeatedly performed ECG leads to further searches for the causes of heart disorders, sometimes with the detection of hiatus hernia [8, 15, 23, 25].

For the differential diagnosis of various diseases of the esophagus, accompanied by pain, it is advisable to use the criteria presented in table. one.

Treatment of HHD involves, first of all, the treatment of esophagitis, the elimination of gastroesophageal reflux, that is, it corresponds to the treatment of GERD (see below). Surgical treatment is advisable with the ineffectiveness of conservative therapy, the impossibility of long-term drug treatment, the development of complications, the combination of HH with other abdominal diseases requiring surgical intervention (cholelithiasis, etc.), large sizes of HH combined with respiratory failure, impaired cardiac activity. Esophagofundoplications are more often performed, and in cicatricial stenosis of the esophagus, it is resected [4, 8, 18].

The main directions of treatment of GERD [17, 26]:

- reduction of aggressive reflux;
- reducing the time of contact of the esophageal mucosa with refluxate by reducing the frequency and duration of reflux episodes;
- increased tone of the lower esophageal sphincter.

First of all, you need to give the patient advice on lifestyle changes and nutrition. The patient must sleep with the raised head end of the bed at least 15 cm; after eating avoid bending forward and do not go to bed; do not wear tight clothing and tight belts; avoid weight lifting more than 8–10 kg, overstressing the abdominals and work related to bending the body forward; fight overweight; stop smoking [17, 26].

They recommend frequent fractional feeding, limiting the amount of food and some foods (animal fats, chocolate, coffee, coarse fiber, carbonated drinks, spicy and spicy foods, fresh bread, flour products, etc.). After eating for at least 3 hours should

be in an upright position. Dinner should be light and no later than 2-3 hours before bedtime. It is necessary to completely abandon not only smoking, but also from the use of alcohol [18].

It is also necessary to exclude, and if this is not possible, then reduce the intake of drugs that can worsen GERD, reducing the tone of the lower esophageal sphincter or irritating the esophageal mucosa. Such drugs include methylxanthines (aminophylline, theophylline, Theodur), anti-shed (atropine, platylline, methacin), antidepressants (amitriptyline, imizin, fluoxetine — Prozac; fluvoxamine — Fevarin), nitrates (nitroglycerin, nitrosorph, and nitrofluxamine, fluvoxamine — Fevarin), nitrates (nitroglycerin, nitrosorcin, cyphine); adrenergic blockers (propranolol, atenolol, metoprolol, bisoprolol, nebivolol, carvedilol), calcium antagonists (verapamil, nifedipine, diltiazem), contraceptives (Triquvilar, Marvelon, Mikroginon, Logest), myotropic spasmolytics (using a referral unit), a myotropic spasmolytic agent (a); flax drugs (ibuprofen, indomethacin), narcotic analgesics (Omnopon, Promedol, buprenorphine) [17, 26].

In the case of drug treatment of GERD, two principal tactics are used [15]:

1. begin treatment with the use of the most powerful antisecretory agents — proton pump inhibitors (PPI) in standard or double therapeutic dosage, and after reaching the clinical effect, reduce the dose of PPI to supportive (step-down therapy);

2. designate incrementally increasing therapy, using successively antacids (alginates), and if they are ineffective, blockers of H2-histamine receptors and, finally, PPI (step-up therapy) [3, 26].

Of course, antisecretory therapy is complemented by prokinetics when choosing any of the two tactics mentioned above.

When treating HH, the step-down tactic is preferred. In this case, treatment begins with PPI. It has been established that for successful treatment of GERD, it is necessary that the pH inside the stomach exceeds 4.0 for 16-18 h/day. To achieve this result, using H2-blockers in therapeutic doses, it is impossible. This result can only provide PPI. This is the main advantage of these drugs. In addition, PPIs do not require an increase in doses during treatment, have a well-established mechanism of

action, have anti-helicobacter properties, use simple dosing regimen (1–2 p/day) for treatment, they are well tolerated, and the frequency of side effects is low [15 21].

The standard dose of omeprazole is 20 mg in the morning and evening, or 40 mg as a single dose; lansoprazole — 30 mg 2 p/day. or 60 mg once; Pantoprazole — 40 mg 2 p/day. or 80 mg once; rabeprazole — 10 mg 2 p/day. or 20 mg once; esomeprazole — 20 mg 2 p/day. or 40 mg once. If necessary, the dose of PPI can be increased [26].

In 1974, the first PPI was synthesized. Since that time, a whole series of generations of these drugs have been created. Although according to research results, each subsequent generation of PPI differs "on average" by a higher activity and duration of effect, a large number of factors affect the real effectiveness of a particular drug: the individual characteristics of the secretory apparatus as a whole (the so-called "hypersecretory status"), receptors on the surface of parietal cells, as well as metabolism (incl. different intensity of microsomal oxidation in the liver). You should also consider the possibility of producing antibodies to the drug [2, 13, 14].

Pantoprazole is available on the pharmaceutical market.

PPIs vary in bioavailability. For example, the bioavailability of omeprazole decreases with repeated administration, esomeprazole increases. The advantage of pantoprazole is a consistently high bioavailability, i.e. it does not change depending on whether the patient has taken the drug first, second or more times. It is also important that the ingestion of food and antacids does not affect the bioavailability of pantoprazole [2, 15, 39].

Pantoprazole is available in the form of tablets of 20 mg and 40 mg, enteric-coated, preventing its destruction by hydrochloric acid in the stomach. After oral administration, pantoprazole is rapidly absorbed, then it undergoes a slight first-pass metabolism. Absolute bioavailability of oral pantoprazole is 77% [34]. For parenteral administration, vials containing 40 mg of pantoprazole are used.

Pantoprazole (unlike omeprazole and esomeprazole) does not accumulate in the body after receiving repeated doses [4, 10, 34].

The PPIs enter the human body as precursors, and then undergo a certain activation, turning into the tubules of parietal cells into tetracyclic sulfenamide, which irreversibly blocks the activity of the proton pump by binding to cystine molecules. Pantoprazole binds to cystine at positions 813 and 822. It is this connection that is key to inhibiting the activity of the transport system. Unlike pantoprazole, omeprazole binds to cystine at positions 892 and 813, lansoprazole — 321, 813 and 892 [2]. Pantoprazole is the only PPI that binds to cystine 822, located deep in the transport domain of the proton pump, as a result of which it becomes unavailable to glutathione and dithiothreitol, which are able to eliminate inhibition. Therefore, it is assumed that pantoprazole has a longer effect than other PPIs [4, 6, 34].

The same is associated with a longer period required to restore acid secretion after ingestion of an PPI. So, for lansoprazole, the recovery time of gastric secretion is about 15 hours, for omeprazole and rabeprazole — about 30 hours, and for pantoprazole — about 46 hours [47]. That is, pantoprazole provides the most prolonged acid-lowering effect. Prolonged inhibition of the production of hydrochloric acid allows us to avoid a “nocturnal acid breakthrough” or a sharp rise in the acidity of refluxate when the patient misses the next dose of the drug [12].

It is this feature that determines the greater clinical efficacy of the drug compared to other IPPs, assessed by the percentage of patients with concurrent heartburn and the overall percentage of successful treatment of GERD [9, 43, 45].

In a neutral environment with moderate acidity (pH = 3.5–7.4) in vitro, pantoprazole is more stable than omeprazole, lansoprazole, and especially rabeprazole; at pH = 5.1, the half-time chemical activation of pantoprazole (4.7 hours) is greater than that of omeprazole, lansoprazole and rabeprazole (1.4; 1.5; 0.12 hours, respectively), while all four medicinal substances in a highly acidic medium (pH = 1.2) were quickly transformed into active forms (activation half-time 4.6; 2.8 ; 2.0; 1.3 minutes, respectively). A higher pH selectivity of pantoprazole means that, unlike omeprazole, lansoprazole and rabeprazole, it is less likely to accumulate in the body or be activated in a moderately acidic medium (pH = 3–5), for example, in

lysosomes, in late endosomes and in the microenvironment under the surface of adhesive macrophages and osteoclasts [42].

Thus, the selectivity of pantoprazole explains the smaller number of side effects and the greater safety of the drug compared with other IPPs [11, 28, 46]. These qualities of pantoprazole are also explained by the peculiarities of its metabolism. Metabolism of PPI occurs mainly in the liver with the participation of cytochrome P450, the main isoenzymes of which are CYP1A, CYP2C8-10, CYP2C19, CYP2D6 and CYP3A4. The key isoenzymes in the deactivation of PPIs are CYP2C19 and CYP3A4, which provide hydroxylation and dealkylation processes. The resulting metabolites are inactive and excreted in the urine (80%). Pantoprazole is an exception: its metabolism passes without the participation of these isoenzymes, and by conjugation (primarily sulphation), which provides a minor effect of the drug on the metabolism of other drugs. This probably explains the constant bioavailability of pantoprazole after the first use [2, 4, 24].

In healthy volunteers, there were no clinically significant drug interactions between pantoprazole and a variety of other drugs. The effect of pantoprazole on the concentration of cyclosporine or tacrolimus in the blood of patients undergoing kidney transplantation was also not observed [34].

The absence of an “overlap” of the metabolism of pantoprazole and other drugs is a significant advantage. When treating pantoprazole, the doctor can be sure that there is no risk of overdose or to reduce the effect of other drugs. Many studies have shown that pantoprazole does not affect the metabolism of clopidogrel, glibenclamide, nifedipine, diazepam, diclofenac, carbamazepine, warfarin, theophylline, and a wide range of other drugs (Table 2). In this regard, pantoprazole is considered the safest PPI [9, 25, 29, 33].

In modern clinical guidelines, most patients who have had an acute myocardial infarction are recommended to take acetylsalicylic acid drugs, many of them will also take clopidogrel and PPI [30]. Pantoprazole was not associated with an increased risk of recurrent myocardial infarction in patients taking clopidogrel because it did not inhibit cytochrome P450 2C19, and, on the contrary, the use of other PPIs was

associated with an increased risk of recurrent myocardial infarction by 40% during 90 days after discharge [36]. At the same time, the FDA (Food and Drug Administration) recommends avoiding the simultaneous use of clopidogrel with other drugs that inhibit CYP2C19 (omeprazole, esomeprazole) [51].

There are no reports of clinically significant changes in the pharmacokinetics of pantoprazole in the elderly or in patients with severe renal failure. Thus, patients in these groups do not need a dose adjustment [16, 33]. Pantoprazole in a dose of 40-120 mg/day. when administered orally for up to 5 years, it was well tolerated by patients with acid-related diseases, including patients with severe cirrhosis of the liver [33]. After two years of treatment with pantoprazole at a dose of 40–80 mg/day. there was no significant change in the number of enterochromaffin-like cells in the gastric mucosa [33].

Oral administration of pantoprazole in a dose of 40-120 mg/day. It is well tolerated by patients with both short-term (less than 8 weeks) and long-term (more than 4 years) treatment [31, 34].

Pantoprazole in eradication therapy regimens is more effective than other PPIs [9], while the healing efficiency of gastroduodenal ulcers with successful Helicobacter pylori eradication after 4 weeks of treatment is 88–91%, and after 8 weeks — 98–100% [39].

Pantoprazole is faster than esomeprazole to relieve the day and night symptoms of GERD [25, 50].

Maintenance therapy of GERD pantoprazole at a dose of 20 or 40 mg/day. within 12-24 months and is safer and prevents the development of relapses of reflux esophagitis in most patients [20, 22, 31, 33, 38, 49].

Pantoprazole suppresses bronchospasm caused by gastroesophageal reflux in most GERD patients (more than 80%) [32, 41, 48].

Pantoprazole is effective for the relief and prevention of ulcerative bleeding, as well as gastropathy caused by nonsteroidal anti-inflammatory drugs [40].

Pantoprazole is a highly effective and safe PPI. At the same time, it has an optimal price/efficiency ratio, which is important for our patients [2, 25].

Thus, pantoprazole, in our opinion, is the optimal PPI for the treatment of GERD on the background of HH, when the disease is often characterized by persistent course and resistance to therapy [21, 35, 37, 52]. As a rule, patients need the appointment of a number of drugs whose metabolism does not suffer when taking pantoprazole. The frequent development of extraesophageal manifestations of GERD in the presence of HH also determines the complexity of treatment. Favorable pharmacoeconomic characteristics of pantoprazole are also extremely important in this situation.

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Diaphragmatic hernia: formation mechanisms, clinical picture, treatment tactics

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Keywords: hiatal hernia, types of diaphragmatic hernia, pathogenesis, clinical picture, treatment, pantoprazole

The article presents current data on etiology, pathogenesis of diaphragmatic hernia. Types of diaphragmatic hernia are described in detail, namely: axial, paraesophageal, mixed; transient and fixed. Pathogenesis of the formation of hiatal hernia includes: failure of the connective tissue structures involved in the formation of the esophago-gastric junction; significant increase in intra-abdominal pressure; increase in motor activity of the esophagus (hypermotor dyskinesia). Clinical manifestations and peculiarities of pain, including pseudo-coronary pain, differential diagnosis, are described. Recommendations for non-drug treatment, including lifestyle and nutritional changes, are presented. Particular attention is paid to pantoprazole as a means of choice for therapy of patients. Advantages of pantoprazole as compared with other proton pump inhibitors are presented: selectivity of action depending on pH, absence of "decussation" with the metabolism of other drugs, efficacy, duration of acid suppressive action, safety, favorable pharmacoeconomic characteristics.

Table 1

Dependence of the nature of pain on the mechanism of occurrence (according to V.S. Golochevskaya, 2009 [5])

Type of pain	Diseases
Hot flashes (angina-like), retrosternal chest pains radiating to the neck, jaw and back May be accompanied by vegetative manifestations (sensation of heat, sweating, trembling in the body). Docked with nitroglycerin, a sip of water, analgesics	Esophageal dyskinesia Achalasia cardia HH GERD
Chest pains of burning character, aggravated in a horizontal position or torso forward. Cured by a change in body position, antacids	GERD
Persistent dull or burning pain behind the sternum	Achalasia cardia Diverticulitis Tumors of the esophagus
Odinophagia (pain when swallowing)	Esophagitis Gullet ulcer
Chest pain with a feeling of fullness in the epigastrium and lack of air, passes after belching	Aerophagia

Table 2

The interaction of various PPIs with other drugs (according to S. M. Cheer et al., 2003 [33], A. Fitton et al., 1996 [34])

Drugs	**Pantoprazole**	Omeprazole	Lansoprazole	Esomeprazole	Rabeprazole
Antiepileptic drugs Carbamazepine	No	↓ Clearance	No	N/A	N/A
Phenytoin	No	↓ Clearance	No	↓ Clearance	No
Diazepam	No	↓ Clearance	No	↓ Clearance	No
Heart drugs Methoprolol	No	No	N/A	N/A	N/A
Nifedipine	No	↑Absorption ↓ Clearance	N/A	N/A	N/A
Warfarin	No	↓ Clearance	No	↓ Clearance	No
Digoxin	No	↑Absorption	N/A	N/A	↑Absorption
Analgetics					

Diclofenac	No	No	N/A	N/A	N/A
Naproxen	No	No	N/A	N/A	N/A
Piroxicam	No	No	N/A	N/A	N/A
Antidiabetic drugs Glibenclamide	No	N/A	N/A	N/A	N/A
Oral contraceptives	No	N/A	Contradictory results	N/A	N/A
Ethanol	No	No	No	N/A	N/A
Anti-asthma drugs Theophylline	No	No	Contradictory results	N/A	No

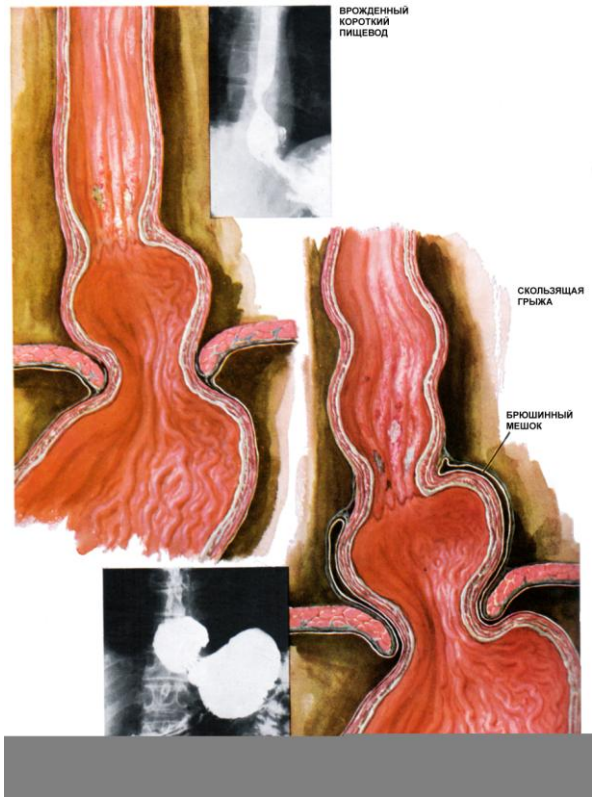

Fig. 1. Short esophagus and axial HH (according to F. H. Netter, 2002 [44]).

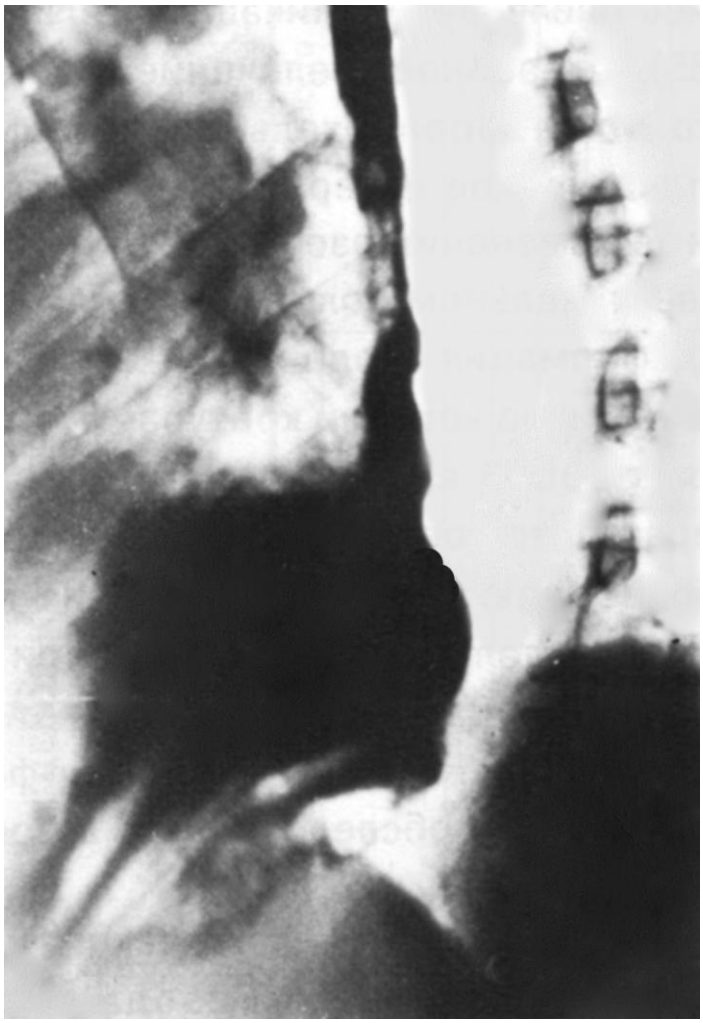

Fig. 2. Рентгенограмма. Axial HH (according to Ya. G. Kolkin et al., 1996 [8]).

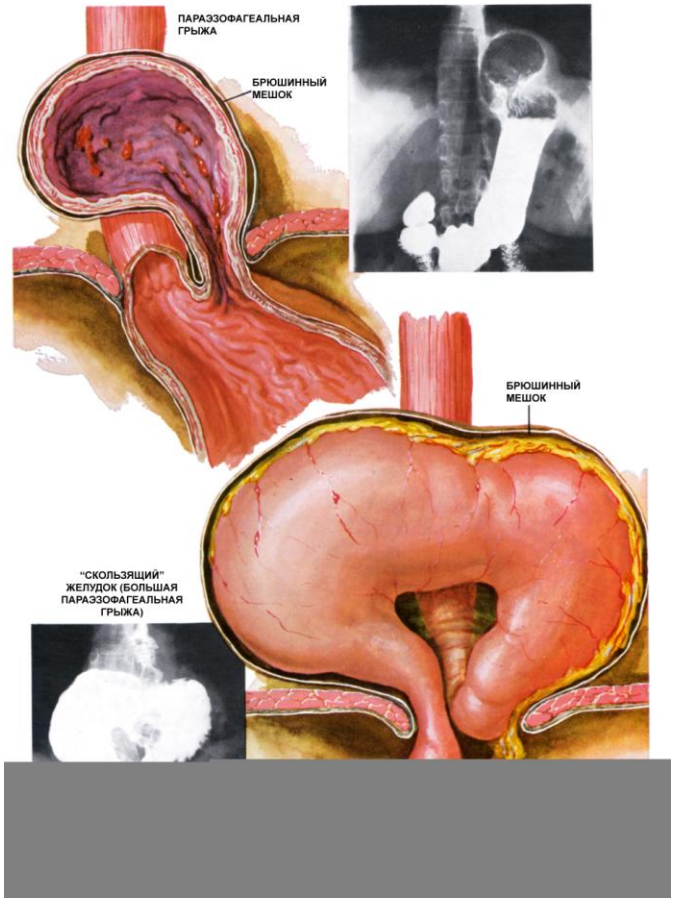

Fig. 3. Paraesophageal HH (according to F. H. Netter, 2002 [44]).

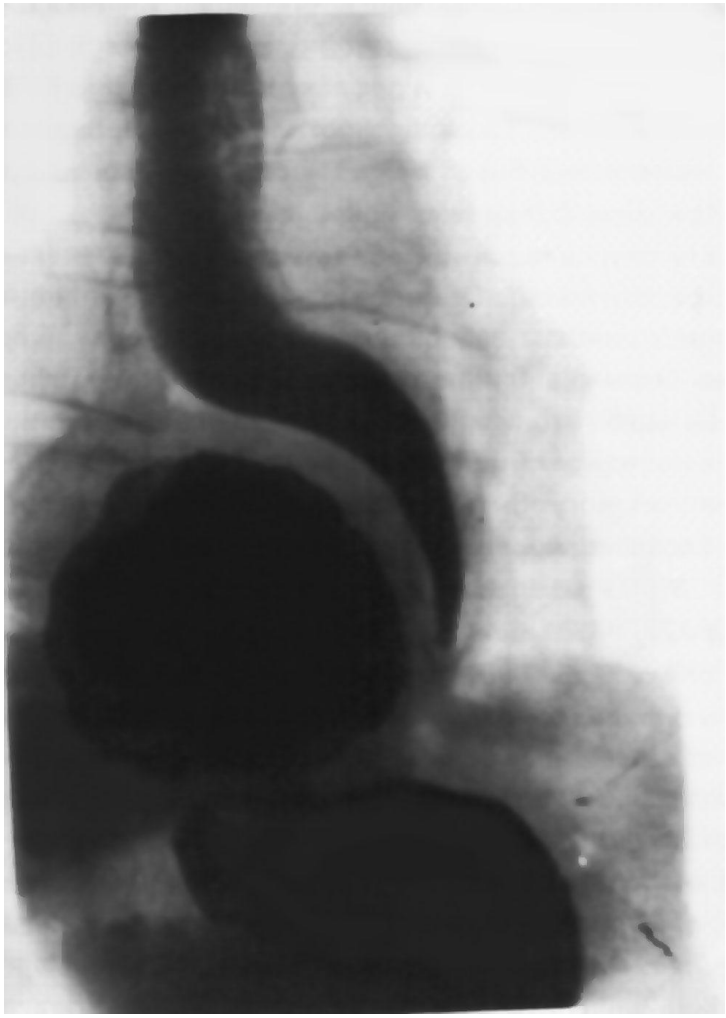

Fig. 4. Roentgenogram. Paraesophageal HH (according to Ya. G. Kolkin et al., 1996 [8]).

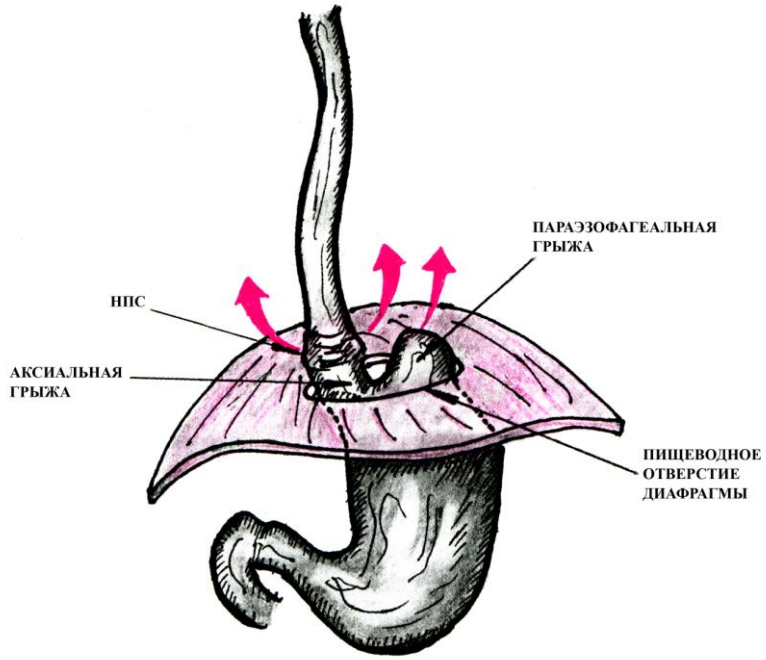

Fig. 5. Schematic representation of a mixed HH, characterized by a combination of signs of axial and paraesophageal hernia (according to G. E. Roytberg at al., 2007 [18]).