# The history of the development of gastroesophageal reflux disease in the Ashkenazi Jewish family.

Michael D. Levin, MD, PhD, DSc. Radiologist,

Department of Pediatric Radiology of the 1-st State Hospital, Minsk, Belarus.

Dorot-Netanya Geriatric Medical Center, Israel.

Amnon VeTamar, 1/2, Netanya, 42202, Israel.

nivel70@hotmail.com; michael.levin@dorot.health.gov.il

https://orcid.org/0000-0001-7830-1944

https://www.anorectalmalformations.com

Scopus Author ID: 7402571390

Zeev Arinzon. MD

Meuhedet Health Care System

Central Distric

arinzon_z@meuhedet.co.il

Gastroesophageal reflux disease (GERD) is a common problem treated by primary care physicians. A systemic review of 28 population-based studies reported an estimated prevalence of 18%-27% in North America, 8-25% in Europa, 2%-7% East Asia, and 23% in South America [1]. The physiology and pathogenesis of GERD are poorly understood. Heartburn, the most common symptom, occurs in most patients and is thought to be due to the stimulation and activation of mucosal chemoreceptors in the distal esophagus [1.2]. In the literature, there are numerous hypotheses about the etiology, pathological pathology, and pathogenesis of GERD. The pathophysiology of GERD is believed to be multifactorial. Several factors are

implicated in GERD, including hypotensive lower esophageal sphincter, frequent transient lower esophageal sphincter relaxation, esophageal hypersensitivity, reduced resistance of the esophageal mucosa against the refluxed contents, ineffective esophageal motility, abnormal bolus transport, deficits initiating secondary peristalsis, abnormal response to multiple rapid swallowing, and hiatal hernia [3]. With an increase in abdominal pressure, the frequency of GERD also increases. For example, de Mello Del Grande et al. showed that an increased transdiaphragmatic pressure gradient might be the main element for GERD in obese patients [4]. Asthma might increase GERD risk by means of certain pathways shared with allergic rhinitis since prolonged coughing and bronchospasm are accompanied by an increase in abdominal pressure [5].

There is no convincing evidence that the above symptoms, which are combined with GERD, are the cause of the disease, and not its consequence. Very little is known about the etiology of GERD. There is evidence of more than 30 genetic risk factors that are associated with GERD [6]. There is good reason to believe that genetically determined lactose intolerance is related to the etiology of GERD [7,8].

We have the opportunity to analyze the medical histories of four generations of the Ashkenazi Jewish family, who, in a significant percentage of cases, had a typical gastroesophageal reflux disease. The deceased members of the older generation of the family, who had typical symptoms of GERD, were not examined by special methods, so we do not give them in the genealogical tree **(Figure 1),** but we mention them in the medical histories of their children.

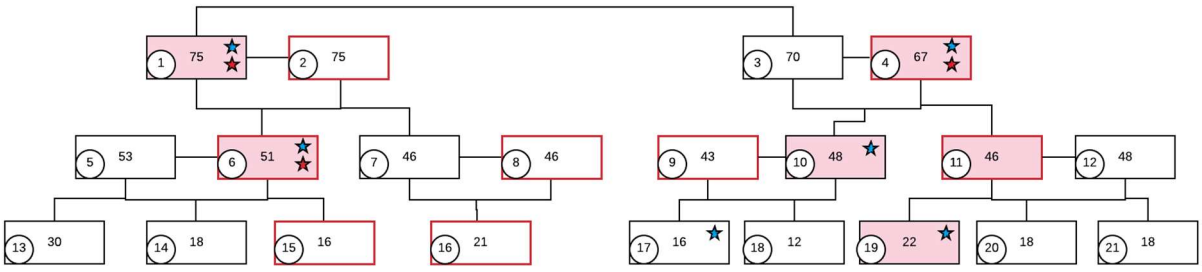


**Figure 1**. Three generations of a family, each member of which has his own number in the circle. Women - in a red frame. In the center of the square shows the age of

the person. A pink color indicates family members with a clear clinical picture of GERD. The blue asterisk is milk intolerance. The red star is a restless baby.

**Material and methods.** We analyze case histories of 21 family members of Ashkenazi Jews in terms of the prevalence of GERD. Eight (38%) had persistent symptoms of GERD, which necessitated either medication or a change in diet. All of these patients were over 18 years old. To assess the condition of patients, examination documents, and a personal conversation with the patient were studied. In 7 cases, to assess the condition of the esophagus and esophagogastric junction (EGJ), an X-ray examination was performed with the provocation of high pressure in the stomach according to the method we proposed. This study was performed in 5 patients with typical GERD symptoms and in 2 patients who complained only of rare heartburn.

**X-ray method for the diagnosis of GERD using high pressure in the stomach.**

The patient on an empty stomach, first drinks one or 2 glasses of water, depending on growth. Then, in the horizontal position on the table of the x-ray machine, he drinks through a straw 200 ml of barium suspension from a can located near his head. When barium ends, the patient raises straightened legs. At this moment, a radiograph produced. In some cases, to evaluate the evacuation from the esophagus, a second radiograph produced 3-5 minutes after the first.

On radiographs, we measured the width of the esophagus at the widest point, as well as the length of the distance between the esophagus and the stomach, in which there was no contrast medium (Figure 2). This distance is due to a contraction of the LES in response to increased pressure in the stomach. Knowing that the normal length of LES in adults ranges from 3.2 to 4.2 cm (3.60 ± 0.08 cm), we can judge the competence of the LES. If the length of the LES is less than the minimum norm, this indicates the weakness of the LES due to the disclosure of its abdominal part [9]. In older children weighing 74 kg, the diameter of the esophagus is 1.4 cm [10].

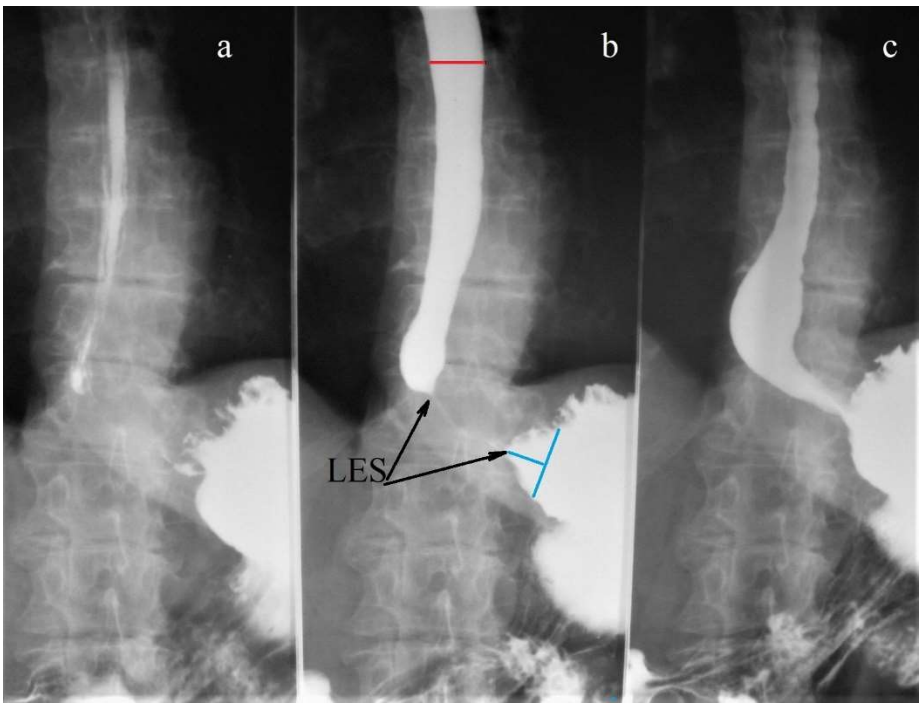


**Figure 2.** Change in the length of the LES in an elderly patient with reflux-esophagitis while drinking barium with abdominal compression. (a) Abdominal compression caused a contraction of LES. Its length (3.6 cm) is maximum after the first swallows of barium. (b) When the volume of barium in the stomach increased and gastric pressure increased, the contracted LES has become shorter due to the opening of its abdominal part in the form of angular deformation of the stomach (blue). (c) The moment of disclosure of the LES recorded. Peristalsis is visible in the ampullary part of the esophagus. The width of the open LES is the same over its entire length since there is no peristalsis in the LES.

Note that during swallowing in Figures 2.a and 2c, the proximal point of the LES is in the same place, 0.8 cm below the upper edge of D-12. The shortening of the LES occurs due to the disclosure of its abdominal part. This is due to the weakness of the LES as the main pathophysiologic mechanism of GERD. This typical x-ray picture indicates, firstly, that during swallowing, the LES does not move cranially. Secondly, the esophagus not shortened. Thirdly, the shortening of the LES is proof of its incompetence and is a reliable sign of GERD.

In adults without pathology of the esophagus and EGJ, we determined the width of the esophagus in an X-ray examination with compression of the abdomen on average as 1.5 cm [11]. Thus, normally the ratio of the width of the esophagus to the length of the LES is from 0.3 to 0.5. We call this ratio the X-ray Reflux Index (XRI).

In patients with GERD, shortening of the LES occurs, which accompanied by the expansion of the esophagus, as a result, the XRI increases and, as a rule, becomes more than one. We are not sure that the norm criteria that were obtained to evaluate studies with compression of the abdomen can be used in x-rays with the highest pressure in the stomach. Therefore, when comparing different studies, we use XRI.

**Results:**

# Case 1.

A man of 75 years, BMI is 24.43 born full-term healthy baby. Both his parents had severe symptoms of GERD. His mother had GERD with pain and she took PPI. His father had regurgitation without a painful syndrome. He sometimes spat out pieces of food that he had eaten a day ago.

He was a restless infant. Rare episodes of heartburn began at age 15. At 39 years old, pain behind the sternum appeared after a plentiful festive dinner. It lasted six months. The pain disappeared after gastroscopy, which did not detect pathological changes. Patient-controlled the situation by going to bed with an empty stomach. At first, he dined for 3 hours before bedtime, and recently for 6 hours. Occasionally he took one tablet PPI before the holiday and for several days after it. From the age of 55, he noticed that abdominal pain and heartburn appear after drinking milk. From the age of 70, pain appeared when eating flour products prepared with milk. A sharp deterioration occurred after the violation of the principles described above. An X-ray examination of the esophagogastric junction (EGJ) (Figure 3.a) revealed an expansion of the esophagus to 3.8 cm and a shortening of the lower esophageal sphincter (LES) to 1.4 cm with the presence of longitudinal folds at the level of the LES. XRI was 2.7. On an x-ray produced 3 minutes after the first one, the duodenal bulb was spastic. There is a suspicion of an ulcer on the right wall of the duodenal bulb (Figure 3.b). Gastroscopy performed 1.5 months after the use of PPI 40 mg x 2 times a day, when the pain behind the sternum was gone, did not reveal any pathology. No histological examination was performed.

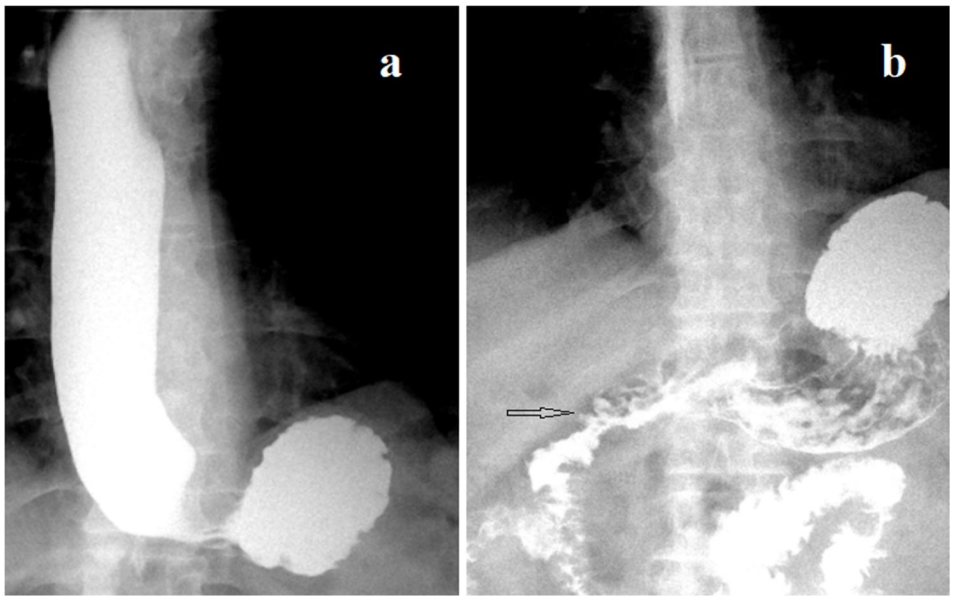


**Figure 3.** X-ray examination of esophagogastric junction during maximal provocation of high pressure in the stomach (Case 1). (a) The entire esophagus is dilated (3.8 cm instead of 1.5 cm) without peristalsis. The narrow segment between the esophagus and the stomach 1.4 cm long is a contracted LES, which is more than 2 times shorter than the minimum normal range. At the LES level, longitudinal folds are determined. (b) In a roentgenogram produced 3 minutes after the first one, barium is detected in the esophagus, which indicates impaired evacuation from the esophagus. Evacuation from the stomach is not impaired. The spasm and deformation of the duodenal bulb are determined. Suspicion of an ulcer in the bulb or in the pyloric canal (arrow). XIR is 2.71

**Conclusion:** Gastroesophageal reflux disease with severe LES failure.

**Analysis of the medical history.** In this observation, for about 40 years, there was an increase in the symptoms of dyspepsia. Double gastroscopy without histology did not diagnose the pathological process. From the point of view of the Roma IV criteria, the disease should be attributed to functional dyspepsia. However, the condition of the esophagus and LES indicates organic damage to the EGJ. The patient did not receive proper treatment due to a false idea about the presence of functional disorders, which were so designated since at 24-hour pH-metering in such patients, pH <4 was found to be less than 4-6% of the time. It follows that the diagnosis of GERD should be based on clinical symptoms without limitation in time and number.

# Case 3.

A 70-year-old man with a BMI of 28.76. Two years ago, BMI was 30.76. Both parents had severe clinical symptoms of GERD. In his mother, the reflux was accompanied by pain and she took PPI. His father had regurgitation without pain. Both of his children had typical clinical symptoms of GERD. Their diagnosis was confirmed by an X-ray examination (Cases 11 and 12).

He does not consider himself sick. Occasionally, he has heartburn after a hearty meal. Given that both of his parents based on clinical symptoms were diagnosed GERD, as well as the fact that reflux disease can progress, despite the absence of symptoms, the patient was offered an X-ray examination (**Figure 4).**

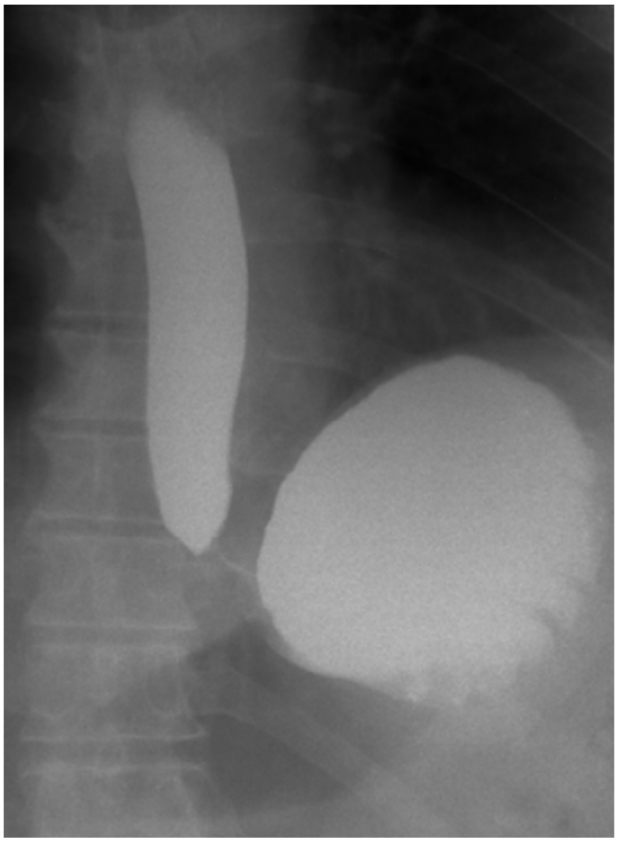

**Figure 4.** X-ray of the esophagus and EGJ at high pressure in the stomach. There is no peristalsis in the esophagus. The width of the esophagus is 2.7 cm, and the length of the LES is 1.9 cm. XRI is 1.4. Conclusion: Mild GERD.

It was proposed to change the diet, reduce body weight and going to sleep with an empty stomach.

# Case 4.

A 68-year-old woman with a BMI of 27.31. Her mother had no symptoms of GERD. Father often complained of abdominal pain and heartburn. She first became ill at the age of 25, when severe coughing attacks with bronchospasm appeared. Throughout the year she received treatment against asthma. X-ray examination revealed GERD. The cough gradually disappeared, but the patient for many decades first took H2-histamine blockers, and in the last 15 years - PPI. A single dose of a 20 mg tablet relieves her of heartburn and chest pain. After a hearty meal, she causes vomiting. In the vomit may be the remains of food eaten a day ago. She fights putrid breath.

At 28, she noticed that after drinking milk, belching and heartburn were appearing, but she continued to drink coffee with milk. For the past five years, she has not eaten foods cooked with milk. If cow's milk accidentally enters the coffee instead of a substitute, severe heartburn and pain behind the breastbone occur after 15 minutes.

At the age of 58 years, during an exacerbation of the disease (heartburn, chest pain, regurgitation), a manometric study was done with the following conclusion: Normal pressure in the lower esophageal sphincter with normal relaxation. Low pressure in the upper esophageal sphincter. Low-pressure waves throughout the esophagus. HRM was done a year later (**Figure 5**).

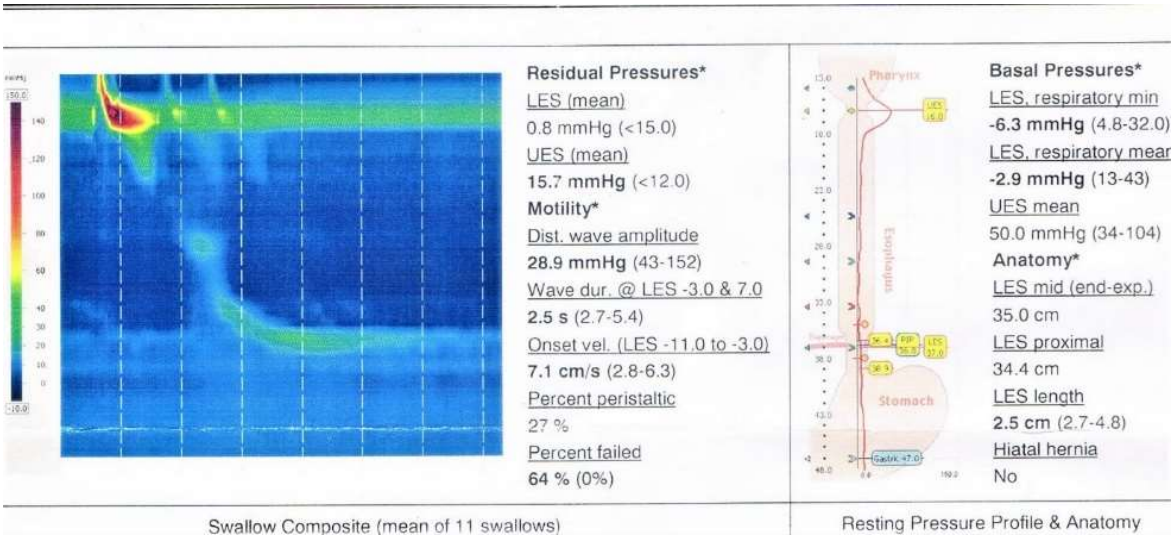

**Figure 5.** Interpretation/Finding: Low basal LES pressure with normal relaxation. Failed esophageal peristalsis in the most swallow. Normal UES pressure with high residual pressure. Impression: hypotensive LES. Ineffective esophageal motility. UES malfunction.

At the age of 62, a gastroscopy was done. Medium hiatal hernia was found. No pathology was found in the esophagus and stomach. After each study, the number of PPI tablets temporarily doubled.

At the age of 68, an X-ray examination of the esophagus and EGJ with the provocation of high pressure in the stomach revealed the failure of the LES with a sharp expansion of the esophagus and suspected esophagitis (**Figure 6**).

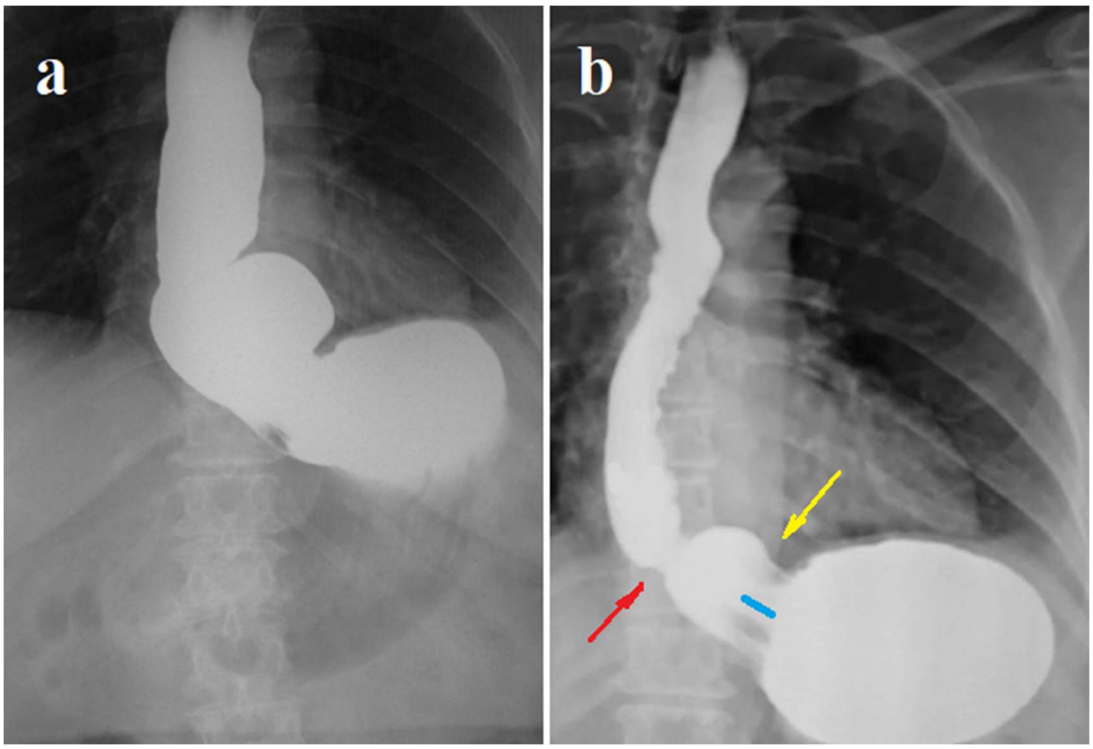


**Figure 6.** An X-ray examination of the esophagus and EGJ with the provocation of high pressure in the stomach. (a) A radiograph was made in a horizontal position. The esophagus is expanded to 4.2 cm, the width of the phrenic ampulla was 6.8 cm and the EGJ was 4.3 cm. LES open despite high pressure in the stomach. (b) After this, the patient got up and lay down again after 5 minutes. You can see the free flow of barium from the stomach into the esophagus to the closed upper esophageal sphincter. The ampulla of the esophagus, which is mistaken for a hiatal hernia, is located between the proximal sphincter (red arrow) and the LES (yellow arrow), which does not close [8,11]. The length of the open channel of the LES (blue line) is 1.2 cm. The serrated contours of the esophagus suggest the presence of

esophagitis. XRI is 3.5. **Diagnosis:** Gastroesophageal reflux disease in the stage of the esophagogastric junction chalasia. Chronic (exacerbation?) esophagitis.

**Analysis of the medical history.** It is likely that lactose intolerance is a provocateur of gastric acid hyperacidity in this observation. This usually manifests itself in early childhood in the form of infantile colic, the symptoms of which appear at the age of 2-4 weeks and disappear by six months. The regurgitation characteristic of this age, in combination with hyperacidity, leads to the initial damage to the function of the LES. After a long period of visible well-being, GERD symptoms appear, which increases in intensity and change in shape. The first symptoms of GERD (heartburn, belching) appeared in youth after drinking milk. Then came bronchospasm, which was mistaken as a manifestation of asthma. For many years, as a result of the absence of pathogenetic treatment, damage to the LES progressed from mild failure to chalasia of EGJ.

An X-ray examination revealed GERD in his youth when the patient was dominated by bronchospasm, but she continued to receive treatment for asthma, which reduces the tone of the LES. Repeated gastroscopy did not detect pathology. Only at the age of 66 years old, a hiatal hernia was diagnosed. The GERD was diagnosed many years earlier than a hiatal hernia. This is further evidence that the so-called hiatal hernia is actually an expanded phrenic ampulla, as a manifestation of an advanced stage of GERD [11].

The results of gastroscopy, as well as manometric studies, were contradictory, did not reflect the pathological physiology of the process and did not affect the treatment tactics. Currently, the attending physician and the patient have a choice: either find a way to control the symptoms of GERD and undergo periodic gastroscopy for the timely detection of Barrett's esophagus or agree to fundoplication.

# Case 6.

A 51-year-old woman, BMI 21.26, was born a healthy full-term baby. Her mother, an East European Slav, never had symptoms of GERD (case 2). The father (case 1)

has a severe form of GERD. She was a restless infant in the first six months. At the age of 15, she first felt a heaviness in the epigastrium 1-2 hours after eating. From the age of 22, heartburn appeared, which most often occurred after coffee with milk. Gastroscopy at 27 years of age revealed no pathology. However, she constantly felt heartburn and pressure behind her breastbone. The use of PPI did not lead to a relief of the symptoms. However, in combination with an antihistamine (Loratadine), a significant effect was obtained. At 46, she underwent repeated gastroscopy. Conclusion: Hiatal Hernia. Antral gastritis. A biopsy revealed Helicobacter pylori. After a course of treatment, reflux symptoms do not bother. She eats in small portions and goes to bed with an empty stomach. Heartburn and/or epigastric pain appears after the accidental use of products prepared using milk (bun or cake). X-ray examination was not applied. On the basis of her genetics, she is likely to be lactose intolerant.

**Analysis of the medical history.** Throughout her life, the patient suffered from a chronic progressive disease and did not receive pathogenetic treatment, because the correct diagnosis was not determined in time. In retrospect, it can be safely stated that infantile colic was caused by lactose intolerance. Both in adulthood and in infancy, lactose caused hyperacidity of the gastric content. During physiological regurgitation, gastric juice with a low pH caused irritation and inflammation of the mucous membrane of the esophagus and LES. When the period of rapid expansion of the stomach has ended and regurgitation has become rare, infant colic has passed, but the problem, i.e. lactose intolerance remained. It did not cause noticeable clinical symptoms but led to progressive weakness of the LES. This is a typical development of the pathogenesis of GERD.

Errors in diagnosis are systemic in nature and are due to some erroneous ideas about the pathological physiology of GERD.

**First,** typical clinical symptoms of GERD appeared in a patient in adolescence. At 27 years, gastroscopy revealed no pathology, but no histological examination was done. And at 46, a hiatal hernia was discovered. This is another confirmation [11]

that it was not the hernia that contributed to the onset of GERD, but the progression of reflux disease that led to the expansion of the phrenic ampulla, which is mistaken for a hernia.

**Secondly**, the idea that lactose causes pathological symptoms as a result of its decomposition by microorganisms in the colon with the release of gases that cause stretching and inflammation of the intestine contradicts scientific facts:

a) after eating a bun with a meager lactose content, this provocateur of symptoms cannot reach the colon in 15-20 minutes. In case 3, heartburn and epigastric pain also occurs 20 minutes after milk intake.

c) From 2% to 43% of patients with lactose intolerance do not have hydrogen-producing bacteria in the colon [13,14].

**Thirdly**, it is known that a significant number of patients with GERD do not experience pathological sensations. Therefore, gastroscopy without histological examination cannot exclude esophagitis caused by reflux disease [15,16]. Because of this, patients with GERD were selected during the initial selection of supposedly healthy individuals, as a result of which the pH-metry reveals only severe cases of GERD. This led to the following erroneous conclusions:

a) The statement that in healthy individuals the reflux of gastric juice into the esophagus with a pH <4 is the norm if it does not exceed 10% of the daily time in infants and 4% in adults is contrary to common sense. Chandrasoma et al. showed that the disease begins with reflux only within the abdominal part of the LES when reflux does not yet enter the esophagus. It is during this period that a complete cure of the patient is possible. In cases where the reflux is constant, damage to the LES is irreversible [15].

b) To classify patients as suffering from a functional disorder based on the weak severity of typical symptoms of GERD, which concern patients less often than a certain period, contradicts scientific data. In some patients with severe GERD, pain

may not be present. Secondly, patients at an early stage of the disease need pathogenic treatment no less than others.

## Case 7.

A 46-year-old man, BMI 26.47, was born a healthy full-term baby. He was a calm infant. His mother, an East European Slav, never had symptoms of GERD. He considers himself healthy. He is a lover of feasts and has the habit of getting up at night to eat. Heartburn rarely occurs at night after a hearty meal.

X-ray examination was performed according to the method described above. One radiograph was taken during a rise in pressure in the stomach (**Figure 7**).

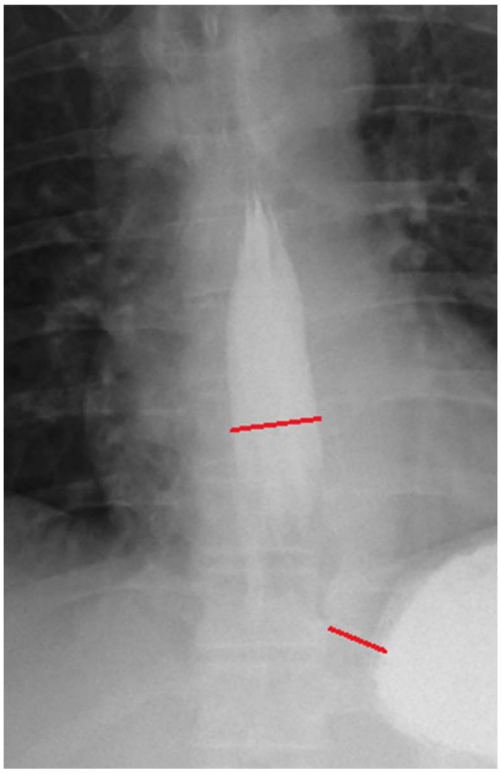

**Figure 7.** A strong peristaltic wave is detected on the x-ray. The esophagus is dilated with the presence of longitudinal folds. Its maximum width is 2.6 cm. The length of the LES is 2.2 cm. The severity of reflux, defined, as the ratio of the width of the esophagus to the length of the LES (X-ray index reflux –XIR), is 1.2. This is the smallest indicator among family members who have had a similar study. Conclusion: Mild GERD.

**Analysis of the medical history.** In this case, there is no reason to assume lactose intolerance, as the patient was a calm baby and his mother never had GERD symptoms. A clinical symptom (rare heartburn), which, according to accepted ideas, is assessed as functional dyspepsia, is combined with a change in the radiological picture relative to the norm. Compared to other family members, the XIR turned out to be minimal. The occurrence of GERD in this case by an unhealthy lifestyle can be explained.

# Case 10.

A 48-year-old man, BMI-24.81, born a healthy full-term baby. He was a restless infant. In youth, red wine caused instant redness of the face. Currently, any alcoholic drink has the same effect. In a US-study, a fatty liver was diagnosed. Since 2011, GGT has been constantly high> 122. At the age of 47, the patient was hospitalized with fever and epigastric pain. Acute acalculous cholecystitis was diagnosed (**Figure 7. a)**. At 48 years old, after a festive dinner, and abdominal pain appeared. He sat in the chair all night. When trying to lie down, there was again severe pain in the abdomen. A month before this attack, the patient felt weak. On that date, the GGT was 273. After the use of PPI, the pain gradually disappeared. At the final stage of treatment, the GGT was 437. An X-ray examination of the EGJ revealed the expansion of the esophagus and shortening of the LES (**Figure 8. b**). In gastroscopy performed 1.5 months after the cessation of pain, pathology was not detected.

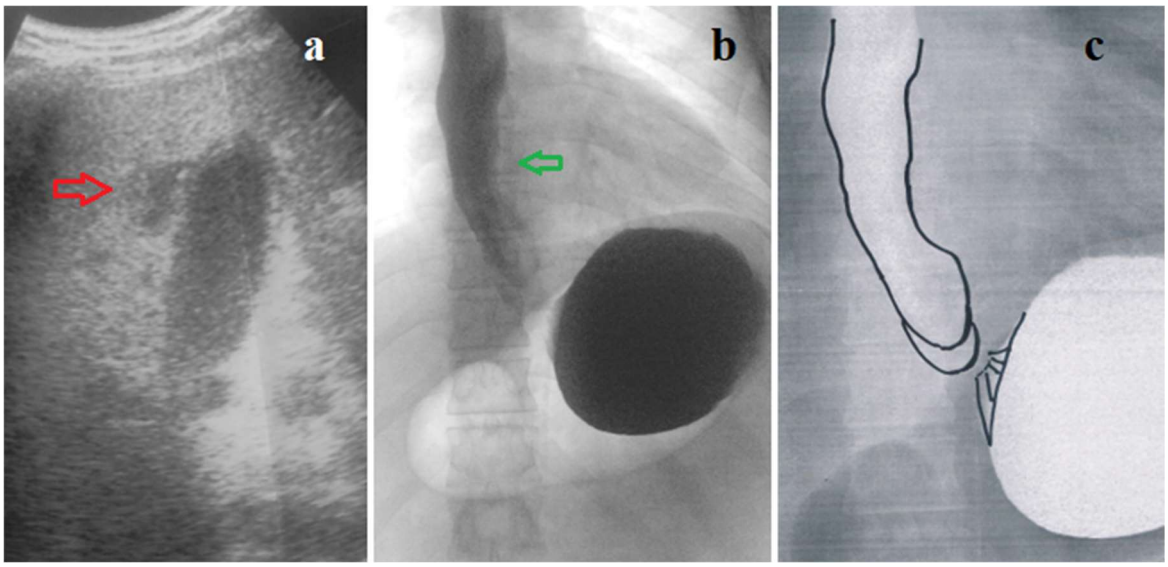


**Figure 8.** Examination of a 48-year-old man with clinical symptoms of GERD. (a) Ultrasound at the age of 47 years was done after antibiotic treatment due to prolonged high fever and abdominal pain. The collection of fluid near the wall of the gallbladder (red arrow) is determined. There are no stones in the gall bladder. **Conclusion**: Acute acalculous cholecystitis. (b) X-ray examination of the EGJ and the scheme to the radiograph (c). The esophagus is unevenly expanded (3.3 cm). Its right contour is not clear and its width seems narrower. This is the result of the reflux of water from the stomach into the esophagus along the left wall (green arrow). LES is noticeably shorter than normal (1.6 cm). This shortening occurred as a result of the opening of the abdominal part of the LES, as indicated by the folds of the mucous that run to the stomach. XRI is 2.0. **Conclusion.** Significant GERD.

**The analysis of the medical history.** The diverse reaction of the body to red wine, which contains a large amount of histamine (60-3800 micrograms / l), is considered evidence of histamine intolerance. It is assumed that patients intolerant to wine seem to have diminished histamine degradation probably based on a deficiency of diamine oxidase [17,18].

Histamine produces many varied effects within the body. Histamine intolerance in the patient in question can cause symptoms from both the liver and the digestive tract. First, histamine stimulates of gastric acid secretion [19].

Ochsner Sphincter normally contracts in response to the penetration of the acidic gastric contents into the duodenum and prevents penetration of chyme with a low pH into the jejunum. During its contraction, a chyme discarded retrogradely to the

sphincter of Kapandji, located between the bulb and the second part of the duodenum. The contraction of the sphincter of Kapandji prevents the penetration of the chyme into the bulb. The repetition of this process is described in the literature as a pendulum motion, leading to the mixing of the acidic gastric contents with the bile and pancreatic secretions. When the pH of the chyme between these sphincters increases, the sphincter of Ochsner opens, allowing the bolus to enter the jejunum in a less aggressive state than the original. Hyperacidity of the gastric contents not only contributes to the development of GERD but also causes dyskinesia of the duodenal sphincters [12]. A simultaneous and severe contraction of the Kapandji and Ochsner sphincters leads to a sharp increase in pressure in the second part of the duodenum. High pressure overcomes the contraction of the sphincter of Oddi and leads to the reflux of an acidic bolus to the common bile duct. Probably this mechanism responsible for the occurrence of acute acalculous cholecystitis (**Figure 9**).

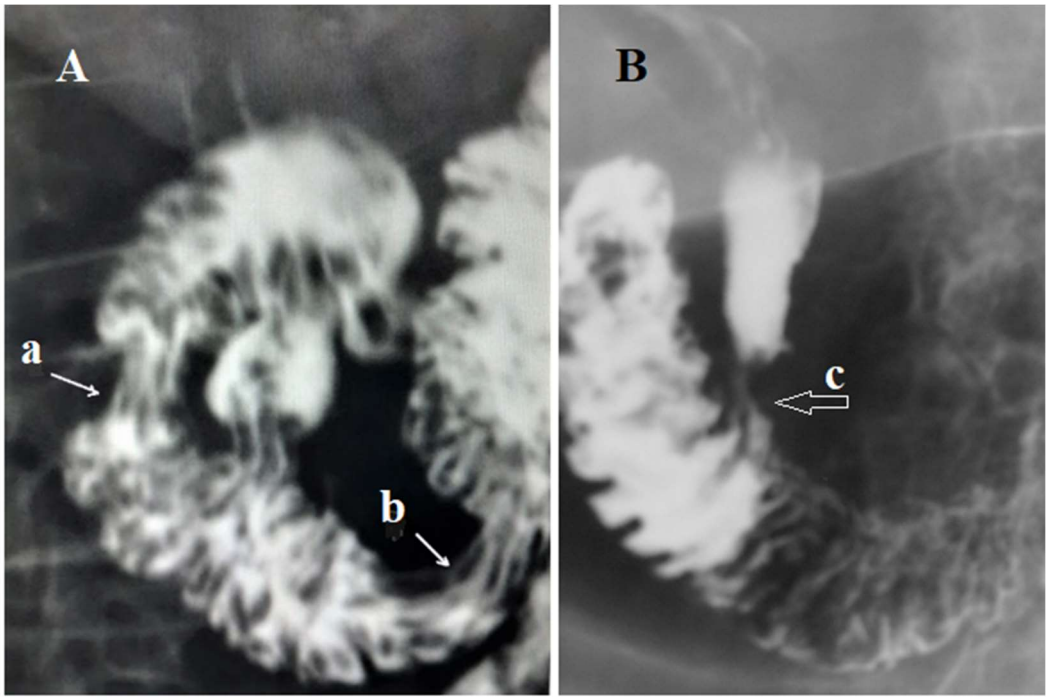


**Figure 9.** Radiographs of the duodenum to demonstrate of the duodenal sphincters. **A.** The simultaneous contraction of the sphincters Kapandji (a) and Ochsner (b) leads to increased pressure, as evidenced by the presence of juxtapapillary duodenal diverticulum. **B.** During ERSP, the contracted sphincter of Oddi is determined (c).

In addition to stimulating the release of hydrochloric acid, histamine has been proposed to be an important regulator of energy intake and expenditure. The study of Wang et al suggest that H1R and H2R signaling may regulate glucose and lipid metabolism and development of hyperlipidemia-induced nonalcoholic steatohepatitis [20]. Both of these mechanisms can explain the sharp increase in GGT, especially during the period of exacerbation, as well as fatty liver in this patient with histamine intolerance.

**Conclusion:** GERD, dyskinesia of the duodenum and bile ducts, fatty liver. One of the probable reasons is histamine intolerance.

# Case 11.

A woman, 46 years old, BMI 25.44, was born a healthy full-term baby. She had an infant colic. She drinks coffee with milk. Heartburn and epigastric pain are very rare. In recent years, almost every Friday after a family evening plentiful meal feels pressure behind the sternum. In the evenings, family members feel a putrid smell in her breath. The results of an X-ray examination with high pressure in the stomach are presented in Figure 10.

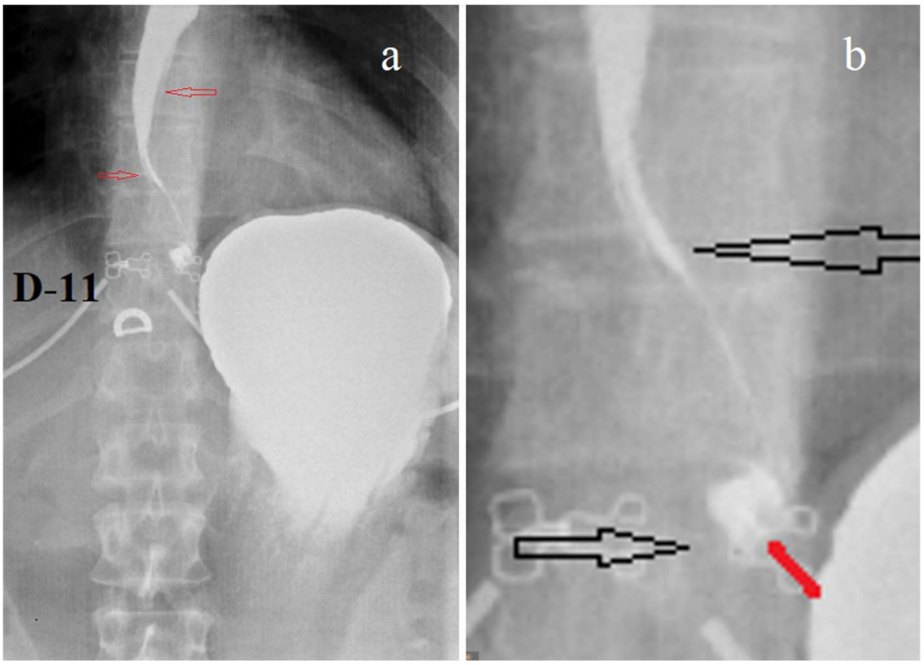


**Figure 10.** Radiograph of the esophagus and EGJ, performed during high pressure in the stomach (a). Scheme to it (b). The maximum width of the esophagus is within

normal limits (1.6 cm). The longitudinal folds (red arrows) are visible in it. Good peristalsis of the esophagus. The moment of contraction of the phrenic ampulla was recorded. The upper big arrow shows the approximate location of the top point of the ampulla. The lower small arrow shows the lower point of the ampoule, which is the proximal point of the LES. The length of the LES (red line) is 9 mm. The package (barium spot) indicates the weakness of the walls of the ampoule. Conclusion: GERD. XIR is 1.8.

It is recommended to consult a dietician to reduce weight, go to bed with an empty stomach, stop consuming milk and products prepared using milk, and take antacids half an hour after eating.

Analysis of medical history. In this case, there is a contradiction between the clinical symptoms that are insignificant in the patient's opinion and the radiological picture. The normal width of the esophagus may be due to an increase in tone, as a reaction to the inflammatory process - esophagitis. This is evidenced by the longitudinal folds in the esophagus. A very short LES indicates the weakness of its anti-reflex function. The barium packet remaining in the ampoule after its contraction explains the origin of the putrid odor from the mouth. Food remains in this pocket, in which odor-producing microorganisms multiply.

In addition, it must be borne in mind that the mother, brother and son (cases 4,10, 19) have a pronounced GERD. Relatives of the older generation (mother and aunt) are intolerant of cow's milk. If the behavioral recommendations do not help her get rid of the symptoms, then she will have to appoint a PPI.

# Case 19.

A young man of 22 years with a BMI of 21.27. He was born a full-term baby. The baby began to receive complementary foods at the age of 1.5 months, after which it became restless. Infant colic stopped at the age of 6 months. During the first years of his life, he screamed at night and it was hard to calm him down. In the same period, stridor was diagnosed. He was a hyperactive child, was examined by a psychologist and psychiatrist but did not receive special treatment. Coughing fits, especially at night, appeared at age 19. It was assumed that this reaction to gasoline

and he had to change the type of professional activity. It has become easier. But at 22, a strong cough appeared again at nights, accompanied by shortness of breath. Based on the clinical picture, asthma was diagnosed. He is observed by an allergist. It was an allergy to dust established, and the patient receives a course of hyposensibilization. The otolaryngologist found redness in the esophagus, which made it possible to suspect GERD.

An X-ray examination according to the method described above is shown in **Figure 11**.

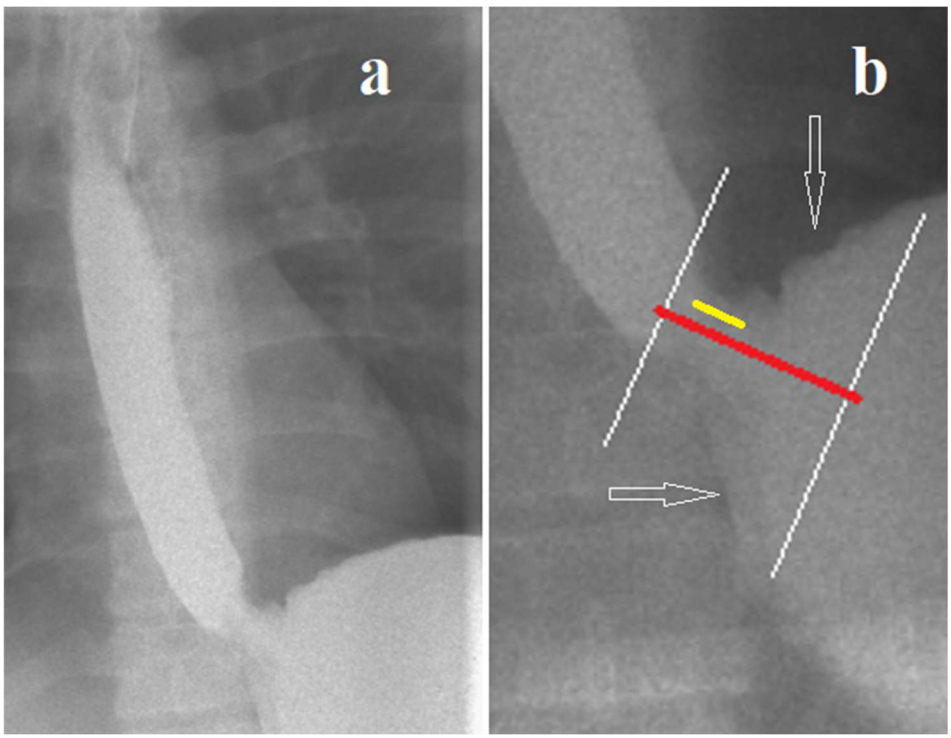


**Figure 11.** X-ray examination of the esophagus and EGJ at high pressure in the stomach (a), and the EGJ scheme (b). The esophagus is evenly widened (2.4 cm) with a weak peristaltic wave. In the diagram, the upper white line is drawn at the base of the esophagus ampoule, i.e., through the proximal point of the LES. The lower white line is drawn approximately through the distal point of the LES. The red line corresponds to the normal location and length of the LES. The disclosure of GEJ is accompanied by a shortening of the LES due to the opening of its abdominal portion. The arrows indicate the longitudinal folds of the open abdominal part of the LES. The length of the open channel of the LES (yellow line) is 1.2 cm. XIR is 2.1. **Conclusion:** Significant GERD.

PPI treatment has significantly reduced coughing. It is recommended that you stop using milk, even though coffee with milk does not affect well-being.

**Analysis of the medical history.** It is believed that infantile colic is due to lactose intolerance [21]. In these patients by pH-metry, GERD is detected [22,23]. In this observation, a typical picture of infant colic passed at the age of 6 months, but the child was restless and screaming at night until 4 years old. Interestingly, later, the clinical picture of the disease was dominated by pulmonary symptoms, as in his grandmother (case 3), in which an upper esophageal sphincter malfunction was detected by a manometric examination.

An analysis of the medical history indicates that in this patient, GERD occurred in infancy. Supplementary nutrition was a provocateur of the disease due to genetically determined lactose intolerance. For 22 years, due to the atypical picture of the disease, a pathogenetic diagnosis was not established, the child did not receive the necessary treatment, as a result of which the weakness of the LES progressed.

The likely cause of coughing is that the pharynx and esophagus are a single system. During irritation of the esophagus with a reflux agent, mucus is released both in the esophagus and in the throat. The mucus from the throat accumulates over the epiglottis, causing a cough reflex.

The remaining family members do not have obvious symptoms from the digestive system. To date, only one of them has an intolerance to cow's milk (case 19). All of them are warned about the high risk of lactose intolerance, which can affect their health.

## Discussion

Among 15 family members over 18 years of age, typical clinical symptoms of GERD were in 6 (40%). Five of them, where an X-ray examination of EGJ with high pressure in the stomach was performed, showed varying degrees of shortening of the LES, which was accompanied by a significant expansion of the esophagus (Table 1). According to the results of x-ray and gastroscopic studies, a clear tendency to the progression of the process is determined. The older the patient, the more severe the

clinical symptoms, a gastroscopic picture of the hernia gradually occurs, the esophagus expands and the LES shortens.

**Table 1.** Average indicators of the esophageal width, LES length, and XRI in patients with typical symptoms of GERD.

| | Esophageal width | LES length | XRI |
|---|---|---|---|
| Older generation (2) | 4 cm | 1.8 см | 2.9 |
| Middle generation (2) | 2.5 см | 1.3 см | 1.9 |
| Younger generation (1) | 2.4 | 1.2 | 2.1 |

Two adults (cases 3 and 7) had rare heartburn. Based on Rome IV criteria, this condition corresponds to functional gastrointestinal disorders. "With Rome III, functional heartburn was associated with no evidence for gastroesophageal reflux. However, with the addition of impedance to esophageal pH monitoring it has been shown that 38% patients did not have acid reflux (pH−), yet had a positive symptom association based on the symptom associated probability (SAP+), in other words, they had esophageal hypersensitivity with only 29% having true functional heartburn (pH−/SAP−). Therefore, a new diagnosis was included, reflux hypersensitivity, defined by the presence of acid sensitivity in the absence of increased acid reflux [24]. The consensus reached by numerous researchers produces many diagnoses that reflect different shades of the same disease. X-ray study with high pressure in the stomach revealed in these patients a shortened LES and an esophageal dilation, which convincing proof GERD. Although these changes (XRI -1.2 and 1.4) were less pronounced than in patients with a typical clinical picture of GERD (XRI -1.9-2.9), they were clearly the morphological rather than a functional one. The selection of the normal range for pH-metry was performed without histological examination, as a result, the data of patients with GERD were taken as the norm. Since then, pH-metry has only detected patients with severe GERD and

has not detected the disease with "in the absence of increased acid reflux" [11]. A likely etiological factor in both of our cases was the habit of plentiful food in the evening, as a result of which they were overweight.

Thus, in a significant part of patients at the initial stage of GERD with a lighter clinical picture, in whom, at pH-metry, the reflux agent with pH <4 was in the supraphrenic esophagus for less than 10% of the time in infants and 4-6% of the time in adults functional dyspepsia is diagnosed. Functional dyspepsia is further subdivided into postprandial distress syndrome and epigastric pain syndrome, depending on whether the symptoms are associated with meal ingestion. Most patients have been treated with or tried anti-acid secretory medications by the time they see a gastroenterologist. Researchers believe that it may be feasible to select a prokinetic for postprandial distress or a central neuromodulator for epigastric pain syndrome [25]. The current state of the problem in childhood is outlined in Barnhart's article: "Several factors contribute to the difficulties in managing gastroesophageal reflux. First, the distinction between physiologic and pathologic gastroesophageal reflux (gastroesophageal reflux disease-GERD) is not always clear. Second, measures of the extent of gastroesophageal reflux often poorly correlate to symptoms or other complications attributed to reflux in infants and children. A third challenge is that the outcome of antireflux procedures, predominately fundoplications, are relatively poorly characterized" [26].

All family members with typical GERD symptoms went through a mild stage of the disease but did not receive pathophysiologic treatment. In patients with typical symptoms of GERD, a clear hereditary dependence is determined. Symptoms of infant colic were reported in 5 of 6 cases. In four cases at different ages, intolerance to cow's milk manifested itself. Heartburn and/or abdominal pain occurred 15-20 minutes after accidentally drinking coffee with milk or buns made with milk.

Studies have shown that the prevalence of lactose intolerance in Ashkenazi Jews is 70%. When using the lactose hydrogen breath test sixty-eight Israeli children (61.8%) were lactose malabsorbers, 41 (60.3%) of whom were lactose-intolerant

with symptoms evidenced during or following the tests, whereas 27 (39.7%) were symptom-free (tolerant malabsorbers). In the youngest age-group (4 months to 3 years), no lactose malabsorption was detected, whereas in the higher age-groups the prevalence of lactose malabsorption increased with age. The percentages of lactose malabsorption in the age-groups 3 to 6, 6 to 12 and 12 to 16 years were 56.5, 65.2 and 75.0%, respectively [27].

It can be no coincidence that peak acidity occurs in all normal babies at around 3–4 weeks of age [28], the classical time that symptoms develop of infantile colic [29], precisely in the period when lactose intolerance is manifested since lactase levels decline from a peak at birth to less than 10% of the pre-weaning infantile level in childhood [29] and when pathological acid reflux into the esophagus is often found [23].

Currently, a hypothesis is widely cited explaining the onset of symptoms by the fact that the unabsorbed lactose is metabolized by colonic bacteria to produce gas and short-chain fatty acids, causing the clinical syndrome of abdominal cramps, bloating, diarrhea, and flatulence [29,30]. Those family members who had infantile colic, after a long period of apparent well-being, developed symptoms of GERD, which worsened after taking milk. This reaction to lactose has nothing to do with the activity of microorganisms in the colon. Firstly, after 15-20 minutes, lactose can reach neither the small nor the large intestine. Secondly, the amount of lactose found in coffee with milk cannot cause excessive gas formation in the colon. Thirdly, heartburn and pain behind the sternum cannot be the result of gas formation in the intestines.

Here's how the H2-breath test is characterized for diagnosing lactose tolerance in an article by Deng et al [31]. "The H2-breath test can be false positive in the presence of small intestinal bacterial overgrowth; however, a larger problem is false-negative tests due to the presence of hydrogen non-producing bacteria in the colon (2%–43%). This problem of “hydrogen non-production” can be mitigated to some extent by examining patient reports of symptoms after the test dose. Patients

with “false positive” breath tests complain of symptoms directly after ingestion. Those with “true positive” lactose intolerance complain of symptoms only after the substrate has entered the colon (usually 50–100 min)." In fact, this text indicates a very low sensitivity of the H2-breath test. First, it is falsely positive in the presence of small intestinal bacterial overgrowth. Secondly, it is false-negative due to the presence of hydrogen non-producing bacteria in the colon. Therefore, there are clinical symptoms of lactose intolerance, but there is no hydrogen in exhaled air due to the presence of hydrogen non-production bacteria. So, the symptoms are not related to gas production in the colon. With “true positive” lactose intolerance complains of symptoms after 50–100 min. However, the normal small bowel transit time is 4.2 hours [32]. The onset of symptoms only after taking lactose 15 or 100 minutes after swallowing a product containing lactose is a reliable sign of lactose intolerance. If the hypothesis cannot explain why the symptoms occur before lactose enters the colon, or in the absence of microorganisms producing hydrogen in the colon, this indicates the need to either abandon the false hypothesis or correct it.

Analysis of the literature and our own observations do not exclude the influence of the unabsorbed lactose is metabolized by colonic bacteria to produce gas and short-chain fatty acids, causing the clinical syndrome of abdominal cramps, bloating, diarrhea, and flatulence. However, in most cases, including the formation of gas in the colon, lactose provokes intestinal symptoms by affecting the body after 20 or 50 minutes of the following lactose ingestion. This means that there is another mechanism for triggering symptoms, which works before lactose enters the colon. Patients with IBS more often reported symptoms following lactose ingestion despite levels of breath hydrogen being like healthy subjects [14]. Very interestingly, the same group of IBS patients that had lactose intolerance on hydrogen breath testing also had heightened activity of the innate mucosal immune system with increased counts of mast cells, intraepithelial lymphocytes and enterochrommafin cells in the terminal ileum and right colon [14]. Based on the foregoing, we hypothesize that

lactose in the absence of lactase provokes the release of histamine from mast cells, which leads to hypersecretion of hydrochloric acid in the stomach. The LES weakened during infant colic is unable to delay aggressive reflux into the esophagus, which causes typical symptoms of GERD - heartburn, abdominal pain, and belching (**Figure 12**).

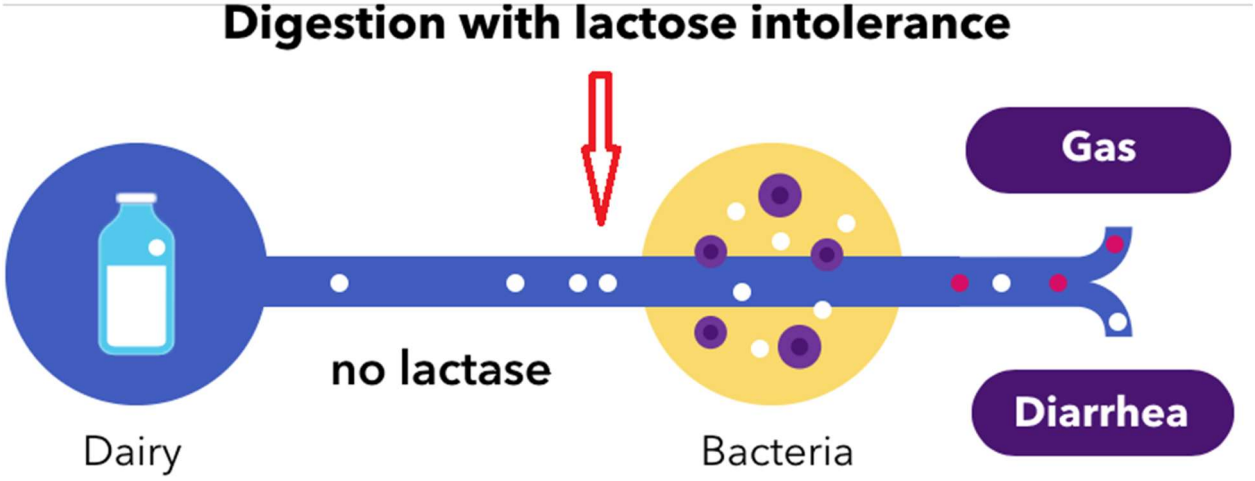


**Figure 12.** Diagram of two options for the effect of lactose on the digestive tract in patients with lactose intolerance. The first common option suggests that unabsorbed lactose is metabolized by colonic bacteria to produce gas and short-chain fatty acids in the colon (yellow circle). The second (our) option suggests that lactose causes release histamine from mast cells in the small intestine (red arrow), which causes hypersecretion of hydrochloric acid in the stomach.

**General conclusions.**

In order to understand the etiology, pathological physiology and pathogenesis of GERD, and to evaluate on this basis the X-ray examination, it is necessary to dwell on the normal physiology of the esophagus and LES. There are two mechanisms that enable LES to prevent the reflux of gastric contents into the esophagus with minimal ATP costs and the ability of the muscle fibers to renew these costs. First, different groups of circular muscle fibers of the LES are in different phases to restore their ability to contract. At that time, when one group relaxes after the contraction, the tone of the LES is ensured by the contraction of another group, which has already regained its contractile potential. Other groups are in different stages of the recovery ability to contraction. Cajal cells coordinate these contractions. Thus, a vicious circle

forms, which provides a constant tone of the LES. Secondly, the tone of the LES is proportional to the pressure in the body of the stomach. If the pressure in the body of the stomach rises, there is a contraction not only of those muscle bundles that are ready to contract but also of those that have almost regained their contractile potential. The number of muscle bundles increases, which accompanied by an increase in the tone of the LES to prevent the possibility of reflux. Conclusion: In healthy people, reflux may be an exception associated with a violation of a healthy lifestyle. Repeatedly reflux indicates impaired LES function.

In healthy individuals, the width of the esophagus is the same throughout and does not exceed 1.5 cm. In the vertical position, the threshold pressure for the LES disclosure is created by the hydrostatic pressure of the food column. In a horizontal position, the last peristaltic wave creates a threshold pressure above the LES, which leads to the disclosure of the LES. This pressure is higher than the pressure in the stomach. Peristaltic wave, while continuing to contract, injects a bolus into the stomach (**Figure 13**).

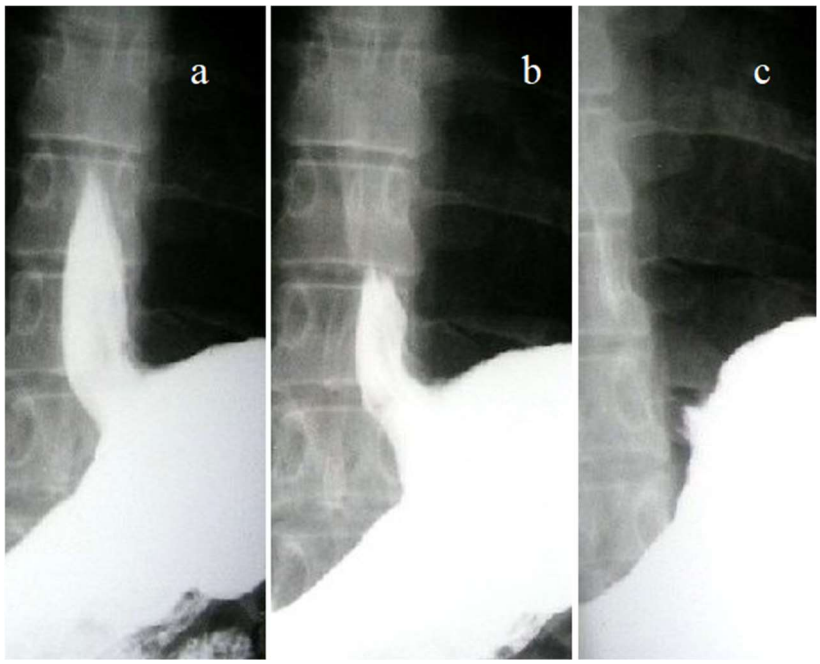


**Figure 13**. The last peristaltic wave creates a high threshold pressure proximal to the LES, which leads to its opening, after which the continuing movement of the wave injects barium into the stomach.

Gastroesophageal reflux disease begins with reflux within the abdominal portion of the LES. Reflux causes local inflammation and weakens the function of the sphincter. This occurs when two conditions are combined: high aggressiveness of the gastric contents and high pressure in the stomach. In many people, reflux occurs in infancy. Lactose intolerance, histamine intolerance, and an allergic reaction to the various components of the food consumed by the mother cause the release of histamine, which stimulates hypersecretion of hydrochloric acid. In infancy, a sharp increase in the volume of the stomach occurs which stretched by high pressure from excess food intake. This leads to physiological burping (regurgitation). If aggressive contents flow through the LES, chemical damage to the LES and esophagus occurs, which leads to a weakening of their function. So begins a chronic progressive disease.

The second, easier variant of the pathogenesis of GERD occurs in adults as a result of overeating, especially before bedtime and drinking alcohol (**Figure 14**).

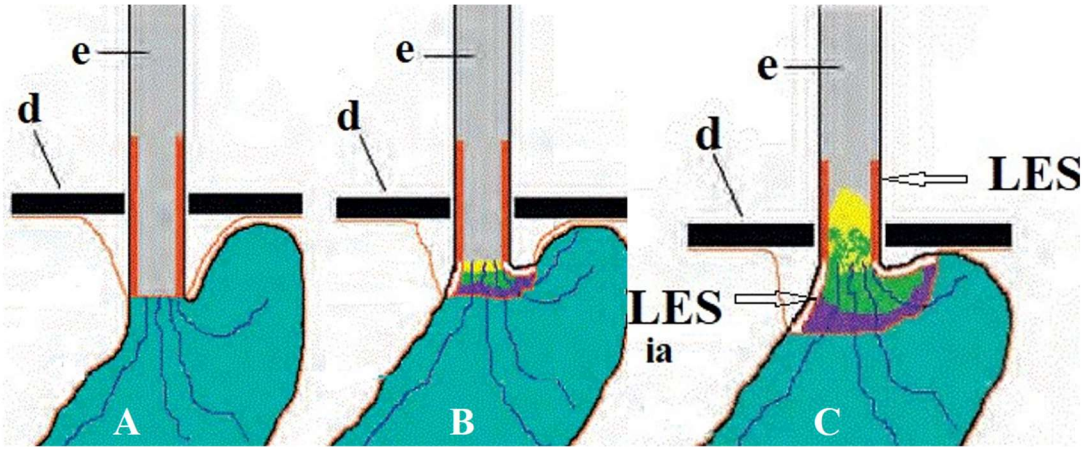


**Figure 14**. The initial stage of the pathogenesis of GERD. (A). GEJ in a healthy person. The normal length of LES (brown). The acute angle of His. (B). Under the influence of hydrochloric acid (yellow), the abdominal part of the LES is dilated (white), resulting in a shortening of the normally functioning part of the LES. (C). Dilation of the entire abdominal segment of the LES as a result of its weakness. Acid enters the esophagus. His angle is almost right. (e - esophagus, d-diaphragm, LES ia - intraabdominal part of the LES).

This scheme clearly reflects the three pathophysiological features that arise with GERD. Firstly, there is a weakness of the LES, which is not able to fully perform the antireflux function. The more severely its damaged, the more uncontrolled

relaxation of the LES occurs. Thus, transient lower esophageal sphincter relaxation is not a cause, but a consequence of GERD. Secondly, in GERD patients during swallowing, the LES is shortened, not the esophagus. Thirdly, the change in the His angle is not the cause of GERD, but the result of the shortening and dilation of the abdominal part of the LES.

Repeated reflux causes a chronic inflammatory process in the LES and in the esophagus. Changes occur not only in the mucosa. In the muscle layers, edema of muscle fibers is observed, between which exudate accumulates. This causes dilatation of the LES and esophagus. They lose elasticity and contraction strength. Therefore, during contraction, longitudinal folds appear both at the level of the LES and in the esophagus. Differences in the thickness of longitudinal folds are due to the different tone of the LES and the esophagus. Over time, fibrous changes appear in the walls of the LES and esophagus. X-ray studies confirm the results of histological observations that the presence of longitudinal folds in the area of the GEJ has no relation to the stomach (**Figure 15**).

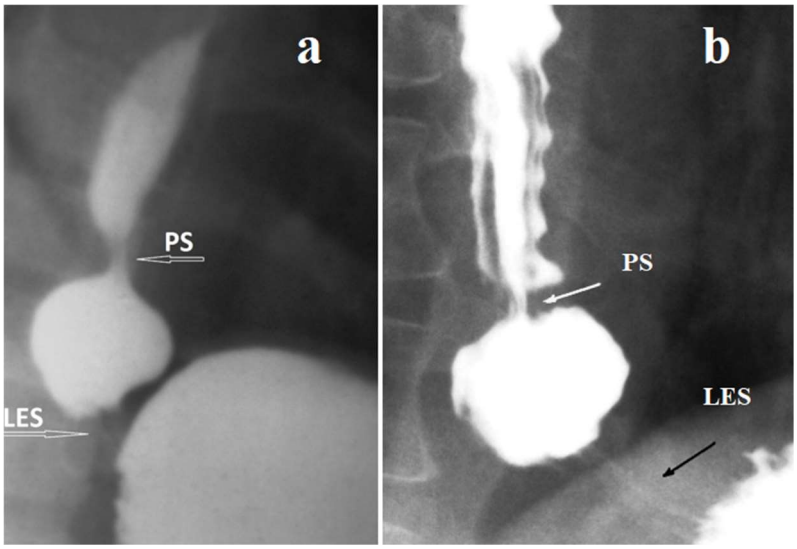


**Figure15.** Radiographs of patients with GERD performed with compressions of the abdomen while swallowing barium. (a) In a 12-year-old child, the contraction in LES with two longitudinal folds is determined. A barium bolus lingered over the contracted sphincter, as a result of which the expansion of the esophagus revealed - phrenic ampulla. To create high pressure in the ampoule and overcome the tone of

the LES, the functional sphincter, which we call the proximal sphincter (PS), contracted in the proximal part of the ampulla. (b). The width of the phrenic ampulla in the elderly patient is 2.3 cm. The length of the LES is 2 cm. Longitudinal folds at the level of the LES differ from folds in the esophagus due to different tonus. Even with great imagination, it is impossible to imagine that the folds between the ampoule and the stomach are folds of the stomach.

In our previous work, numerous evidence was presented testifying that both in the normal state and in GERD the esophagus does not shorten, and the LES does not move. Phrenic ampulla occurs with GERD as a result of the expansion of the esophagus. What is commonly called a hiatal hernia is essentially a wide phrenic ampulla. This means that the detection of the signs possessed by the so-called hiatal hernia is convincing evidence of advanced reflux disease [11].

Thus, the cause of GERD is the weakness of the LES, which is damaged by the aggression of hydrochloric acid, trypsin and bile acids. Sliding hiatus hernia, transient lower esophageal sphincter relaxation, the acid pocket, increased distensibility of the esophagogastric junction and prolonged esophageal clearance are pathogenesis mechanisms that occur at different stages of this chronic progressive disease. In cases where hypersecretion of hydrochloric acid is involved in the etiology of GERD, this should be considered as part of a peptic disorder. Dyskinesia of the stomach and gastritis cause a delayed gastric emptying and an increase in pressure in the fundus. Dyskinesia of the duodenum leads to the duodeno-gastroesophageal reflux, as well as bile reflux into the common bile duct.

In most cases, when GERD occurs in adults as a result of overeating, alcohol abuse, and frequent nonphysiological loads on LES, the disease proceeds with milder clinical symptoms.

Gastroesophageal reflux disease is a clinical diagnosis. Any of the symptoms and risk factors that are observed with GERD should be an occasion for clinical examination and observation (**Table 2**).

**Table 2. Clinical symptoms and risk factors for the diagnosis of GERD.**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Up to 2 years | vomiting | poor weight | dysphagia | fussy infant | cough | putrid breath | wet pillow | anemia |
| Over 2 years | chest or abdominal pain | heartburn | sinusitis | dental erosion | pulmonary fibrosis | recurrent otitis | cough after eating | asthma |
| Risk factors | Pre-maturity | Cow's milk intolerance | Acid hyper-secretion | Allergy | Family history | | Obesity | Stress |

If the treatment of GERD does not relieve symptoms; it is necessary to clarify the diagnosis and severity of the process. X-ray examination of the esophagus and EGJ with high pressure in the stomach is the simplest, most visible and reliable method of instrumental research.

**References.**


1. Böhmer AC, J Schumacher J. Insights Into the Genetics of Gastroesophageal Reflux Disease (GERD) and GERD-related Disorders. Neurogastroenterol Motil. Feb 2017, 29 (2): DOI: 10.1111/nmo.13017
2. Mikami DJ, M Murayama KM. Physiology and Pathogenesis of Gastroesophageal Reflux Disease. Surg Clin North Am. 2015 Jun. 95 (3), 515-25. DOI: 10.1016/j.suc.2015.02.006.
3. Lin S[1,2], Li H[2], Fang X[1].Esophageal Motor Dysfunctions in Gastroesophageal Reflux Disease and Therapeutic Perspectives. J Neurogastroenterol Motil. 2019 Oct 30;25(4):499-507. doi: 10.5056/jnm19081.
4. de Mello Del Grande L1, Herbella FAM2, Katayama RC, et al. Transdiaphragmatic Pressure Gradient (TPG) Has a Central Role in the Pathophysiology of Gastroesophageal Reflux Disease (GERD) in the Obese and it Correlates with Abdominal Circumference but Not with Body Mass Index (BMI). Obes Surg. 2019 Dec 19. doi: 10.1007/s11695-019-04345-x. [Epub ahead of print]
5. Kung YM1, Tsai PY2, Chang YH3, et al. Allergic rhinitis is a risk factor of gastro-esophageal reflux disease regardless of the presence of asthma. Sci Rep. 2019 Oct 29;9(1):15535. doi: 10.1038/s41598-019-51661-4.
6. .Böhmer AC[1,2], Schumacher J[1]Insights into the genetics of gastroesophageal reflux disease (GERD) and GERD-related disorders. Neurogastroenterol Motil. 2017 Feb;29(2). doi: 10.1111/nmo.13017
7. Pérez Lara FJ[1], Hernández Gonzalez JM[1], et al. Prospective Study of Lactose Intolerance as a Potential Cause of Gas Bloat Syndrome in Patients Treated Surgically for Gastroesophageal Reflux. . Surg Innov. 2019

Dec 19:1553350619891351. doi: 10.1177/1553350619891351. [Epub ahead of print]
8. Douglas PS. Diagnosing gastro-oesophageal reflux disease or lactose intolerance in babies who cry a lot in the first few months overlooks feeding problems. J Paediatr Child Health. 2013 Apr;49(4):E252-6. doi: 10.1111/jpc.12153. Epub 2013 Mar 15.
9. Levin MD. Reaction to articles on high resolution manometry, the length of the lower esophageal sphincter and the diagnosis of gastroesophageal reflux disease. Arq Gastroenterol. 2019;56(2): 209-210. Open access.
10. Bott TS, von Kalle Th, Schilling A, et al. Esophageal Diameters in Children Correlated to Body Weight. Eur J Pediatr Surg. Dec 2019, 29 (6), 528-532. PMID: 30477027. DOI: 10.1055/s-0038-1675776.
11. Levin MD. The function of the esophagus and gastroesophageal junction in normal and in gastroesophageal reflux disease. https://4d90110e-2e9f-4032-b658-72b6d84114fd.filesusr.com/ugd/4d1c1d_2a4e2d59fb2b484c810c07b763904c64.pdf
12. Levin MD. Ochsner's Sphincter Dyskinesia Is the Cause of Superior Mesenteric Artery Syndrome. J Gastrointest Surg. 2019 May 29. doi: 10.1007/s11605-019-04246-5.
13. Deng Y[1], Misselwitz B[2], Dai N[3], Fox M[4,5]. Lactose Intolerance in Adults: Biological Mechanism and Dietary Managem ent. Nutrients. 2015 Sep 18;7(9):8020-35. doi: 10.3390/nu7095380
14. Rana SV[1], Malik A[2].Hydrogen breath tests in gastrointestinal diseases. Indian J Clin Biochem. 2014 Oct;29(4):398-405. doi: 10.1007/s12291-014-0426-4. Epub 2014 Mar 21.
15. Chandrasoma P[1,2], DeMeester T[3].A New Pathologic Assessment of Gastroesophageal Reflux Disease: The Squamo-Oxyntic Gap. Adv Exp Med Biol. 2016;908:41-78. doi: 10.1007/978-3-319-41388-4_4.
16. Boeckxstaens GE. Review Article: The Pathophysiology of Gastro-Oesophageal Reflux Disease. Aliment Pharmacol Ther. 26 (2), 149-60. 2007 Jul. PMID: 17593062 DOI: 10.1111/j.1365-2036.2007.03372.x
17. Wantke F[1], Götz M, Jarisch R. The red wine provocation test: intolerance to histamine as a model for food intolerance. Allergy Proc. 1994 Jan-Feb;15(1):27-32.
18. Maintz L, Novak N. Histamine and Histamine Intolerance. Am J Clin Nutr .May 2007, 85 (5), 1185-96. DOI: 10.1093/ajcn/85.5.1185
19. Schubert ML. Physiologic, Pathophysiologic, and Pharmacologic Regulation of Gastric Acid Secretion. Curr Opin Gastroenterol. Nov 2017, 33 (6), 430-438. DOI: 10.1097/MOG.0000000000000392.
20. Wang KY, Tanimoto A, Yamada S, et al. Histamine Regulation in Glucose and Lipid Metabolism via Histamine Receptors: Model for Nonalcoholic Steatohepatitis in Mice. Am J Pathol. Aug 2010, 177 (2), 713-23. DOI: 10.2353/ajpath.2010.091198

21. Johnson JD, Cocker K, Chang E. Infantile Colic: Recognition and Treatment. Am Fam Physician, Oct 2015, 92 (7), 577-82.
22. Heine RG[1], Jordan B, Lubitz L, et al. Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress. J Paediatr Child Health. 2006 Mar;42(3):134-9.
23. Van Howe RS[1], Storms MR. Gastroesophageal reflux symptoms in infants in a rural population: longitudinal data over the first six months. BMC Pediatr. 2010 Feb 11;10:7. doi: 10.1186/1471-2431-10-7.
24. Schmulson MJ, Drossman DA.What Is New in Rome IV. J Neurogastroenterol Motil. 2017 Apr; 23(2): 151–163. doi: 10.5056/jnm16214
25. Xiao Jing Wang XJ, Camilleri M. Personalized medicine in functional gastrointestinal disorders: Understanding pathogenesis to increase diagnostic and treatment efficacy. World J Gastroenterol. 2019 Mar 14; 25(10): 1185–1196.Published online 2019 Mar 14. doi: 10.3748/wjg.v25.i10.1185
26. Barnhart DC.Gastroesophageal Reflux Disease in Children. Semin Pediatr Surg. Aug 2016, 25 (4), 212-8. DOI: 10.1053/j.sempedsurg.2016.05.009
27. Bujanover Y, Katz A, Peled Y, Gilat T. Lactose Malabsorption in Israeli Children. Isr J Med Sci. Jan 1985 , 21 (1), 32-5.
28. Rogers IM, Drainer IK, Dougal AJ, et al. Serum cholecystokinin, basal acid secretion and infantile hypertrophic pyloric stenosis. Arch Dis Childhood 1979;54:773–5.
29. Vandenplas Y[1]. Lactose intolerance. Asia Pac J Clin Nutr. 2015;24 Suppl 1:S9-13. doi: 10.6133/apjcn.2015.24.s1.02.
30. Bhatnagar S, Aggarwal R. Lactose intolerance. BMJ. 2007 Jun 30;334(7608):1331-2.
31. Deng Y[1], Misselwitz B[2], Dai N[3], Fox M. Lactose Intolerance in Adults: Biological Mechanism and Dietary Management. Nutrients. 2015 Sep 18;7(9):8020-35. doi: 10.3390/nu7095380.
32. Roland BC[1], Ciarleglio MM, Clarke JO, et al. Small Intestinal Transit Time Is Delayed in Small Intestinal Bacterial Overgrowth. J Clin Gastroenterol. 2015 Aug;49(7):571-6. doi: 10.1097/MCG.0000000000000257.
33.