

Dear colleagues,

Since pH monitoring has been proposed, all research has focused on the esophagus and EGJ in GERD. The broader approach to the study of GERD, which was in the previous period, was completely forgotten. As if the interests of hardware manufacturers determined the direction of research. Meanwhile, it remains unclear why GERD occurs only in 30-40% of the population of developed countries? What happens in the stomach in GERD patients? And why is GERD often combined with the pathology of the stomach, duodenum, and biliary tract?

I want to raise the issue of lactose intolerance, which causes GERD symptoms. I will give five typical examples from my practice that rejects the generally accepted pathogenesis of this phenomenon. I hope that they will prompt us to study the pathogenesis of GERD.

Case 1. A 78-year-old woman complained of frequent heartburn. A high-pressure x-ray of the stomach diagnosed GERD with a suspected ulcer in the upper esophagus (**Figure 1**, red arrow).

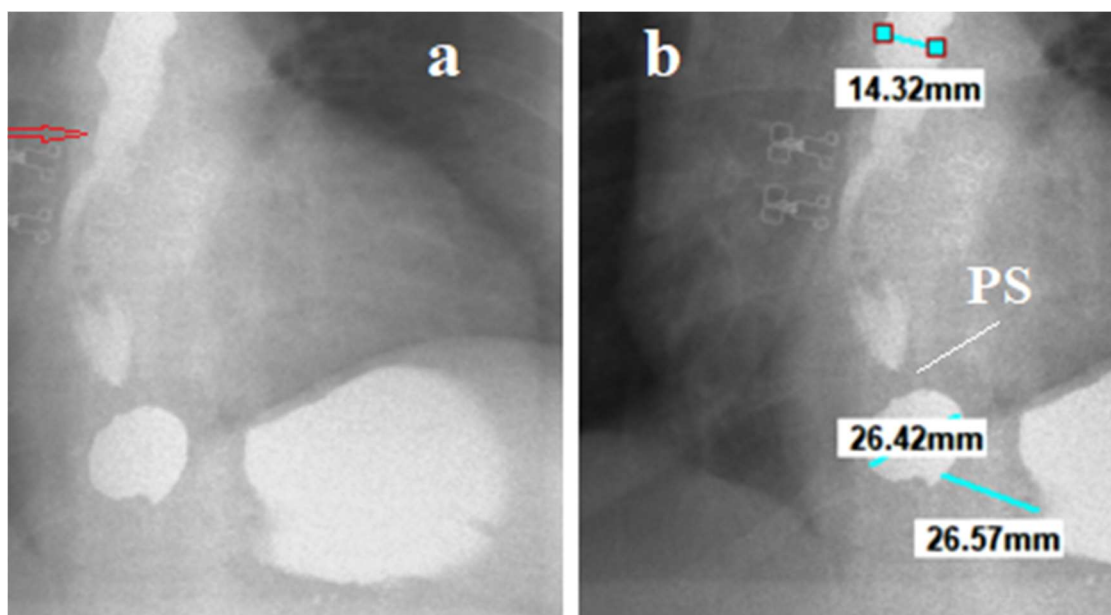
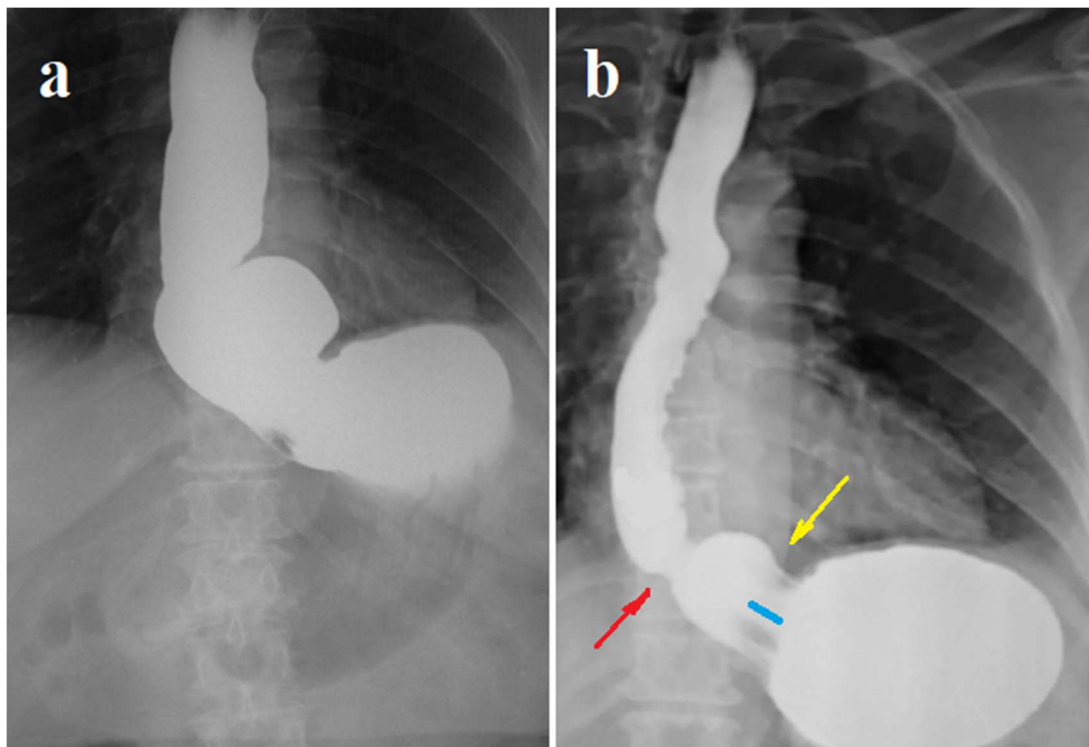


Figure 1. A 78-year-old patient with GERD. **(a)** X-ray of the esophagus and EGJ during barium drinking and straight legs raise. **(b)** Schematic to Figure 1.a. High pressure in the stomach caused a contraction of the 2.6 cm long lower esophageal sphincter (the green line between the stomach and phrenic ampulla). The width of the ampulla is 2.6 cm. The contracted gap between the ampulla and the proximal esophagus is the proximal sphincter (PS). The lower part of the esophagus is spasmodic. On the right wall in the upper part of the esophagus, an impression is determined, suspicious of ulceration (red arrow).

Endoscopy revealed erosion in the upper esophagus and PPI was prescribed. She did not consume dairy products. However, the gastroenterologist told her that

yogurt contains almost no lactose. The patient ate a jar of yogurt several times. Moreover, every time after 20-30 minutes she had strong and prolonged heartburn.

Case 2. A 65-year-old patient considers herself ill since the age of 24 when she developed bouts of bronchospasm. She took antispasmodics ostensibly for asthma. X-ray examination revealed GERD and bronchospasm attacks were gone. Heartburn after taking milk appeared at the age of 40 years. She stopped drinking milk but consumes dairy products (cheese, butter, cottage cheese) in the background of continuous long-term use of PPI. She can accurately test for the presence of milk in coffee by experiencing heartburn 30 minutes after drinking



it.

Figure 2. An X-ray examination of the esophagus and EGJ with the provocation of high pressure in the stomach. (a) The radiograph did in a horizontal position. The esophagus is expanded to 4.2 cm, the phrenic ampulla to 6.8 cm, and the width of the EGJ to 4.3 cm. The LES is 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. 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. XIR (X-ray index reflux is the ratio of the width of the esophagus to the length of the LES) equal to 3.5.

She is currently taking 20 mg PPI once and is doing well. Sometimes, after bending over, a remnant of the food she ate yesterday may appear in her mouth.

Case 3. A 53-year-old patient felt worse after drinking milk in her youth. She avoided drinking whole milk, but over time she found that any foods containing lactose caused symptoms ranging from heartburn to diarrhea. Lately, cheese has been causing stomach pain and diarrhea 2 to 4 minutes after eating it.

Case 4. A 53-year-old man complained that 30 minutes after coffee with milk he has epigastric pain. The family has dinner late (at 20-21 o'clock). After that, he feels bad. Constantly worried about belching. A high-pressure x-ray of the stomach revealed GERD with esophagitis (Figure 3). A year after the exclusion of foods containing lactose from food, he considers himself healthy.

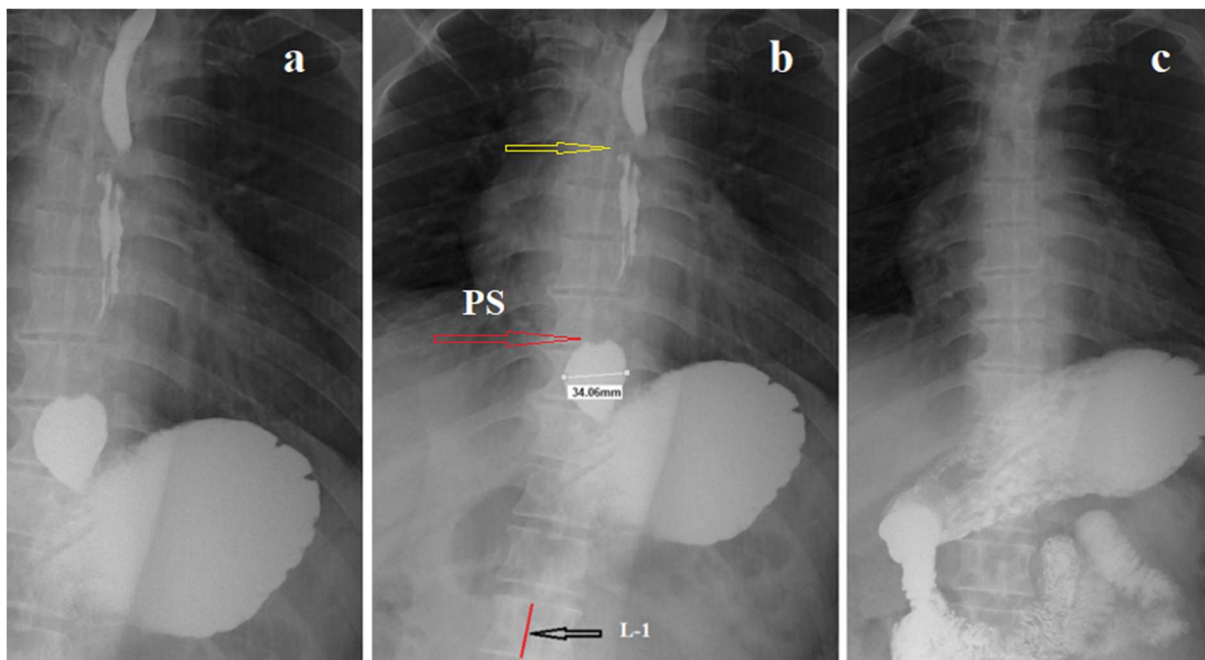


Figure 3. X-rays of the esophagus and EGJ of a patient with GERD (a) With high pressure in the stomach. (b) The diagram to it. (c) After 5 minutes without pressure. Since the true height of L-1 in adults is 2.2 cm, the width of the upper part of the esophagus is 0.7 cm (normal -1.5 cm). The spasm of the esophagus is seen at the level of the aortic arch. Rough longitudinal folds are visible in the middle third of the esophagus, indicating esophagitis. The esophageal ampulla, 3.4 cm wide, is blocked from above by the proximal sphincter (red arrow). The ampoule is emptied through the open LES, which is probably short since it is not visible at all. (c) Normal evacuation from the stomach.

Case 5. A 63-year-old patient with a long history of typical GERD, repeated studies (endoscopy -3, manometry -1, pH -1) was diagnosed with chronic gastritis, hiatal hernia, and laryngopharyngeal inflammation. However, GERD was not established, as $\text{pH} < 4$ was observed for 3.4% of the time. She took PPI for a long time without significant improvement. X-ray examination of the EGJ with the provocation of high pressure in the stomach was performed during a period of exacerbation of the disease (Figure 4. a).

After she swallowed 2 tablets with a diameter of ≈ 2.5 cm and started eating 6 hours before bedtime, the abdominal pain subsided and she gradually stopped using PPI. She believed that

she had been successful in her treatment. A re-X-ray examination 1.5 years after the first study revealed a clear deterioration in X-ray parameters. (c-d) The width of the esophagus became wider (3.3 cm vs. 2.8 cm) and the length of the LES became shorter (1.5 cm vs. 2 cm). XIR (X-ray index reflux- the ratio of the width of the esophagus to the length of the LES) increased from 1.4 to 2.2. An asymmetric constriction (arrow) suspicious of an ulcer appeared in the upper part of the esophagus. It turned out that for 1.5 years the patient had consumed milk and dairy products because she did not feel that products containing lactose worsened her well-being. Secondly, she did not find information on the Internet about the association of GERD with lactose consumption. For the past 1.5 months, she has been lactose-free and claims to feel much better than before.

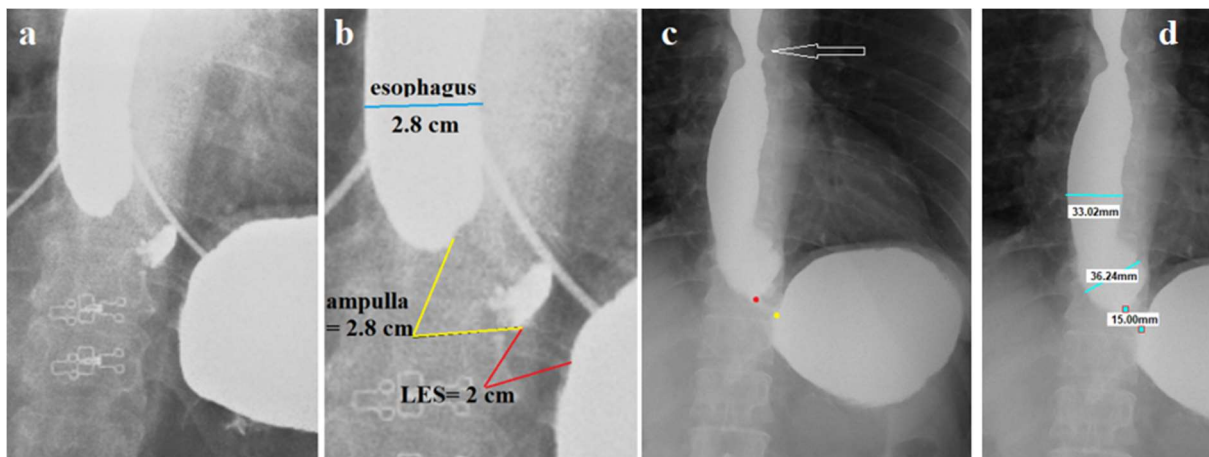


Figure 4. (a,b). X-ray studies of the EGJ with provocation high pressure in the stomach which was performed during a period of exacerbation of the disease. Significant expansion of the esophagus was found (2.8 cm vs. 1.5 cm in normal). After contraction of the phrenic ampulla, a small amount of barium remained in it in the form of a diverticulum on the left wall. The LES is shorter than normal (2 cm versus 3.6 cm). XIR = 1.4 (normal <1). (c,d). At re-examination 1.5 years later, the esophagus became wider and the length of the LES became shorter. XIR = 2.2.

This observation shows that the pathological process caused by GERD can progress despite the absence of serious symptoms. Secondly, it is not always easy to understand that the disease (symptoms) are provoked by milk (lactose). A clear relief after a long cessation of the consumption of products containing lactose, and a particularly sharp deterioration after taking milk, allows us to accurately establish lactose as a provocateur of hydrochloric acid hypersecretion.

Discussion

The above examples are not an exception, but typical cases of GERD. In cases where patients refused all products containing lactose, a pronounced therapeutic effect was observed, which made it possible to refuse the use of PPI. In cases where patients did not want to give up low-lactose foods (cheeses, butter), they felt good using the minimum dose of PPI - 20 mg per day.

Analysis of typical cases of GERD allows us to draw the following conclusions:

1. GERD occurs predominantly in people with lactose intolerance, which is probably the trigger for hypersecretion of hydrochloric acid.
2. GERD can occur and progress for many years without significant symptoms.
3. The older the patient, the less amount of lactose causes GERD symptoms.
4. Symptoms may occur 2-30 minutes after drinking coffee with milk. These parameters exclude the possibility of symptoms as a result of the metabolization of lactose by the microflora of the colon. The probable mechanism of action of lactose is the release of histamine from the mast cells of the small intestine, which leads to hypersecretion of hydrochloric acid [1].
5. Many patients cannot relate the occurrence of symptoms to the intake of products containing lactose. Only the complete exclusion of these products for a long period, followed by a provocation with milk intake, allows us to establish this connection.
6. All patients with hypersecretion of hydrochloric acid gradually develop GERD, gastritis (ulcer), duodenitis (ulcer), biliary dyskinesia (cholelithiasis, cholecystitis).

It follows from this that most patients with GERD turn to doctors at those stages of the disease when they can no longer be cured (due to the irreversible expansion of the esophagus with fibrous changes in its wall, as well as shortening and weakness of the LES), but only more or less fully control symptoms. Although it is believed that lactose causes GERD symptoms in some patients, the recommendation to reduce the amount of milk to an acceptable limit of sensitivity is absolutely not acceptable. The disappearance of symptoms does not exclude the progression of the disease. Secondly, the minimum amount of lactose (in buns, in coffee with milk, etc.) each time leads to the damaging effects of hydrochloric acid.

I offer an objective test to determine lactose intolerance and hydrochloric acid hypersecretion. Prior to the introduction of pH monitoring into practice, hypersecretion of hydrochloric acid was determined by studying the pH of gastric juice after taking meat broth [2,3]. I suggest a study of the pH of the gastric juice after taking milk.

However, to test the methodology, it is necessary to prove: (1) that lactose causes hypersecretion of hydrochloric acid in patients with lactose intolerance. (2) that hypersecretion of hydrochloric acid causes GERD.

I propose a research program in the hope that it will be tested by many researchers, which will open a new path to the early and accurate diagnosis of GERD and improve treatment outcomes by ruling out the trigger, i.e., lactose. All patients should be divided into 4 groups.

The first, control group should be selected volunteers without the symptoms of GERD. During esophagogastroduodenoscopy, there should be no visible signs of an inflammatory process in the esophagus, stomach, and duodenum, as well as dilation of the esophagus in the form of an ampulla or "hiatal hernia". The absence of cardiac epithelium at the LES level on histological examination [4] makes it possible to exclude GERD quite accurately. Such examination of persons without complaints is not only ethical but also highly beneficial to patients. These people should be aware that GERD can be asymptomatic, and early diagnosis can prevent severe complications in the future. For example, Yoo et al among 6,683 health examinees in 1,154 (17.26%) found esophageal diseases. Gastroesophageal reflux disease was the most common disease (14.66%). The prevalence of erosive reflux esophagitis, minor change esophagitis, and Barrett's esophagus was 8.45%, 5.01%, and 1.12%, respectively. Hiatal hernia was at 2.0% [5].

An alternative selection to the control group can be made on the basis of an X-ray functional examination with high pressure in the stomach. The norm will be considered the case if, during the rise of gastric pressure (when lifting straightened legs), the LES does not contract and the contrast agent penetrates the stomach without delay. Or, with LES contraction, the width of the esophagus is no more than 1.5 cm throughout and XIR (the ratio of the width of the esophagus to the length of the LES) is <1 [6].

The second group should consist of those persons without symptoms who, after the above examination, cannot be considered healthy (симптомы воспаления в пищеводе, наличие кардиального эпителия на уровне НПС и выше; расширение пищевода, укорочение НПС, $XIR > 1$).

The third group should include patients with symptoms suggestive of GERD, but without evidence of milk intolerance.

The fourth group should include patients with symptoms suggestive of GERD, in whom the intake of products containing lactose cause an obvious but non-painful reaction.

The objectives of the study are to determine:

1. Is lactose a trigger for hydrochloric acid hypersecretion?

2. Is there a connection between hypersecretion of hydrochloric acid and GERD?
3. Is hypersecretion of hydrochloric acid detected before symptoms appear?
4. How long does it take to determine the peak of hydrochloric acid release after the introduction of milk?
5. Can this test be used for the early diagnosis of GERD?

To address these issues, the probe is inserted into the stomach in a horizontal position of the patient. The chyme from an empty stomach is sucked into the first vial. 100 ml of milk is injected into the stomach with quick drops. It is advisable to take gastric juice into test tubes every 20 minutes for 2 hours to determine the pH. Perhaps, after the first samples, the time of the peak release of hydrochloric acid will be determined, and then it will be possible to reduce the number of chyme samplings.

I wish success to everyone, but the first one always wins.

Michael D. Levin. MD, PhD, DSc.

nivel70@hotmail.com;

<http://www.anorectalmalformations.com>

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