Part 3. Esophageal achalasia in Chicago Classification

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The third period in EA research began in 2009 when the first full version of the Chicago Classification was published, зfollowed by two updates. In the 4th version, published in November 2020 [1], changes were made with an "attempt to minimize ambiguity in prior iterations of Chicago Classification and provide more standardized and rigorous criteria for patterns of disorders of peristalsis and obstruction at the EGJ" [1].

1. Is the research methodology scientific?

A) «Co-chairs and sub-group members were tasked with developing statements to define a conclusive diagnosis of the motility disorder assigned to their sub-group. These statements were based on literature review and expert consensus. After two rounds of independent electronic voting thee statements were considered appropriate when meeting ≥80% agreement, and are included in the final CCv4.0» [1].

Only at Christian councils and congresses of communist parties were decisions made in this way. Until now, in the scientific world, decisions made by voting were not considered scientific. The fact that this project has existed since 2009 testifies to the civilizational change in society.

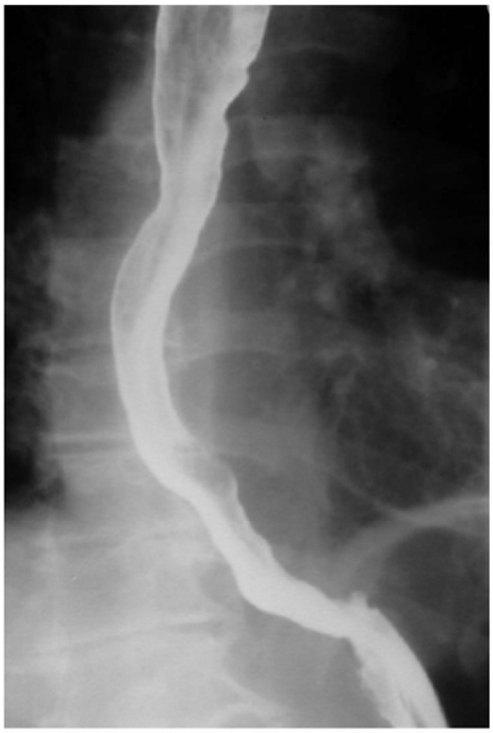
B) Any pathology is distinguished by changes in relation to the norm. Determining the exact boundaries of the norm is a mandatory initial stage of any scientific research. You will not understand a blood test if you do not know the normal range. However, it is a methodological error to select control patients to determine manometric standards based on the absence of complaints, since it is widely known that many patients have no symptoms at all, and the majority patients GERD do not have the typical symptoms (regurgitation and heartburn). This error is typical for all studies

devoted to HRM [2]. Because of this, all manometric measurements are not accurate.

C) "The key HRM metrics utilized in the CCv4.0 consist of assessment of deglutitive relaxation across the LES/EGJ using integrated relaxation pressure (IRP), vigor of esophageal body contraction using distal contractile integral (DCI), contractile wavefront integrity at 20 mmHg isobaric contour setting, and latency of deglutitive inhibition using distal latency (DL)" [1].

These characteristics of the manometric graph have no physiological meaning. They were suggested by the engineers of the manufacturer's company, who tried to determine the difference in relation to the norm. But firstly, the control persons were selected by mistake. Secondly, ...

D) ... secondly, the confidence of the new method is checked when comparing it to the results with the previously applied methods. Before the introduction of HPM, EA diagnostics was carried out by the X-ray method. But parallel studies of HRM with X-ray examination were not carried out. It is now impossible to determine in which articles the false information was injected, that HRM is the gold standard for the diagnosis of achalasia" [3]. This information has drowned in numerous articles. For example, only PJ Kahrilas published 525 articles (17.5 articles per year). However, in some cases, we can compare the results of the X-ray examination with HRM [3] **(Figure 1)**.



Example of nondiagnostic barium swallow x-ray in a patient with manometrically confirmed idiopathic EA

Figure 1 from an article by El-Takli et al with signed by the authors [3]. There is not a single sign of EA on this radiograph: the esophagus is not dilated, the gas is in the stomach, the LES is open, and there is no violation of the evacuation of the contrast agent to the stomach. A narrow lumen and uneven contours of the esophagus indicate esophagitis. I submit that a patient with reflux esophagitis was misdiagnosed with the EA. I am sure that EA treatment, in this case, could only worsen the patient's condition.

Our task is to establish who made the mistake: the authors of the article [3] of the authors of the HRM.

Let's leave aside all variants of disorders of the motor function of the esophagus and LES, except for esophageal achalasia, because, supposedly, only it can be diagnosed using HRM. This means that if the manometric indicators meet certain criteria, then these patients, without any other examination, should undergo procedures that weaken the tone of the LES.

A conclusive diagnosis of achalasia is defined as an abnormal median IRP and a lack of contractility. In 2008, Pandolfino et al proposed to subdivide EA into 3 types [4]. Analysis of the literature shows that such a subdivision, firstly, has no physiological justification, and, secondly, it has no practical meaning, because it does not affect the tactics of treatment. For example, in Chuah et al's table, type 1 and type 2 are put together, and type 3 patients receive the same treatment (Figure 2) [5]. An attempt was made in the article by Kahrilas & Boeckxstaens [6] to propose the pathophysiology of EA. In it, differences in the prognostic value of 3 types of achalasia are shown as the only merit of the EA subdivision. However, and this function of subdivision into 3 types is questionable, because «POEM, PD (pneumatic dilation), and LHM (laparoscopic Heller myotomy) were all

effective in improving esophageal function in achalasia at short-term. There was no difference in efficacy between the three treatments» [7].

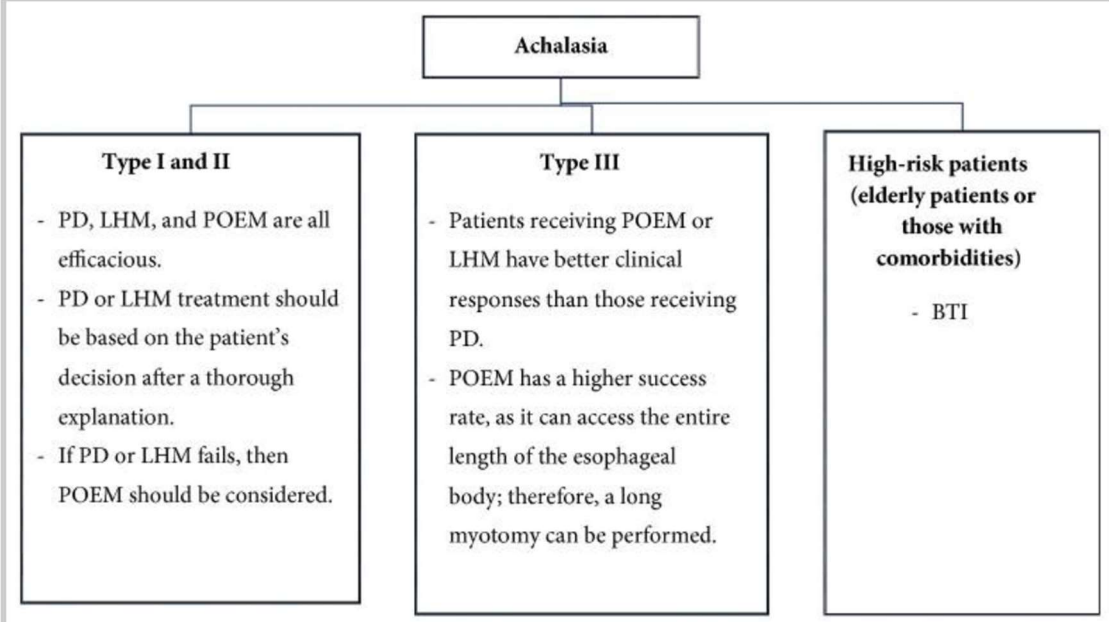


Figure 2. Proposed treatment algorithm based on the subtype of achalasia [5].

Why is this recommendation is supported by the latest Chicago classification? [1]. The answer is obvious: because Kahrilas and Pandolfino are the organizers and theorists of the Chicago classification. The second question is: who pays for research, the only merit of which is the dubious prognostic value of HRM? (Kahrilas - 24 grants, Pandolfino - 32 grants).

2. How reliable are the works of these authors?

I took for analysis the article by Kahrilas and Boeckxstaens [6].

A) "In the early days, achalasia was diagnosed radiographically with the demonstration of esophageal dilation along with retention of swallowed food and contrast material. Subsequently, esophageal manometry became the method of choice, with the defining characteristics of incomplete LES relaxation and absent peristalsis [2,3].

In fact, there is nothing like this in these links. In summary of the Recommendations for the Clinical Use of Esophageal Manometry it is specifically written: "manometry not indicated: (1) For making or

confirming a suspected diagnosis of gastroesophageal reflux disease. (2) As the initial test for chest pain or other esophageal symptoms because of the low specificity of the findings and the low likelihood of detecting a clinically significant motility disorder" [8]. I started checking other links but stopped after I saw that they were not convincing. Often, articles referenced by authors contain links to other articles on the topic under discussion. Less often in the links, we are talking about unreliable hypotheses, which, due to numerous repetitions began to be considered axioms. Even less often there were links on single observations that prove nothing.

B) The assertion that "Distally, the esophagus is anchored to the diaphragm by the phrenoesophageal ligament at the level of the squamo-columnar junction" is a serious error that leads authors to be misleading in HRM's assessment.

The LES about 4 cm long is located between the esophagus and the stomach. Two of the 4 cm of LES are located intra-abdominal. Thus, in healthy adults, the true GEJ is the proximal extent of the gastric oxyntic epithelium 2 cm caudal to the diaphragm. "If there is cardiac mucosa lining proximal rugal folds, that cardiac mucosa-lined region is the dilated distal esophagus, not the proximal stomach. The dilated distal esophagus is the pathologic expression of damage to the abdominal segment of the LES" [9]. The EGJ schematics are shown in Figure 3.

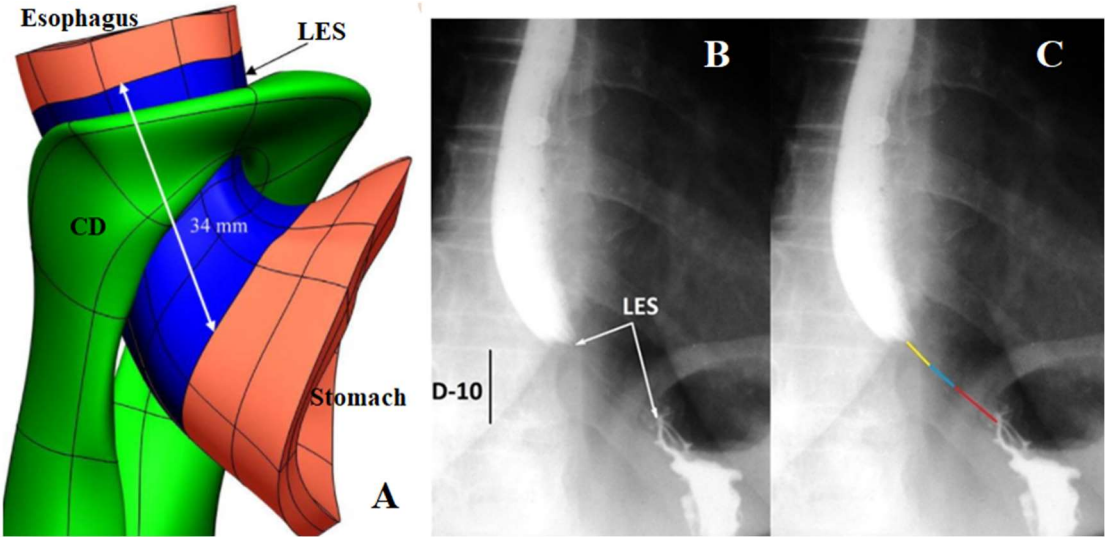


Figure 3. (A) Three-Dimensional Model of the Esophageal Gastro Junction [10]. The length of the LES is 3.4 cm (blue). Its abdominal part is ≈2 cm. About 1 cm is located at the level of the crural diaphragm (CD) and 0.4 cm above the diaphragm. **(B)** Radiograph of a patient with GERD in an upright position taken during abdominal

compression. The LES contracted in response to the increased pressure in the stomach. It is visible as two longitudinal folds between the esophagus and stomach. Since the actual height of D-10 is ≈2 cm, the actual length of the LES is ≈3.3 cm. **(C)** Diagram of the LES parts: red - the abdominal segment, blue - inside the diaphragm, yellow - above the diaphragm.

The LES in patients with GERD is shortened due to the opening of the abdominal part. In severe cases, it is short at rest. In lighter observations, it is shortened during provocative tests (**Figure 4**).

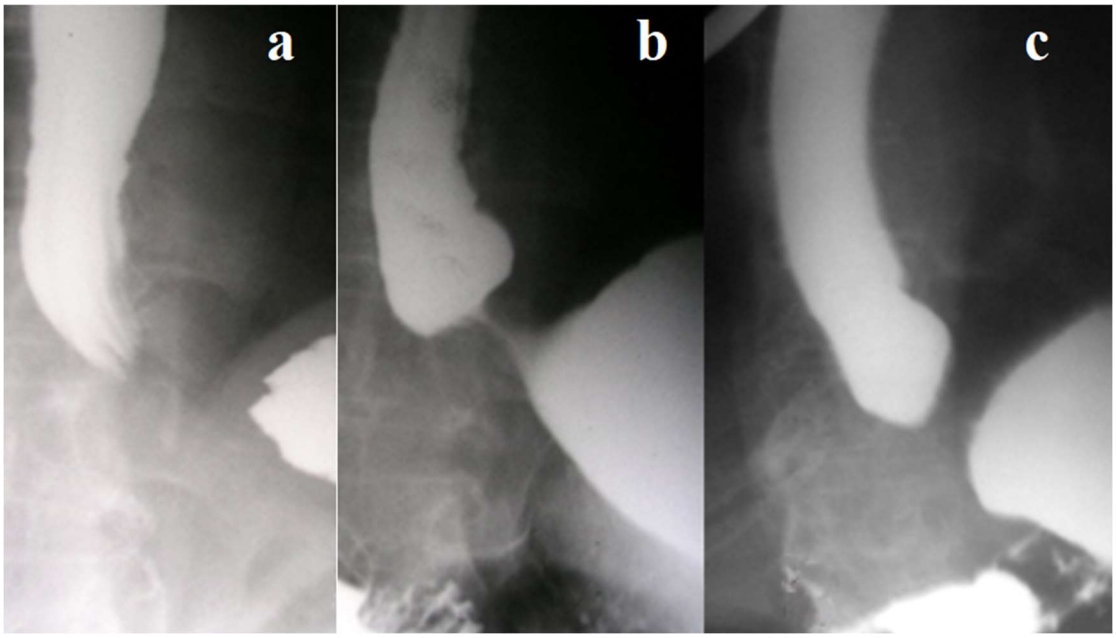


Figure 4. The EGJ radiographs in patients with GERD. **(a-b)** During the compression of the abdomen, at first, the relatively long LES (a) became significantly shorter (b) due to the opening of its abdominal part. **(c)** The length of the LES is 1 cm, i.e., only the diaphragmatic part of the LES is contracted.

On the radiographs of this figure, the shortening of the esophagus-LES complex occurs due to the shortening of the LES. The distal esophagus contour does not change its position in relation to the bony landmarks - NEVER.

In the work of Kwiatek et al [11], a patient with GERD has been examined as a control (healthy) person due to an incorrect selection of persons for control. There were a parallel manometry and X-ray examination. During swallowing, a shortening of the LES occurred because of the opening of its abdominal part. The authors mistakenly interpreted this as a shortening of the esophagus. The clip was attached at the proximal end of the rugal folds, which are considered the folds of the stomach. Figure 5 shows a similar situation. In fact, the clip was not attached to the bottom end of the LES, but to the top. Because of what the authors came to the paradoxical

conclusion that the LES, when swallowed, turns into an ampoule. During swallowing, the clip changed its position relative to the ampulla, which the authors regarded as confirmation of the shortening of the esophagus. However, it did not move relative to the bony landmarks.

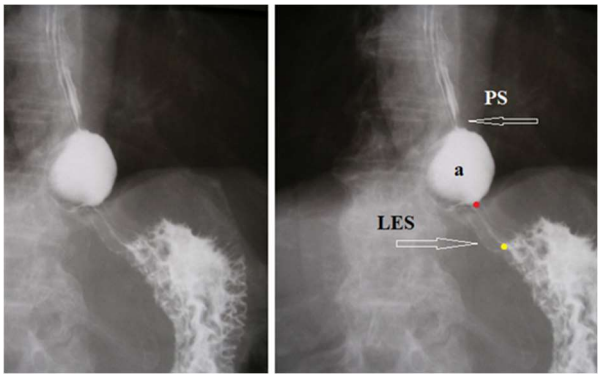


Figure 5. X-ray of an elderly person with GERD. The LES находится в сокращенном состоянии между желудком и ампулой. However, without evidence, rugal folds between the colored dots are considered to be the folds of the stomach. Therefore, the clip in the article by Kwiatek et al was allegedly attached to the end of the stomach at its junction with the LES (red dot). This leads to the dubious conclusion that the proximal end of the LES should be located in the phrenic ampulla of the esophagus (a), i.e., the LES and the ampulla merge with each other [4,6].

The X-ray shows that the inflammatory process has led to the formation of longitudinal folds along the entire length. At the LES level, between the stomach and the ampulla, the folds are wide because the LES contracted in response to abdominal compression. The contrast agent is in a closed cavity between two sphincters: the proximal sphincter (PS) proximally and the LES distally. The length of the LES is about 2 cm, then almost 2 times shorter than the norm, which is typical for GERD. This X-ray shows that the LES is not moving, but it is getting shorter due to the opening of the abdominal part. And two pressure peaks are created by the contraction of two sphincters - PS cranially and LES with CD caudally.

The authors of the Chicago classification link their conclusions with widely known, but not proven hypotheses, which appeared long ago and became generally accepted "theories" over the years. But, ...

a) There is no evidence that rugal folds are gastric folds. I have provided evidence that these folds are formed in the inflamed LES. Histological studies support this statement [9].

b) There is no evidence that the LES shifts upward during swallowing or other provocations. LES in patients with GERD is shortened due to the opening of its abdominal part.

c) The ampulla of the esophagus is the result, not the cause, of GERD. This is an expansion of the lower esophagus, and it is located above the LES, regardless of size. A functional sphincter (PS) is formed above the ampulla of the esophagus, which facilitates the evacuation of the contents of the ampoule into the stomach.

e) Neither the LES nor the stomach moves upward. The so-called sliding hernia is the ampulla of the esophagus that is bounded cranially by the proximal sphincter. The two pressure peaks in GERD are due to the contraction of the PS proximally and LES with the CD distally.

I invite you to a broad discussion of each of these provisions.

C). Scientific articles do not allow for uncertainty and ambiguity. They should clearly distinguish between known patterns and hypotheses. Hypotheses that contradict scientific ones, i.e. credible facts should not be quoted at all. In the article by Kahrilas and Boeckxstaens there are no references to known physiological laws, perhaps because the assessment of manometric studies conflicts with them. Secondly, many phrases are written in an incomprehensible language and can be interpreted differently. For example, “Hence, detailed assessment of postdeglutitive LES opening shows that this is associated with both radial effacement and elongation to form a structure referred to radiographically as the phrenic ampulla. It has also been proposed that a primary stimulus for deglutitive LES relaxation is contraction of the more proximal longitudinal muscle and that the longitudinal muscle within the LES itself then relaxes, serving as a yield zone to accommodate the resultant shortening" [6].

It is known that stretching of the esophagus over the EGJ causes relaxation of the LES. The methodologically flawless studies of Shafik et al. showed that in patients with EA, the LES tone is above normal and that stretching of the esophagus causes a contraction in the LES (esophagosphincter inhibitory reflex) [12]. The authors of the peer-reviewed article refer to non-physiological studies in small animals, the results of which are interpreted without knowledge of the fundamentals of physiology.

In healthy individuals, the esophagus has the same lumen throughout. The phrenic ampulla occurs only in a horizontal position in patients with GERD. It is the result of extensions of the esophagus in response to an inflammatory process [13]. The ampulla is mistakenly considered the norm since GERD patients without typical symptoms were selected as a control to determine the normal pH-metry limits. When determining the limits of the norm for HRM [14], the same mistake was made as for pH-metry.

From the point of view of the normal physiology of EGJ, the following phrase is erroneous: "Temporary lower esophageal sphincter relaxation (TLESR) is a reflex that allows gas to escape from the stomach, which is also a key mechanism underlying gastroesophageal reflux" [6]. It is known that an increase in pressure in the stomach in healthy individuals causes a reflex increase in the tone of the LES, which corresponds to the law of the gut and the role played by the LES [15]. In the GERD patients, the crural diaphragm and LES showed diminished resting electromyographic activity, with either no response or paradoxical response to esophageal or gastric distention [16]. The TLESR is considered normal due to erroneous selection of the norm for pH-metry. Although, in fact, this is a symptom of GERD. In this example, we see what a destructive role for science and medical practice is played by not adhering to the methodological principles of science.

3. What is the purpose of the authors' of CC, reflected in the discussion?

It is known that EA patients often have typical symptoms of GERD. There is a portion of overlap between achalasia and GERD, and it is still controversial whether these conditions co-exist or whether one disease transforms into the other. Heartburn was reported in 13.2–68.0% of patients with achalasia. According to a previous report, proton pump inhibitors were prescribed to 53% of achalasia patients, histamine H2 blockers to 10%, and both to 6% on the assumption that GERD was the cause of heartburn and regurgitation [17]. Spechler et al demonstrated that in some patients, the dissolution of heartburn and regurgitation and appearance of dysphagia could be a symptom of achalasia. They insisted that achalasia could develop in patients with chronic GERD [18]. Smart et al described 5 cases of EA diagnostics 2-10 years after GERD [19].

Scientific principles oblige to discuss all possible variants of the pathogenesis of EA. The peer-reviewed article does not mention EA as a possible cause of GERD. The authors discuss the only hypothesis of the

pathological physiology of EA proposed by them. “Achalasia is now conceptualized as a “plexitis” of sorts, with immune attack on these controlling neurons leading to dysfunction” [6].

Links usually do not match the stated effects. Either these are isolated observations with the assumptions of the authors, or they are descriptions of other people's hypotheses. The conclusions of the authors correspond to this. For example, “Tissue samples obtained during myotomy showed persistent myenteric plexus neurons and ganglia surrounded by inflammatory cells, supporting the concept of achalasia as an autoimmune disease that targets the esophageal myenteric plexus. 72–78”. From my point of view, the presence of persistent myenteric plexus neurons and ganglia contradicts the diagnosis of EA, and inflammatory cells are evidence of an inflammation of the esophagus, which is called esophagitis.

I think the purpose of this article is expressed in the following sentence: "The key to understanding the pathogenesis of achalasia is understanding that contraction LES is orchestrated by the postganglionic neurons, precisely the neurons targeted in achalasia" [6]. Only it is not clear who is targeting whom, why, and when?

4. Analysis of X-ray studies with EA

I reviewed 121 free full-text articles in PubMed to evaluate radiological examinations EA. In 79 (65.3%) X-ray examinations were not performed, as HRM is considered to be the gold standard in the diagnosis of EA. In 19 (15.7%) radiographs were presented to demonstrate a sharp expansion of the esophagus over the narrowed EGJ. In 23 (19%), I found a typical GERD pattern, which was evaluated as EA, and these patients were operated and only two patients had balloon dilatation of the EGJ. Here are some of them **(Figure 6).**

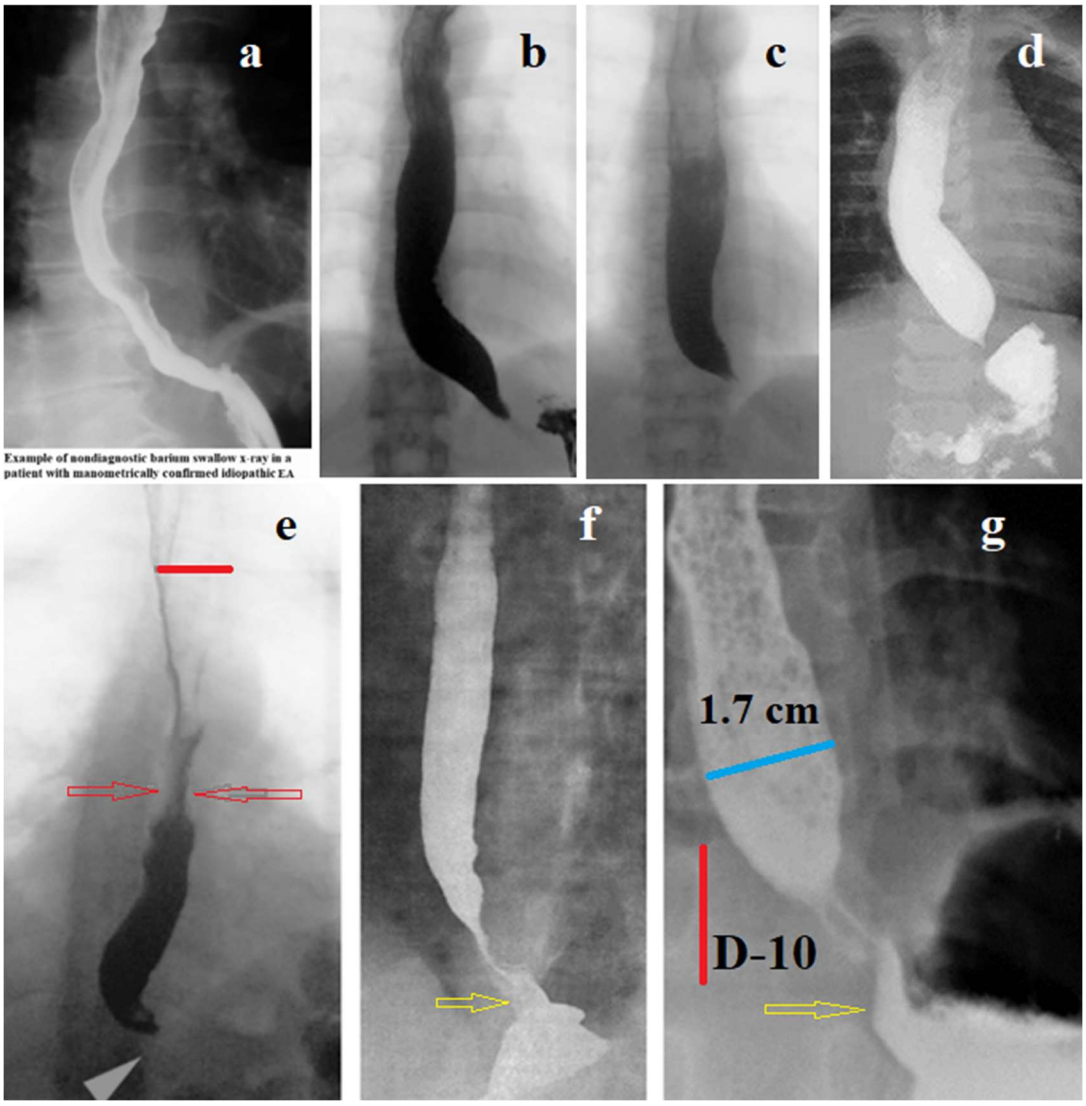


Figure 6. Radiographs of the esophagus and LES of patients operated on for EA (from articles published in PubMed). **(a)** The esophagus is unevenly constricted compared to the norm. The LES is opened. Normal evacuation of the contrast agent into the stomach. Conclusion: GERD, esophagitis. **(b)** The esophagus slightly extended and the LES contracted. The LES is shorter 2 times than the normal length because the abdominal part of the LES is open and visible as the "beak" of the stomach. Conclusion: GERD. **(c)** Mild esophageal dilatation with low fluid levels and contracted LES are typical signs of GERD (see Figure 7.a). **(d)** Radiograph of the infant in a horizontal position during continuous swallowing. It was taken at the time of the LES contraction. The length of the LES is significantly less than the norm. Conclusion: GERD. (e) The lower part of the esophagus is slightly dilated with irregular contour. In the middle third, a relative narrowing of about 3 cm long is visible (red arrows). Above it, an expansion of the esophagus (red line) containing gas is determined. A contracted LES is defined between the esophagus and the stomach. During its opening, barium entered the stomach and small intestine. Conclusion: GERD, esophagitis, narrowing in the middle third of the esophagus. (f) The width of the esophagus is about 2 cm, which is slightly wider than normal (1.2 cm). The abdominal part of the LES is opened in the form of

the beak of the stomach (yellow arrow), and the proximal part has contracted. (g) The esophagus is slightly dilated (1.7 versus 1.2 cm). Good evacuation from the esophagus. The proximal part of the LES has contracted and the abdominal part is opened in the form of a beak of the stomach (yellow arrow) (see 7.d). Conclusion: GERD.

The analysis of these radiographs indicates that the authors of the articles do not know what the LES looks like on the radiographs and what a “bird’s beak” is. The physiology of the esophagus and EGJ, in health and in GERD, is described in detail here [20]. **Figure 7** shows samples of radiographs of patients with GERD from my archive.

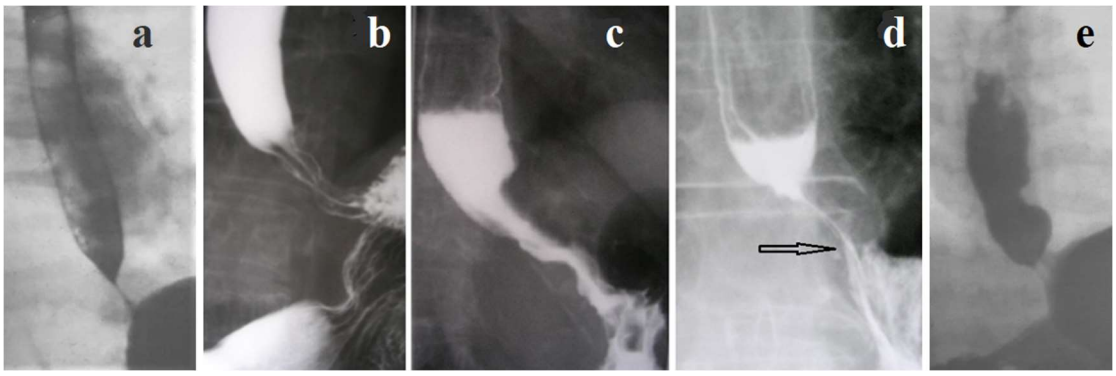


Figure 7. Radiographs of the EGJ in patients with GERD. **(a)** The esophagus is slightly dilated. The space between the esophagus and the stomach does not contain a contrast agent because the LES contracted in response to the increased pressure in the stomach. The tapered end of the esophagus is a sign of GERD, not EA. **(b)** During abdominal compression, the LES contracted. Longitudinal folds indicate an inflammatory process. **(c)** Thickened and deformed folds in the LES indicate a pronounced inflammatory process, the progression of which can lead to narrowing of the lumen and achalasia syndrome. **(d)** Minor extension of the esophagus is combined with a shortening of the LES due to the opening of its abdominal part, which looks like the beak of the stomach (arrow). **(e)** A sharp expansion of the esophagus and a very short LES in a 3-year-old child.

In healthy individuals, the LES is not visible since it does not contract under any circumstances until the contrast agent penetrates the stomach. The LES is contracted in GERD because the weak peristalsis of the dilated esophagus cannot overcome the LES tone. Thus, an easy extension of the esophagus and contraction of the LES are symptoms of GERD. The narrowing of the esophagus relative to the norm (1.2 cm in the vertical and 1.5 cm in the horizontal position) with uneven contours indicates severe reflux esophagitis.

Authors of articles, as a rule, define the primary EA based on the "typical" bird's beak. At the same time, they indicate the conical end of the LES (see

Figure 6). However, this is the usual ending of LES in GERD (see Figure 7.a). A bird's beak is a bird's head with a long beak, where the beak is a contracted and not deformed LES with normal length (Figure 8.a). The length of the LES is about 4 cm.

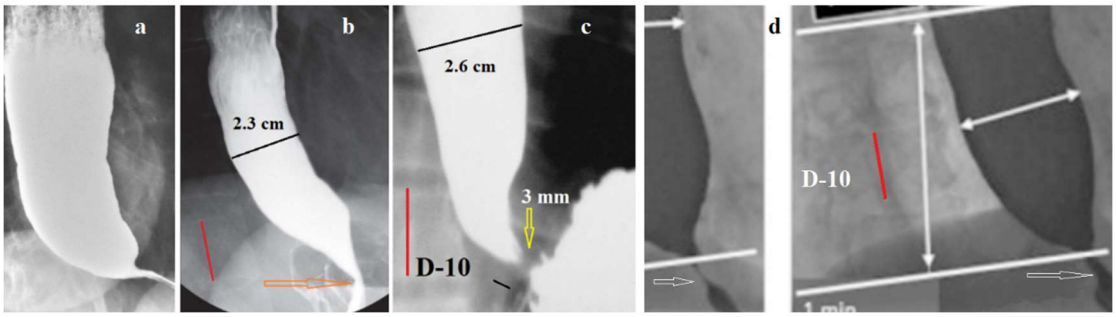


Figure 8. Cases described as EA based on HRM. **(a)** Primary or classical EA. **(b)** Moderate esophageal dilatation due to GERD. Possibly there is a very limited constriction at the LES level (arrow). **(c)** In the horizontal position, there is a moderate expansion of the esophagus and a very short (3 mm) LES due to the opening of its abdominal part. Good evacuation of the contrast medium into the stomach. Typical X-ray picture of GERD. **(d)** The extension of the esophagus is due to the narrowing of only the upper portion of the LES, which is about 1 cm long (arrows).

The shortening of the LES is possible only as a result of its damage with GERD. The length of the LES in classic (idiopathic) EA is always within normal limits. Even if we assume that "precisely the neurons targeted in achalasia" [6], it cannot be explained that they are targeted in the fourth part of the LES (Figure 8 d). It is more likely that the inflammatory process led to hypertrophy and fibrosis of the LES wall.

It is impossible to determine exactly how many patients with GERD were operated on with a diagnosis of EA, where the esophageal dilatation was due to reflux esophagitis and there was no obstruction in the EGJ. With more than 50 years of experience as a medical researcher, I argue that instead of pathogenetic treatment for GERD, in all children and infants already weak LES it was dissected by, depriving them of the chance for minimal restoration of the LES function. Here are some typical observations (**Figure 9**).

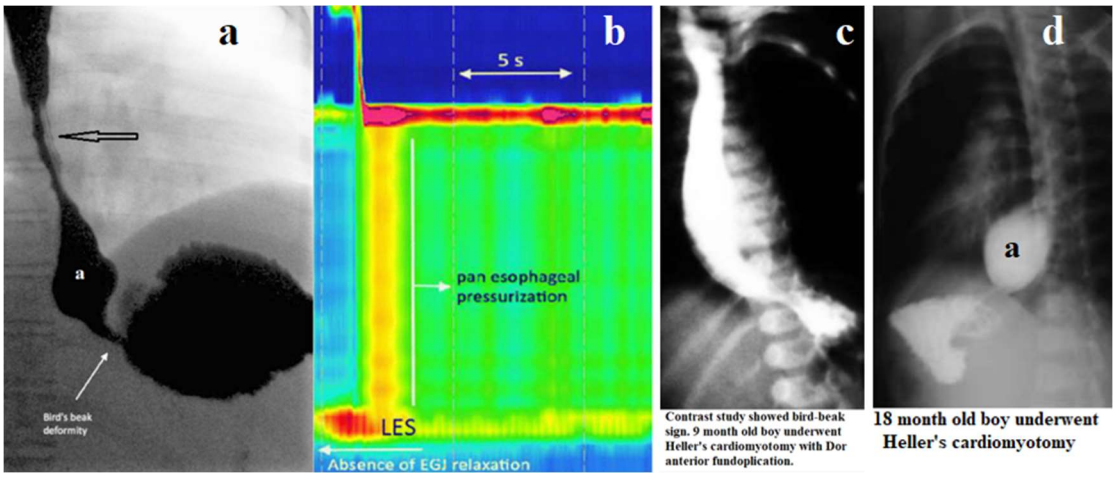


Figure 9. Children with GERD operated on with a diagnosis of EA. **(a, b**) Reflux esophagitis (arrow). During the contraction of the phrenic ampulla, barium passes into the stomach through a short LES and partially returns proximally, since the PS does not function. (**b**) HRM of this patient. **(c)** Dilated esophagus and wide-open and short LES. **(d)** Wide phrenic ampulla between contracted PS and LES.

The authors argue that "because the diagnosis (EA) is established on the basis of manometric anomalies, it will never be 100% specific; this is the nature of manometric findings" [6]. HRM, considering the above analysis, cannot serve as a diagnostic test, firstly, because it cannot determine the width of the esophagus, the elasticity of its wall, and the presence of esophagitis. For example, the absence of peristalsis can be in a very wide esophagus, as well as in the presence of a rigid wall with esophagitis. Secondly, HRM does not measure the length of the LES and its lumen during bolus evacuation, which leads to erroneous conclusions, as, for example, in Figures 6,8,9.

In order to determine how accurate, the manometric method is, it should be compared with another research method. Why, despite the huge stream of articles on EA, the reliability of HRM has not been determined in comparison with the X-ray method? I think the answer is clear: then it will be obvious that there is no point in HRM. X-ray examination allows you to accurately determine in which cases treatment of GERD is necessary (Figure 10 a), and in which cases the segment that prevents the evacuation of barium should be expanded in different ways (Figure 10 b).

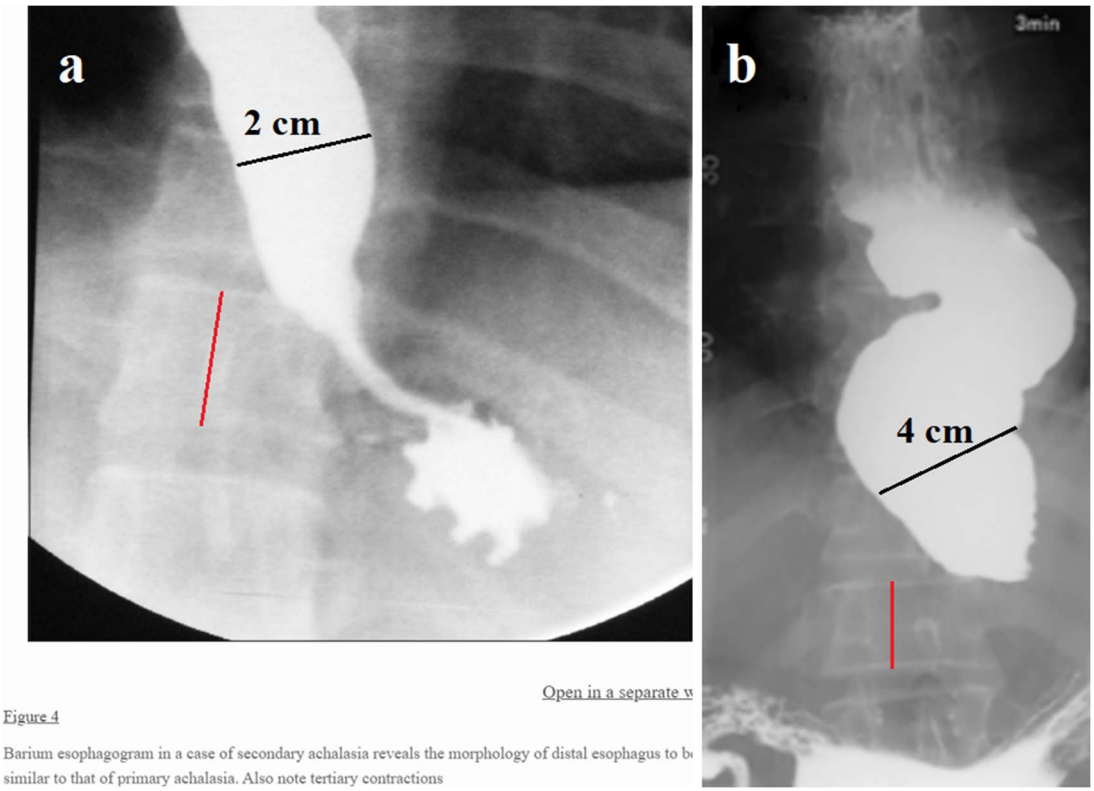


Figure 10. Two patients with a manometric diagnosis of EA. (a) Research in a horizontal position. Moderate extension of the esophagus (2 cm versus 1.5 cm is normal). Shortened LES (2 cm versus 4 cm) with normal clearance and good evacuation. These are typical signs of GERD). (b) This demo snapshot is offered as evidence of EA. Since there is a large amount of contrast agent in the stomach, it was necessary to take an X-ray during its passage through the LES. This would facilitate the choice of a pathophysiological treatment for EA syndrome.

Conclusion. The HRM method is not physiological, the research methodology is not scientific, and the research results are not reliable. 2) Most of the examined patients with suspected EA had a clinical and radiological picture of GERD, despite the recommendations of the American Gastroenterological Association that manometry not indicated for making or confirming a suspected diagnosis of gastroesophageal reflux disease because of the low specificity of the findings and the low likelihood of detecting a clinically significant motility disorder. 3) HRM findings cannot be considered diagnostic because they often contradict radiological findings. As a result, GERD patients requiring pathogenetic treatment undergo procedures, including surgeries, that damage the function of an already weak lower esophageal sphincter. 4) High resolution manometry

and Chicago classification is an advertising project of the manufacturers of them equipment [1] **(Figure 11).**

Figure 11.

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