ISSN 2228-9860 eISSN 1906-9642 CODEN: ITJEA8

International Transaction Journal of Engineering, Management, & Applied Sciences & Technologies

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Nociception Problems in Gastroesophageal Reflux Disease: Diagnosis and Therapy of Irritated Esophagus

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Paper ID: 13A11M

Volume 13 Issue 11

Received 08 April 2022
Received in revised form 08 July 2022
Accepted 15 July 2022
Available online 23 July 2022

Keywords:
GERD; Irritated esophagus; Nociception; Proton pump inhibitors; Antireflux mechanisms; Gastroesophageal reflux; Functional heartburn.

Abstract

Gastroesophageal reflux disease (GERD) is considered one of the "diseases of the twenty-first century" due to its widespread prevalence and a clear tendency to increase the frequency of cases. According to population studies, the incidence of GERD is about 13%, and the frequency of weekly symptoms varies from 10% to 20%, depending on the area of residence and ethnic composition. In this regard, great importance is attached to the early diagnosis of the disease, which allows you to choose the right therapy tactics for the corresponding GERD phenotype. To date, the generally accepted standard of treatment for gastroesophageal reflux disease is the long-term course and further supportive use of proton pump inhibitors. Further in the article, the key links of pathogenesis, clinical variants of the course and rational treatment tactics for each patient will be considered.

Discipline: Medicine, Gastroenterology.

Cite This Article:

Adilsultanov, E.B., Tsakhkhaeva, K.K., Kulieva, A.T., Abdulaeva, N.A., Kurbanova, N.G., Kurbanova, B.Sh., ... Magarramova, Z. N. (2022). Nociception problems in gastroesophageal reflux disease: diagnosis and therapy of irritated esophagus. *International Transaction Journal of Engineering, Management, & Applied Sciences & Technologies, 13*(11), 13A11M, 1-10. http://TUENGR.COM/V13/13A11M.pdf DOI: 10.14456/ITJEMAST.2022.223

1 Introduction

The basis of GERD pathogenesis is motor disorders that lead to inadequate functioning of antireflux mechanisms. As a result, there is a pathological condition known as gastroesophageal reflux (GER) [1]. There is a high-pressure zone between the stomach and esophagus, which prevents the formation of GER. This zone consists of internal, or sphincter, and external, or extra-sphincter, components. The first is due to the tone of the lower esophageal sphincter, whose function is to prevent the stomach contents from getting back into the overlying sections. The second component includes the acute angle of the Gis, circular muscle fibers of the cardiac part of the stomach, the diaphragmatic-esophageal ligament and the socket of the cardia. With adequate work of the internal and external components, the intra-thoracic pressure remains lower than the intra-abdominal pressure [2,3]. Also, a hernia of the esophageal orifice of the diaphragm is considered one of the factors that can lead to both the development of GERD and the aggravation of it. The problem with its formation is that the lower esophageal sphincter moves from the abdominal to the thoracic, where the pressure is lower, as a result of which the adequate work of not only the sphincter itself but also the antireflux mechanisms as a whole is disrupted [4]. In further pathogenesis, the reflux itself, which for one reason or another entered back into the esophagus, its composition, duration of exposure, depending on the state of esophageal clearance, and the state of the mucous membrane itself, is of key importance. Based on the results of long-term observations, the scientific community came to the conclusion that there is a clear relationship between the duration of acidification of the esophagus and the probability of GERD formation. When the acidic contents of the stomach enter, inflammatory and destructive changes in the mucous membrane occur, but they are less pronounced than when the bile enters since it has an alkaline pH [5,6]. It is important to mention that it is the presence of bile in the refluxate that significantly increases the risk of developing Barrett's esophagus, which is considered a precancerous condition, and esophageal cancer itself [7].

2 Diagnosis of GERD and Clinical Variants of the Course

The main clinical manifestations of GERD include heartburn, chest pain, pain when swallowing and a feeling of coma behind the sternum. The feeling of pain can be called the main indicator, since it is she who, as a rule, forces the patient to see a doctor [8]. This indicator determines the choice and scope of diagnostic measures and also allows us to clearly track the dynamics, positive or negative, during therapy [9-11]. Visceral sensitivity is considered responsible for nociception. This must be remembered since the more severe the reflux lesions in GERD, the more sensitivity decreases. In practice, there are often cases of severe esophagitis, ulcers and Barrett's esophagus, which occur without obvious symptoms and do not reduce the quality of life of the patient but are diagnosed by endoscopic examination absolutely by chance. At the same time, some cases of GERD that are lighter in their course can be detected without invasive research methods, since patients will make characteristic complaints [12,13].

One of the most relevant research methods remains the use of endoscopy (Figure 1). With its help, it is possible to assess the condition of the esophageal mucosa, determine the presence of a hernia of the esophageal orifice of the diaphragm, as well as take a biopsy for histological examination [14].

A less common, but necessary in some cases, the examination is an X-ray of the esophagus and stomach, which makes it possible to evaluate such anatomical criteria as the shape, size and position of the esophagus and stomach. This may be necessary in cases of anatomical features or various kinds of pathological changes that can affect the appearance or further complications of the disease [14-16].

The etiological factor of symptoms in ulcerative esophagitis is most often the effect of acid. At the same time, symptoms of an irritated esophagus will, as a rule, be caused by hypersensitivity to the mucosa itself. It is caused, in turn, by the hypersensitivity of either peripheral pain receptors or spinal neurons [17-19].

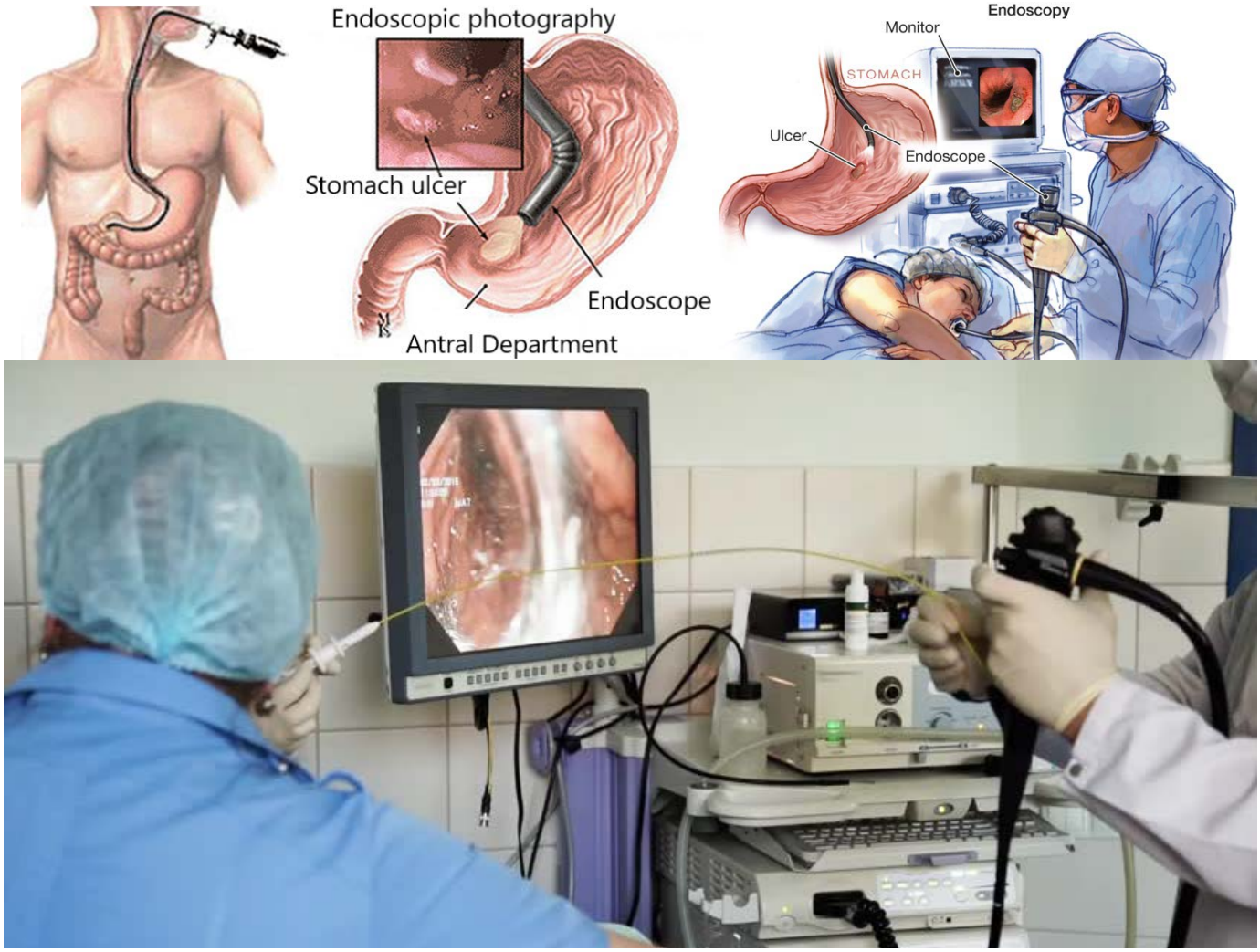

Figure 1: Application of endoscopy

The necessary and reliable information about the nociception of the esophageal mucosa can be obtained with the help of long-term intraesophageal impedance-pH monitoring. With the help of this diagnostic method, it became possible to identify patients with various variants of GERD, as well as the selection of appropriate therapy [20].

Scientists have proposed to distinguish 4 phenotypes of this disease, basing the classification on diagnostic criteria and prognosis of treatment effectiveness [21-24].

Phenotype 1 is symptomatic GERD. It is considered the most favorable variant of the course of the disease, accompanied by reflux and an increased symptom index (characterizes the number of symptoms of one type that are associated with reflux, relative to the total number of symptoms of this type recorded during the study). The higher the value of this indicator, the stronger the relationship between reflux and symptoms.

Phenotype 2 is a hypersensitive esophagus. Patients with a similar variant of the course of the disease were diagnosed with physiological reflux and also an increased index of the symptom.

Phenotype 3 is gastroesophageal reflux disease. A distinctive feature of this variant of the course is the lack of connection with gastroesophageal reflux. With intraesophageal impedance-pH monitoring, pathological reflux and a reduced symptom index are observed.

Phenotype 4 is functional heartburn. The diagnosis of functional heartburn is defined as a burning sensation or pain that does not respond to therapy with drugs that reduce secretion. With this phenotype, the patient will not have any histological changes in the mucous membrane of the esophagus, nor structural and motor abnormalities that could cause complaints by the patient. In such clinical cases, it is important to correctly interpret complaints of heartburn, since in practice there are cases when the patient understands the burning sensation in the oral cavity under the term "heartburn", which, as a rule, has no connection with reflux.

According to the Roman criteria of the 4th edition, the diagnosis of functional heartburn can be made if the patient has had it for the last 3 months (assuming a total duration of at least 6 months) 2 times a week or more, the following signs are established:

1. Chest pains or burning.

2. Therapy with proton pump inhibitors does not give positive dynamics.

3. Lack of connection between symptoms and gastroesophageal reflux. This sign is confirmed on the basis of the results of the endoscopic examination and pH-impedance measurement.

4. Maintaining normal esophageal motility.

As for the term "irritated esophagus", there is currently no generally accepted definition for it. According to the Roman criteria of the 4th edition, hypersensory esophagus is understood as heartburn and chest pains that occur during physiological GER, taking into account the presence of a normal endoscopic picture and pH impedancometry. To make an appropriate diagnosis, symptoms should be observed for at least the last 3 months from twice a week or more, provided the total duration of the disease is from 6 months or more. It is also necessary to have the following symptoms:

1. The presence of heartburn or pain in the chest area.

2. The normal condition of the esophageal mucosa according to the results of endoscopy and the absence of eosinophilic esophagitis.

3. Maintaining adequate esophageal motility.

4. The presence of a relationship between the patient's symptoms and gastroesophageal reflux based on pH-metry or pH-impedansometry under the condition of normal indicators of acid exposure in the esophagus [25,26].

It is important to note that in clinical cases of the irritated esophagus, an increased level of basal impedance of the esophagus is often found [27].

3 Therapy

For the rational therapy of gastroesophageal reflux disease, it is necessary to use an integrated approach. Mandatory conditions for recovery are [28]:

- diet,
- lifestyle modification, including avoiding bad habits, playing sports and losing weight in case of excess weight,
- reduction of the damaging properties of reflux,
- normalization of esophageal clearance,
- restoration and protection of the esophageal mucosa.

The last three points imply the use of acid-neutralizing or acid-absorbing medications or inhibiting acid production in the stomach, this is necessary to increase the pH of the reflux coming from the stomach. Such drugs include proton pump inhibitors (PPIs), alginates and antacids [29].

If we talk about the treatment of GERD according to phenotypes, then 1 and 2 phenotypes are considered the most successful in treatment than 3 and 4. For the treatment of symptomatic gastroesophageal reflux disease, PPIs and antireflux surgery are actively used. According to studies, preserved esophageal clearance is considered a prerequisite for successful therapy [30]. The treatment of an irritated esophagus has its own problems, namely, in some cases, when treating PPIs, alginates and antacids, it does not give the desired effect. In such cases, it is considered rational to prescribe tricyclic antidepressants and selective serotonin reuptake inhibitors. Prokinetics, in cases of esophageal hypersensitivity, do not give the expected positive effect, this is due to the presence of normal esophageal clearance and preserved secondary peristalsis. Therefore, their appointment is not considered appropriate [31]. For the treatment of gastroesophageal reflux disease, symptomatically unrelated to reflux, the above treatment options are ineffective. It is considered advisable to use alginate monotherapy [32]. Ivashkin et al (2020) in their studies show that according to the results of the course treatment of 148 patients by day 7, heartburn was stopped in 48.6% of cases, and regurgitation 64.6% of cases [20]. With further administration of alginate, an increase in efficiency was observed. On day 14, heartburn was steadfastly eliminated in 84.2% of patients, and regurgitation 88.5%. Based on the conducted research, it can be concluded that there is a significant improvement in the tested indicators, and, consequently, the well-being and quality of life of patients.

In the case of functional heartburn, as mentioned earlier, it is necessary to make a differential diagnosis with paresthesia of the oral mucosa, since the patient himself may

misinterpret the concept of heartburn. In case of confirmation of the diagnosis of functional heartburn, the use of antidepressants is recommended, since the cause of the disease is hypersensitivity of peripheral or central genesis. If paresthesia occurs, then the use of mast cell membrane stabilizers, H1-histamine receptor blockers (medications are prescribed in Table 1 and inhibitors of the production of inflammatory mediators is considered rational [33].

Table 1: H1-receptor blockers

1st generation	2nd generation	3rd generation
Diphenhydramine	Loratadine (Claritin)	Descarboethoxy loratadine (Erius)
Clemastine (Tavegil) Dimethinden (Fenistil)	Terfenadine (Treksil)	Fexofenadine (Telfast)
Promethazine (Diprazine, pipolfen)	Astemizole (Gismanal)	–
Chloropyramine (Suprastin)	Ebastin (Kestin)	–
Mebhydroline (Diazoline) Dimebon	Acrivastin (Semprex)	–
Hifenadine (Fencarol)	Cetirizine (Zirtek)	Levocetirizine (Xizal)

4 Conclusion

Gastroesophageal reflux disease is a pathology that requires careful diagnosis to correctly determine the etiological factor, which directly affects the course of disease therapy and further prognoses regarding the health of patients. Long-term intraesophageal impedance-pH monitoring, which allows differentiating GERD within its phenotypes, is of great practical importance in the diagnosis of the disease today. Also, the use of endoscopic research methods does not lose its relevance, which allows not only for visually assessing the condition of the esophageal mucosa but also for histologically examining the biopsy. Proton pump inhibitors are also the basis of GERD therapy, with the exception of the treatment of functional heartburn, in which the effectiveness of antireflux therapy is insufficient. In such patients, it would be rational to use drugs with an antidepressant effect. Timely course and further supportive treatment, regardless of the GERD phenotype, make it possible to maintain a high quality of life and avoid serious complications.

5 Availability of Data and Material

Data can be made available by contacting the corresponding author.

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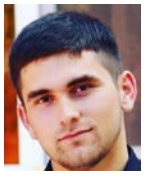

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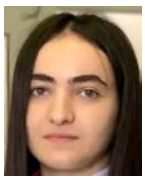

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