



European Society of Neurogastroenterology and Motility Consensus on Gastroparesis (2020): What Issues Remain Unresolved?

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Aim: to analyse the document of the European Society for Neurogastroenterology and Motility consensus on gastroparesis, held in 2020.

Key findings. The evaluation of the voting results on the submitted statements of the consensus meeting shows that there is a high level of agreement among the experts regarding the definition of gastroparesis, the main diseases in which it occurs, and the existing diagnostic methods. At the same time, there is a divergence of views regarding the role of individual pathogenetic factors of gastroparesis and their relationship with clinical symptoms, as well as the effectiveness of drugs of various groups and other treatment methods.

Conclusion. The pathophysiological mechanisms of gastroparesis and the effectiveness of various treatment methods need further research.

Keywords: gastroparesis, disorders of gastroduodenal motility, prokinetics

Conflict of interest: the authors declare no conflict of interest.

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Согласительное совещание Европейского общества нейрогастроэнтерологии и моторики по гастропарезу (2020): какие вопросы остаются нерешенными?

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Цель исследования: провести анализ итогового документа согласительного совещания Европейского общества нейрогастроэнтерологии и моторики по гастропарезу, состоявшегося в 2020 г.

Основные положения. Оценка результатов голосования по представленным положениям согласительного совещания показала, что среди экспертов наблюдается высокий уровень согласия в отношении определения гастропареза, основных заболеваний, при которых он возникает, существующих методов диагностики. В то же время отмечается расхождение взглядов, касающихся роли отдельных патогенетических звеньев гастропареза и их связи с клиническими симптомами, а также эффективности лекарственных препаратов различных групп и других методов лечения.

Заключение: патофизиологические механизмы гастропареза и эффективность различных методов лечения нуждаются в дальнейших исследованиях.

Ключевые слова: гастропарез, нарушения моторики желудка и двенадцатиперстной кишки, прокинетики

Конфликт интересов: Авторы заявляют об отсутствии конфликта интересов.

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In 2020, under the leadership of the President of the Rome Foundation for Disorders of Gut-Brain Interactions (DGBIs) J. Tack (Belgium) was adopted the final document of the consensus of the European Society of Neurogastroenterology and Motility (ESNM) on gastroparesis. The consensus was attended by 40 experts from 22 countries, including such well-known gastroenterologists as G. Barbara (Italy), D. Dumitrascu (Romania), G. Karamanolis (Greece), C. O'Morain (Ireland), E. Savarino (Italy), H. Törnblom (Sweden), T. Vanuytsel (Belgium), F. Zerbib (France). Russia was represented by staff members of the Chair and Clinic of Internal Diseases Propedeutics, Gastroenterology and Hepatology, Sklifosovsky Institute of Clinical Medicine, I.M. Sechenov First Moscow State Medical University (Sechenov University) A.A. Sheptulin, O.A. Storonova and D.E. Rumyantseva. The experts assessed the fairness of a total of 88 statements and the statement was considered as accepted if more than 80 % of the experts were agree for it.

The purpose of this meeting was to reach consensus on the following aspects of gastroparesis: definition and clinical characterization, etiological factors and pathophysiological mechanisms, diagnosis and treatment with an emphasis on such a form of this disease as idiopathic gastroparesis. The final meeting of experts, scheduled for October 2020, was canceled due to the COVID-19 pandemic. Approval of the adopted final document was held remotely [1].

The first section of the final document of the consensus meeting contains statements concerning the definition of gastroparesis and a description of the symptoms of such patients.

Statement 1.1. Gastroparesis refers to symptoms or set of symptoms that is (are) associated with delayed gastric emptying in the absence of mechanical obstruction. Overall agreement (OA): 100 %.

Statement 1.2. Gastroparesis refers to a symptom or set of symptoms that is (are) associated with severely disturbed gastric motor function in the absence of mechanical obstruction. OA: 85 %.

Statement 1.3. Nausea and vomiting are cardinal symptoms in gastroparesis. OA: 95 %.

Statement 1.4. Dyspeptic symptoms such as postprandial fullness, early satiation, epigastric pain, as well as bloating in the upper abdomen and belching are often present in gastroparesis patients. OA: 95 %.

Statement 1.5. Symptoms in gastroparesis patients overlap mainly with postprandial distress syndrome (PDS) and less with epigastric pain syndrome (EPS) symptoms of functional dyspepsia (FD). OA: 90 %.

The presented statements are characterized by a high degree of approval and emphasize, on the one hand, the obligation of patients with gastroparesis to slow down the evacuation from the stomach and the absence of a mechanical obstacle to its emptying, and, on the other hand, note, that patients with gastroparesis

may have other disorders of the motor function of the stomach (for example, disorders of stomach accommodation or antroduodenal coordination).

Important in practical terms is the noted high frequency of combining the symptoms of gastroparesis (nausea, vomiting) with the symptoms of FD (predominantly manifestations of PDS), which may be due to the common pathophysiological mechanisms of both diseases and cause difficulties in conducting a differential diagnosis [2–5].

The second section of the final document of the consensus includes statements relating to the epidemiological aspects of gastroparesis as well as its etiological factors.

Statement 2.1. The epidemiology of gastroparesis is not established, mainly because it requires gastric emptying testing which has not been done at the population level. OA: 93 %.

Statement 2.2. Diabetes is a risk factor for development of gastroparesis. OA: 100 %.

Statement 2.3. Acute gastrointestinal infection is a risk factor for development of gastroparesis. OA: 59 %.

Statement 2.4. Partial gastric resection/vagotomy, bariatric surgery, anti-reflux surgery are risk factors for development of gastroparesis. OA: 85 %.

Statement 2.5. Hypothyroidism is a risk factor for development of gastroparesis. OA: 56 %.

Statement 2.6. Some neurological disorders (e.g., Parkinson's disease, multiple sclerosis, amyloid neuropathy) are associated with increased risk for gastroparesis. OA: 90 %.

Statement 2.7. Some connective tissue diseases are associated with increased risk for gastroparesis. OA: 85 %.

Statement 2.8. Some drugs (e.g. opioids) are associated with increased risk for gastroparesis. OA: 100 %.

Since the diagnosis of gastroparesis involves the mandatory determination of the time of emptying the stomach and the exclusion of mechanical obstruction of the upper gastrointestinal tract (which can only be done with special studies), this explains the lack of population data on the frequency and prevalence of this disease.

Experts showed unanimity in assessing the proven etiological factors of gastroparesis (absent in idiopathic gastroparesis), attributing to them diabetes mellitus (OA: 100 %), surgical interventions (gastric resection, vagotomy, bariatric and anti-reflux operations) (OA: 85 %), neurological diseases (Parkinson's disease, multiple sclerosis, amyloid neuropathy) (OA: 90 %), some connective tissue diseases (OA: 85 %), taking certain medications (opioids) (OA: 100 %). Food toxicoinfections and hypothyroidism were not classified as factors contributing to the occurrence of gastroparesis (OA, respectively, 59 % and 56 %), although there are publications on the possible significance of the transferred enterovirus infection for the subsequent development of gastroparesis [6].

The third section assesses the impact of gastroparesis on the socio-economic sphere of life of patients. It was approved by the experts that gastroparesis is a significant cause of financial costs for the health care system (OA: 85 %), associated with a significant decrease in the quality of life (OA: 93 %) and such psycho-social factors as increased anxiety and depression (OA: 83 %). The statement on the ability of gastroparesis to cause weight loss did not receive the necessary percentage of approval (OA: 70 %), but when it was detected, it was considered necessary to exclude the presence of eating disorders in patients (OA: 98 %).

A comparatively high (but insufficient for acceptance) level of approval was given to the statements that gastroparesis leads to a significant financial expenditure of the patient himself (OA: 65 %), is an important reason for the decline in labor productivity (OA: 78 %), that the severity of symptoms affects the access availability of medical care (OA: 54 %), concomitant psycho-social disorders (OA: 40 %). It was not approved that gastroparesis is associated with reduced life expectancy (OA: 18 %).

The fourth section of the final document, devoted to the pathophysiological mechanisms of gastroparesis, begins rather unexpectedly with the non-acceptance of the following statement:

Statement 4.1. Delay in gastric emptying underlies symptom generation in gastroparesis. OA: 28 %.

As mentioned above, slowing down the emptying of the stomach is the cornerstone of the definition of this condition. It is logical to reason that these disorders will also play the role of a leading pathophysiological mechanism in the occurrence of complaints. In a recently published review by the leading American gastroenterologist M. Camilleri and his colleagues, who focused on gastric motility disorders [2], emphasized that the slowing down of the evacuation of solid food from the stomach, noted in gastroparesis, has as a consequence the occurrence of the main clinical symptoms of this disease: early satiety, feeling of fullness and bloating in the epigastrium after eating, nausea, vomiting, belching.

In turn, the statements on the importance in the development of gastroparesis of such factors as impaired accommodation of the stomach and increased visceral sensitivity of the stomach to stretching, although they did not gain the necessary minimum in the voting, but still received a fairly high percentage of votes (OA, respectively, 75 % and 73 %). These disorders are currently considered as important pathophysiological mechanisms of gastroparesis [2, 7].

There did not get the necessary percentage of votes the statements on the role in the occurrence of gastroparesis of such pathophysiological factors as a decrease in the content of Cajal cells in the stomach wall (OA: 60 %), loss of nerve endings in it (OA: 65 %) and smooth muscle fibers in it (OA:

53 %), dysfunction of the parasympathetic nervous system (OA: 68 %), impaired perception of signals coming from the gastroduodenal region (OA: 58 %), the presence of depression and anxiety (OA: 43 %), as well as hereditary predisposition (OA: 55 %), although in the available literature these factors play a significant role in the development of gastroparesis [2].

Despite the rather high level of approval, there was also not accepted, that such factors as *Helicobacter pylori* infection (OA: 60 %), changes in hydrochloric acid secretion (OA: 78 %), impaired release of gastrointestinal peptides (OA: 60 %), hypersensitivity duodenal mucosa to the contents of the duodenum (OA: 70 %), changes in the composition of the microbiota in its lumen (UO: 59 %). This can be explained by the inconsistency of published data on the importance of the above factors in the development of gastroparesis.

The fifth section of the final document contains statements relating to the diagnosis of gastroparesis.

Statement 5.1. Upper gastrointestinal endoscopy is mandatory for establishing a diagnosis of gastroparesis. OA: 93 %.

Performing esophagogastroduodenoscopy in patients with suspected gastroparesis should precede the assessment of the evacuation function of the stomach, since it allows to exclude mechanical obstruction, that cause disorders of gastric emptying, which is a mandatory condition for making this diagnosis.

Statement 5.3. An abnormal gastric emptying test is mandatory for establishing a diagnosis of gastroparesis. OA: 95 %.

Statement 5.4. Scintigraphic gastric emptying assessment is a valid test for diagnosing gastroparesis. OA: 98 %.

Statement 5.5. Breath test assessment is a valid test for diagnosing gastroparesis. OA: 95 %.

The need for mandatory detection of a slowdown in the emptying the stomach is inherent in the definition of gastroparesis, and gastric scintigraphy and a breath test with octanoic acid labeled with an isotope of ¹³C are currently the most common diagnostic methods for this disease [2].

There were not approved such statements, that the detection of food residues in the stomach during fasting esophagogastroduodenoscopy is a significant sign of gastroparesis (OA: 40 %), that the use of a wireless capsule and ultrasound examination of the stomach helps in the recognition of this disease (OA, respectively, 33 % and 18 %).

The most voluminous was the sixth section, which contains 39 statements concerning the currently used methods of treatment of patients with gastroparesis. There were approved statements on the advisability for such patients following dietary recommendations (OA: 85 %) and providing them with nutritional support in the form of enteral and parenteral nutrition in cases of significant weight loss or persistent vomiting (OA: 98 %).

The results of the vote on the statements regarding the effectiveness of prokinetics in the treatment of gastroparesis were contradictory.

On the one hand, there was approved the statement on the efficacy of D2-dopamine receptor antagonists in gastroparesis (OA: 86 %); on the other hand, the thesis on the effectiveness of prokinetics in this disease did not gain the necessary percentage of votes (OA: 75 %), although D2-dopamine receptor antagonists are included to this group. In addition, the statement on the efficacy of itopride, which is partially a blocker of D2-dopamine receptors was also not approved (OA: 35 %). At the same time, there was approved the statement on the effectiveness of 5-HT4-serotonin receptor agonists in gastroparesis (OA: 85 %).

Commenting on these results, it should be noted that the antagonist of D2-dopamine receptors metoclopramide is officially approved by the FDA (Food and Drug Administration) for the treatment of diabetic gastroparesis, however, serious side effects due to the central action of the drug (in particular, extrapyramidal disorders) can complicate its use [8]. Domperidone, a blocker of peripheral D2-dopamine receptors, is also proving effective in the treatment of gastroparesis [9], but its use is constrained by the possibility of this drug affecting the duration of the Q–T interval. And the 5-HT4-serotonin receptors cisapride and tegaserod are withdrawn from circulation due to the risk of developing serious cardiovascular complications. As for prucalopride, also included in this group, this drug has proven itself in the treatment of patients with gastroparesis [10], however, in accordance with the current instructions for its use, it is recommended only for the treatment of constipation.

There were not approved the statements on the effectiveness of other drugs capable of enhancing gastric motility, in particular neurokinin-1 receptor antagonists (OA: 40 %), 5-HT3-receptor antagonists (OA: 63 %), motilin-receptor agonists (OA: 58 %) and ghrelin-receptors agonists (OA: 40 %), proton

pump inhibitors (OA: 10 %), as well as tricyclic antidepressants (OA: 8 %), selective serotonin and norepinephrine reuptake inhibitors (OA, respectively, 10 % and 0 %), 5-HT1A-receptor agonists (OA: 15 %), herbal preparations (OA: 23 %), hypnotherapy (OA: 8 %), cognitive therapy (OA: 15 %), and acupuncture (OA: 3 %).

Such methods of gastroparesis treatment as electrical stimulation of the stomach (OA: 38 %), botulinum toxin (OA: 13 %), pyloric myotomy (OA: 13 %), partial or subtotal gastrectomy (OA: 18 %) were also considered as noneffective.

The seventh section of the final document of the consensus meeting is devoted to assessing the prognosis of patients with gastroparesis. There was approved the statement, that the prognosis for gastroparesis depends on its cause (OA: 88 %), and conversely, there were not approved the statements, that the current prognosis in patients with gastroparesis should be considered unfavorable (OA: 35 %) and that such patients have a shorter life expectancy (OA: 25 %).

The low level of approval of many drugs and methods of non-drug treatment of gastroparesis is explained by the residual number of conducted studies, their weak evidence base, the inconsistency of the obtained results, the use of many drugs for unregistered indications (off-label) [11–13].

Thus, an assessment of the results of voting on the statements of the final document of the ESNM consensus meeting shows, that currently there are common opinions among experts regarding the definition of gastroparesis, the range of diseases in which it occurs, modern methods of its diagnosis. At the same time, however, there is a divergence of views regarding the role of individual etiological and pathophysiological factors of gastroparesis and their possible relationship with the clinical symptoms of the disease, as well as the effectiveness of drugs of various groups and non-drug methods of treatment. All this indicates the need for further study of this actual problem.

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