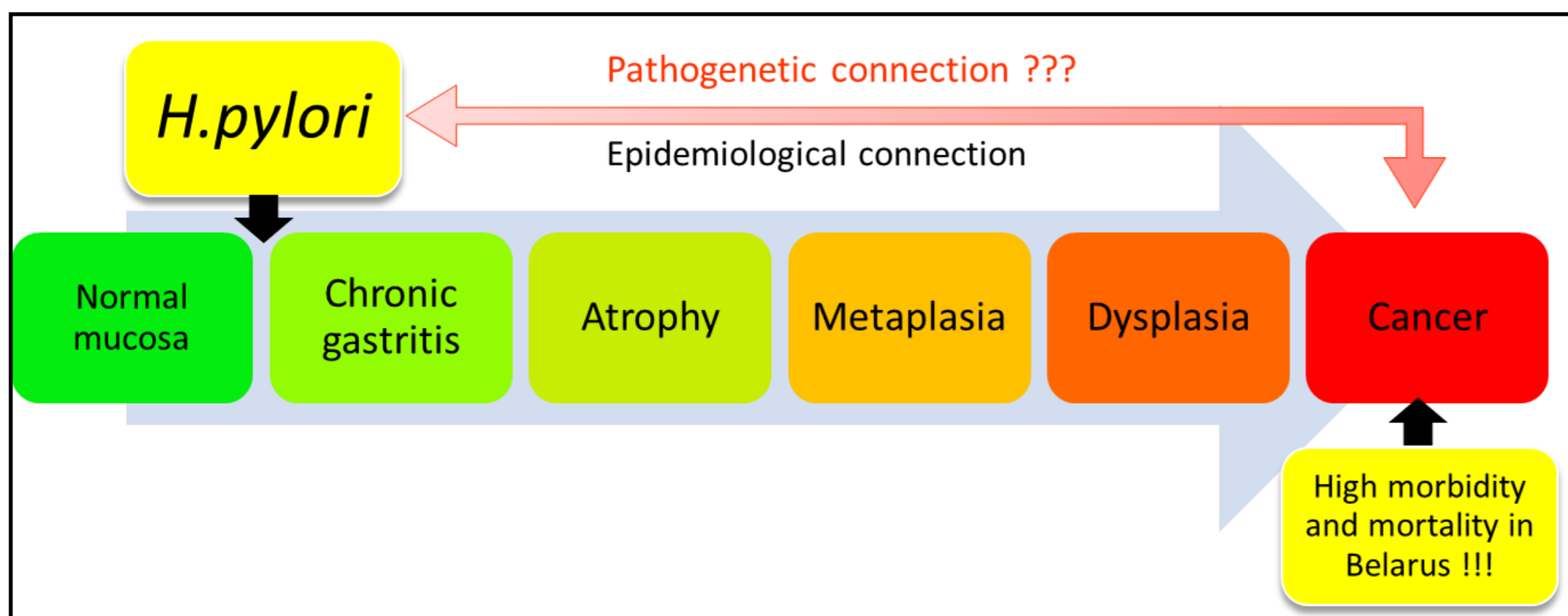




THE ROLE OF HIGH EXPRESSION OF TGFβ1 AND MYOFIBROBLAST DIFFERENTIATION IN MORPHOGENESIS OF CHRONIC ATROPHIC GASTRITIS IN YOUNG PATIENTS WITH MARFAN SYNDROME AND MARFAN-LIKE STATES

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BACKGROUND. Chronic gastritis is the most common disease of the gastrointestinal tract, and also one of the initial stages of neoplastic reorganization of the gastric epithelium - the Correa cascade. The main etiological factor triggering the Correa cascade is *H. pylori* infection. At the same time, the Republic of Belarus is one of the countries with high *H. pylori* infection and at the same time it is included in the group of the countries with high morbidity and mortality from gastric cancer (30 per 100000). This makes the study of precancerous changes in the gastric mucosa extremely important.

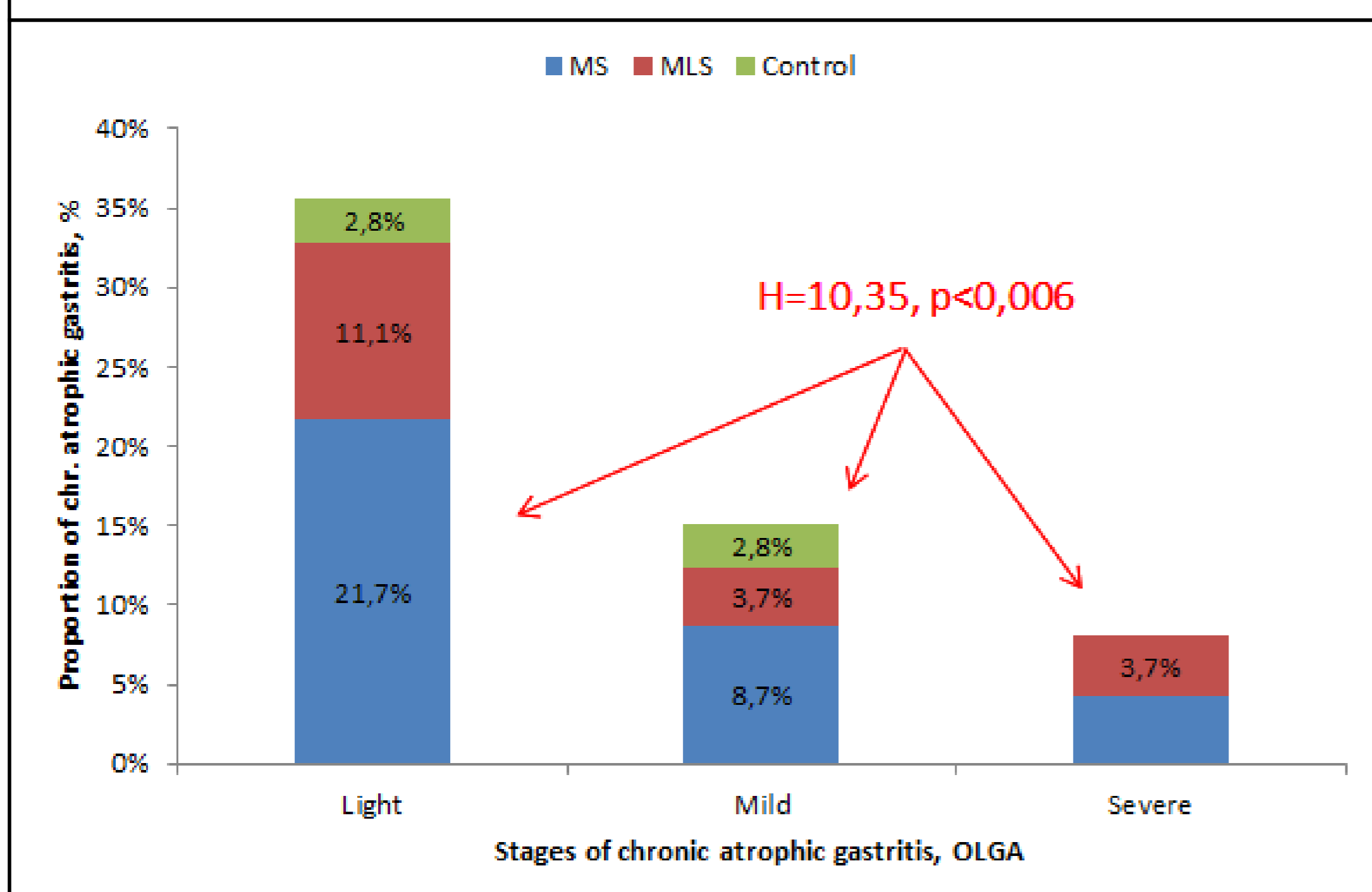
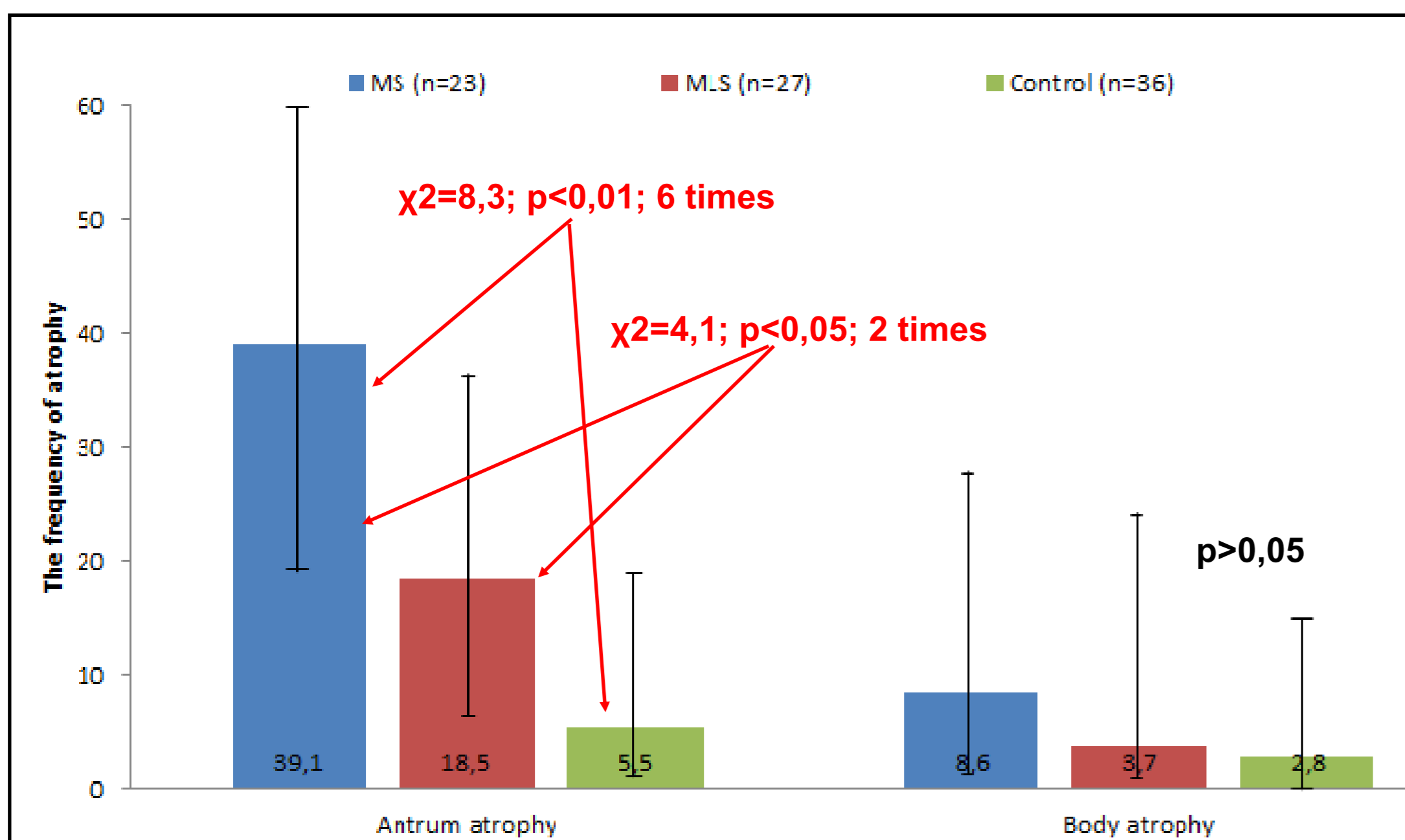


The epidemiological link between infection of *H. pylori* and gastric cancer has been proved, but direct pathogenetic mechanisms are still being studied. In a number of studies, the influence of heritable connective tissue disorders (HCTD) as an additional factor of formation of gastrointestinal pathology with an atypical clinical picture, pathomorphological features (early atrophic gastritis), and the relative role of *H. pylori* infection is shown. The classical model of HCTD is Marfan syndrome (MS), with which the main pathogenetic link is the increase in the activity of transforming growth factor-β1 (TGFβ1) in tissues (in connection with the genetic defect of fibrillin-1). At the same time, the expression of the TGFβ1 also increases in the stages of the Correa cascade.

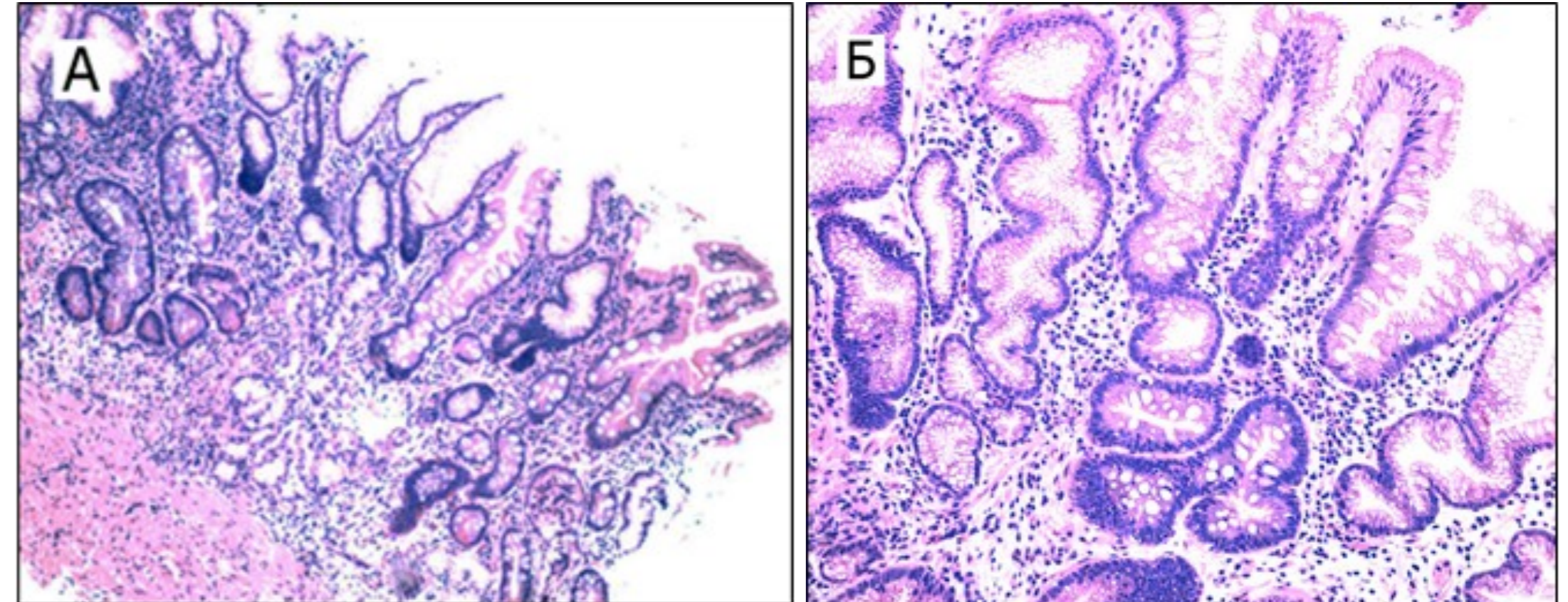
AIM. To study the severity and prevalence of chronic atrophic gastritis (CAG), and morphometric evaluation of the expression of the TGFβ1, α-smooth muscle actin (αSMA), collagen type III (Col III) in the patients with Marfan syndrome (MS) and Marfan-like states (MLS).

Methods. 89 from 24 to 42 year old patients with chronic gastritis (CG) were examined: 1-st group – MS (n=23), 2-nd group – MLS (n=28), 3-rd group – control (n=38). The degree of atrophy was scored for all specimens (OLGA). Staining of the stomach biopsies was performed by an immunohistochemical method (IHC) using antibodies to αSMA, Col III, TGFβ1. The expression index (EI) equal to the ratio of the number of positive pixels to their total number was calculated.

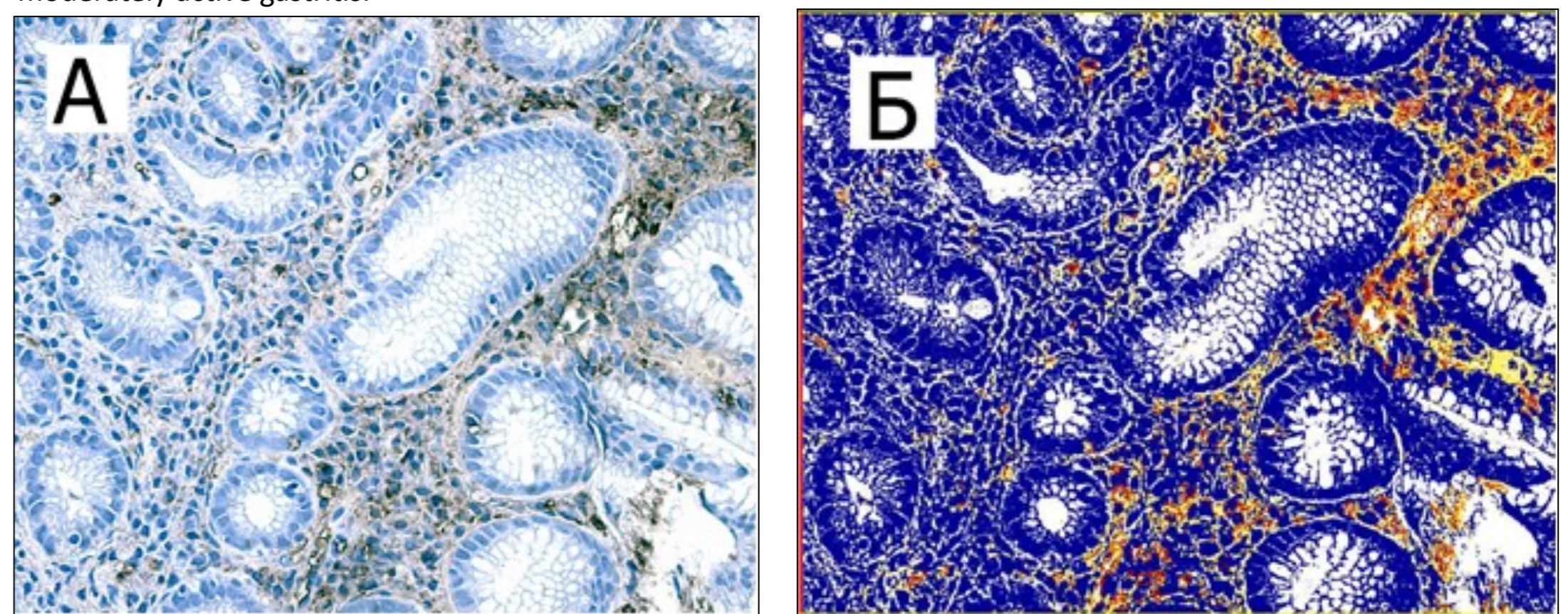
Results. The frequency of CAG in MS was 39.1%, significantly exceeding in the 2-nd group 18.5% (p<0.01)



Chronic gastritis in patients of the 1-st and 2-nd groups is accompanied by the development of atrophy and proceeds more severely, which is confirmed by the assessment of the severity of chronic gastritis according to the OLGA system



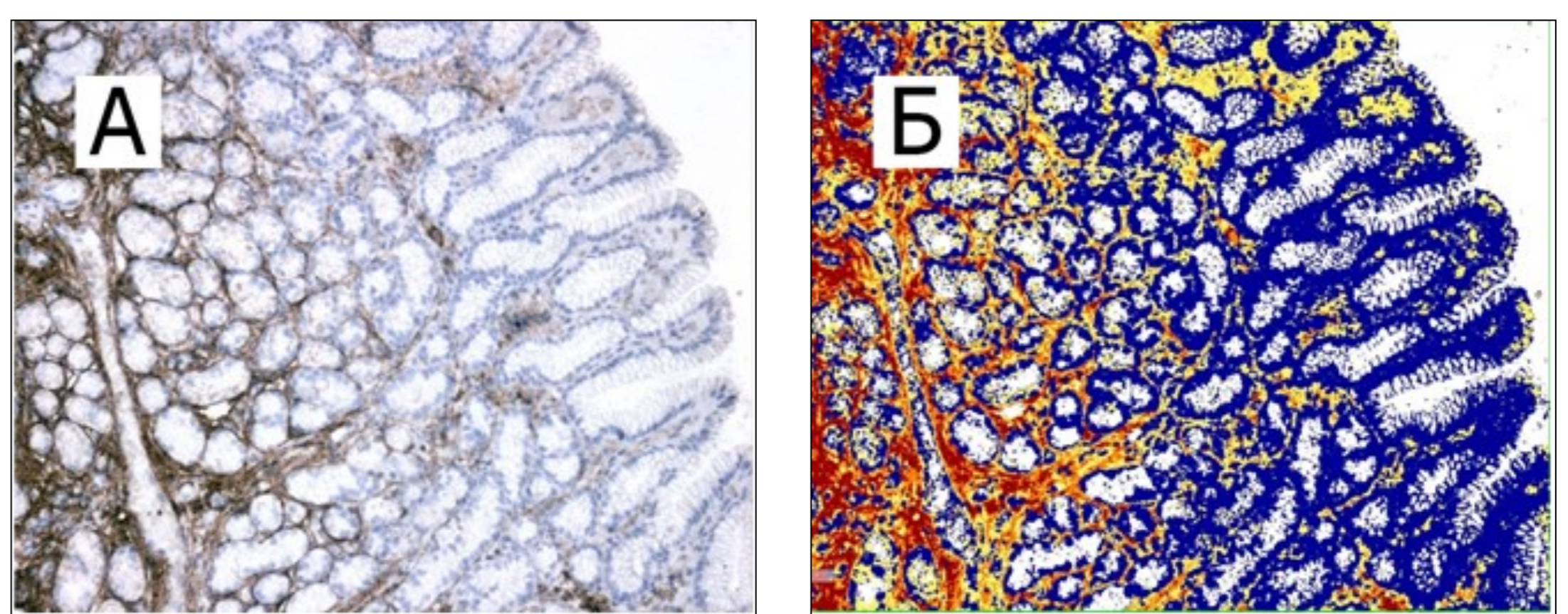
The mucous membrane of the antral stomach of a patient with MS (woman) with chronic *H. pylori*-negative gastritis. Staining with hematoxylin and eosin. A - magnification of the microscope: lens × 10. Pronounced gland atrophy, expressed intestinal metaplasia, full type, Pannet cells. Moderate, moderately active gastritis; B. - lens × 20. Deformation, tortuosity of the glands of the glands (foveolar hyperplasia), enteralization with moderately expressed, moderately active gastritis.



The expression of TGFβ1 in the epithelium of the gastric mucosa in a patient with Marfan syndrome. A - Immunohistochemical staining with antibodies to TGF-1. Chromogen diaminobenzidine; Lens × 40. B - The result of the work of the algorithm "positive pixel count" of the Image Scope (red fields - pronounced expression, orange - moderately expressed, yellow - mild, blue and white color - lack of expression). The expression index (TGFβ1) = 0.17

Immunohistochemical characteristics (expression) of TGF-β1, αSMA, Col III in the gastric mucosa in the MS and MLS

Comparison groups		Expression index			U Mann-Whitney
TGFβ1					
		25%-й Percentile	median	75%-й Percentile	
MS	n = 23	0,07	0,09	0,13	72, p<0,05
MLS	n = 27	0,04	0,06	0,1	330, p=0,09
Control	n = 36	0,03	0,05	0,07	
αSMA					
		25%	median	75%	
MS	n = 23	0,16	0,22	0,29	265, p=0,04
MLS	n = 27	0,11	0,15	0,27	112, p=0,12
Control	n = 36	0,1	0,14	0,22	
Col III					
		25%	median	75%	
MS	n = 23	0,26	0,27	0,39	272, p<0,05
MLS	n = 27	0,21	0,23	0,37	121, p=0,1
Control	n = 36	0,15	0,17	0,27	



The expression of type III collagen in the epithelium of the gastric mucosa in a patient with Marfan syndrome. A - immunohistochemical staining with antibodies to collagen type III. Chromogen diaminobenzidine, × 10. B - The result of the "positive pixel count" algorithm of the Aperio Image Scope program (red fields - pronounced expression, orange - moderately expressed, yellow - mild, blue and white color - absence of expression). Expression index = 0.39

MS revealed a higher incidence of intestinal metaplasia (up to 30.4%) compared with control (5.5%), which in 85% of cases associated with CAG. CAG in MS and MLS was characterized by expression of TGFβ1 in the 1-st group and, to a less extent, in the 2-nd group Vs the control (U=179, p=0.005, U=370, p=0.09). The 1-st group patients had higher EI of αSMA compared with the 2-nd (U=112, p=0.1) and the 3-rd groups (U=266, p=0.02). The maximum expression of Col III was noted in MS (U=131, p=0.001) and MLS (U=255, p=0.001). Conclusion. HDCT in the form of MS and MLS are adverse background factors of the course of chronic gastritis and they define a more severe course of chronic gastritis with young patients in the form of more frequent atrophy and intestinal metaplasia of gastric mucosa and are accompanied by minimal clinical manifestations with a decrease in frequency and severity of pain syndrome, there is no difference in the frequency and extent of contamination of *H. pylori*, prevalence and severity of inflammation mucosal response versus control. The key role of TGFβ1 in the activation of subepithelial myofibroblasts (αSMA+) with high expression of type III collagen in the lamina propria of the gastric mucosa was proved. MS and MLS are adverse background factors and they determine a more severe course of CG with young patients in the form of more frequent CAG. The key role of TGFβ1 in the activation of myofibroblasts (αSMA+) with high expression of Col III in the lamina propria of the gastric mucosa was proved.