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Detection of *Helicobacter suis* bacteria in pigs of different age groups

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SUMMARY

Currently, the pathogenesis of gastric ulcer in pigs remains largely unexplored. The origin of this pathology is most often associated with the type and the technologies of feeding, stresses and disorders of homeostasis of the animal body. The possible involvement of bacteria of the genus *Helicobacter* in the development of chronic gastritis and gastric ulcer disease in pigs was suggested by the researchers relatively recently. The article comprises the results of investigations aimed at detection of *Helicobacter suis* bacteria and the contamination degree of porcine gastric mucosa in pigs of different age groups. The stomachs, obtained from suckling pigs, fattening pigs and sows in the slaughterhouse of the Mari El Republic, were examined. The study determined the dependence of pathomorphological changes in the gastric mucosa of pigs on the detection of *H. suis* in microscopic and biochemical tests as well as in PCR. Thus, no pathomorphological changes in the gastric mucosa of suckling pigs were detected. Severe hyperkeratosis, erosions, and ulcers were found on the stomach mucosa of fattening pigs and sows that were infected with *H. suis* bacteria. Sows also had ulcerative lesions in the non-glandular region of esophagus. In the biomaterial of suckling piglets the DNA of *H. suis* bacteria was found only in the pyloric region of the stomach, while in fattening pigs, the DNA of these bacteria was most often isolated from the fundal region, and in sows – from the fundal and cardial regions. This indicates a shift in colonization by helicobacters of the mucous membrane of the stomach from the pyloric to the cardiac section increased with animal age. The obtained research data provide the additional evidence of the etiological role of *H. suis* in the pathogenesis of gastric ulcer in pigs.

Key words: *Helicobacter suis,* gastric mucosa, pigs, laboratory diagnostics.

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Выявление бактерий *Helicobacter suis* у свиней разных возрастных групп

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РЕЗЮМЕ

В настоящее время патогенез язвенной болезни желудка свиней остается в значительной степени неизученным. Возникновение данной патологии наиболее часто связывают с типом и технологией кормления, стрессами и нарушениями гомеостаза организма животных. Сравнительно недавно исследователями было выдвинуто предположение о возможном участии бактерий рода *Helicobacter* в развитии хронического гастрита и язвенной болезни свиней. В статье приводятся результаты исследований по выявлению *Helicobacter suis* и степени обсемененности слизистой оболочки желудка свиней разных возрастных групп. Материалом для исследования служили желудки, полученные от молочных поросят, откормочных свиней и свиноматок в убойном пункте Республики Марий Эл. Определена зависимость выявленных патоморфологических изменений слизистой оболочки желудка свиней от наличия *H. suis*, обнаруженной в микроскопических и биохимических тестах, а также с помощью полимеразной цепной реакции. Так, выраженных патоморфологических изменений на слизистой желудка молочных поросят выявлено не было. У откормочных свиней и свиноматок, у которых было установлено инфицирование бактериями *H. suis*, на слизистой оболочке желудка обнаруживали выраженный гиперкератоз, эрозии и язвы. Также у свиноматок наблюдали язвенные поражения нежелезистой части желудка в области пищеводного отверстия. У молочных поросят ДНК бактерий *H. suis* была выделена только в биоматериале из пилорического отдела желудка, тогда как у откормочных свиней наиболее часто ДНК обнаруживали в фундальном отделе, а у свиноматок – в фундальном и кардиальном отделах. Это указывает на сдвиг колонизации хеликобактериями слизистой оболочки желудка

от пилорического к кардиальному отделу с увеличением возраста животного. Полученные данные представляют дополнительные доказательства этиологической роли *H. suis* в патогенезе язвенной болезни желудка свиней.

Ключевые слова: *Helicobacter suis,* слизистая оболочка желудка, свиньи, лабораторная диагностика.

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INTRODUCTION

Helicobacter suis – is a spiral-shaped gram-negative bacterium characterized by 0.6–0.8 μm in diameter and 2.3–6.7 μm in length, forming 4–8 closely spaced spirals. Periplasmic fibrils are not observed. Such type bacteria are characterized by active motility and amphitrichous flagellation type, with 4 to 10 flagella seen at both ends of the cells. The flagella are blunt-ended or have spherical ends that are twice the mean diameter of the flagella body. *H. suis* is a non-capsulating and non-sporulating bacterium [1, 2].

For *H. suis* cultivation the following media are used: brucella agar, meat-liver peptone agar (MLPA), meat peptone agar (MPA), supplemented with 20% fetal calf serum or 10% defibrinated horse blood. The seeds are cultivated under microaerophilic and capnophilic conditions at 37 °C for 5–7 days. Slight growth of bacteria is observed under the anaerobic incubation conditions. *Spirillum*-like forms are transformed into coccoid forms in the course of cultivation in growth media [1, 3].

The possible involvement of *H. suis* in the development of chronic gastritis of the pyloric region of porcine stomach was proposed at the end of the XX century when M. M. Queiroz et al. in 1990 described in their paper a spiral organism detected in the course of microscopic examination of swabs taken from the pig stomachs [4]. Then ensued the studies performed by E. N. Mendes et al. [5], M. M. Queiroz et al. [6], C. De Witte et al. [7] and other authors who examined the correlation between the bacteria presence in the stomach mucosa and gastric ulcer disease in pigs. However, G. M. Grasso et al. [8], S. I. Melnichouk et al. [9] detected no such correlation.

It is should also be stated that currently *H. suis* – is the most prevalent (after *H. pylori*) type of *Helicobacter* in humans capable to induce diseases of gastrointestinal tract [10–12]. Nowadays the most acceptable point of view is that *H. pylori* represents an important risk factor of chronic gastritis development in humans. The study of such bacteria type led to a fundamental change in treatment of human ulcer disease. In particular, implementation of preventive measures in Moscow in 2016 led to reduction in the burden of ulcer disease by 77% and by 64% in its spread compared to 1994 [10]. *H. pylori* eradication as a strategy of stomach cancer prevention in humans in type B atrophic gastritis generates a considerable interest. Largely thanks to it, a significant reduction of stomach cancer is observed in Western Europe, USA and Japan [10, 13].

However, the pathogenesis of gastric ulcer in pigs remains largely unexplored [7]. The origin of this disease is most often associated with such factors as: ration, size of feed particles, permanent stress and homeostasis disorders in animal body. Multiple ulcer processes are observed in animal body due to metabolism disturbance, alimentary dystrophy, poisonings, infectious diseases (foot-and-mouth disease, necrobacillosis, tuberculosis). Sulfate or copper carbonate feeding, swill feeding (as well as toxic and excessive sour feed), protein and selenium deficiency, imbalance of the main and sour equivalents and hypovitaminosis are considered as the predisposing causes. Some authors claim that *H. suis* bacteria causing hyperkeratosis, erosions and ulcers play a certain role in ulcer disease pathogenesis in pigs. Various data on the spread of such type bacteria in pigs are given in papers. For example, E. N. Mendes et al. [5] detected *H. suis* in 10.8% cases, M. M. Queiroz et al. [6] – in 90%, A. Hellemans et al. [14] – in 80%. Currently it can be concluded that *H. suis* morbidity in pigs vary from 10.8 to 90.0%, but most studies report on 60% [2, 7, 11].

Influence on animal health, economic losses in pig breeding industry and zoonotic value of *H. suis* bacteria prove the necessity of a detailed study of the microorganism itself and the epidemiology of lesions which it may cause [2, 3, 15, 16].

The aim of this study is to detect *H. suis* bacteria, to determine the contamination degree of the stomach mucosa of pigs belonging to different age groups and to compare the pathomorphological changes in the mucosa with the degree of its colonization with *Helicobacter* bacteria.

MATERIALS AND METHODS

Stomachs obtained from 5 suckling pigs (1–2 months), 20 fattening pigs (8–10 months) and 4 sows (3 years) of Large White breed were used as a research material. All pigs came to a specialized slaughterhouse from one and the same holding of the Republic of Marij El during one work shift.

After the pre-mortem inspection of animals, conducted by the state veterinarian only healthy animals were allowed for slaughter. The removed stomachs were opened

by incising along the greater curvature and washed with sterile water in the slaughterhouse. The pathomorphological properties of the stomach mucosa were examined according to the method of M. J. Hessing et al. [17], who proposed to use the scale from 0 to 5, where 0 stands for the intact mucosa; 1 – moderate hyperkeratosis, covering less than 50% of the surface; 2 – severe hyperkeratosis covering more than 50% of the surface; 3 – hyperkeratosis and several small erosions (less than 5 single lesions, 2.5 cm^2 in area); 4 – hyperkeratosis and extensive erosions (more than 5 lesions and/or more than 2.5 cm^2); 5 – hyperkeratosis, large erosions (more than 10 lesions or more than 5 cm^2) and/or ulcers.

In order to evaluate the level of microorganism contamination of the stomach mucosa of cardial, fundal and pyloric stomach regions of pigs the imprint smears were prepared and subject to Gram-staining. Contamination level was determined using a semi-quantitative method by three degrees: I – to 10, II – from 10 to 20, III – more than 20 microbial bodies per light microscope with ×1000 magnification [18].

The results of microscopic investigations were proved by CLO-test, which principle is based on the property of *Helicobacter* bacteria to recover urease, an enzyme that catalyzes the hydrolysis of urea, forming ammonia and carbon dioxide. As a result of the reaction which takes place in the course of the test, the pH of the media shifts to alkaline which is identified by the indicator. Speed of the indicator colour change depends on the urease activity, which in its turn depends on the bacterial count. Thus, the colonization degree of the stomach mucosa with *H. suis* can be indirectly assessed – the higher the contamination degree the faster the speed of the indicator colour change. In order to conduct the test, biopsy samples (5 × 5 mm) were aseptically taken from the mentioned areas of the stomach mucosa in the first 10 minutes after the slaughter and were put into tubes with reagents. CLO-test results were considered after 1, 3 and 24 hours, evaluating the speed of solution colour change.

Specific detection of *H. suis* bacteria was performed by polymerase chain reaction (PCR) according to D. De Groote et al. [19]. For this purpose, the samples of mucosa from cardial, fundal and pyloric regions of the stomach were collected into Eppendorf tubes. Genomic DNA from the biomaterial was extracted using "DNA-SORBENT" reagent kit (OOO NPF "Lytech", Moscow) in accordance with manufacturer's instruction. Homologous regions of *H. suis* 16S rDNA gene 433 bp in size represented the identifiable DNA fragments. Species-specific PCR was performed using V832f TTGGGAGGCTTTGTCTTTCCA and V1261r GATTAGCTCTGCCTCGCGGCT primers, proposed by D. De Groote et al. [19], according to the following programme: 94 °C – 4 minutes; 94 °C – 30 seconds; 60 °C – 60 seconds; 72 °C – 10 seconds during 40 cycles. Detection of amplification products was performed using horizontal electrophoresis by their electrophoretic separation in 2% agarose gel with ethidium bromide added and fluorescent visualization in UV-transilluminator.

RESULTS AND DISCUSSION

Macroscopic evaluation of suckling pig stomach mucosa condition demonstrated that in 3 samples the mucosa was not damaged (0 points according to J. J. C. Hessing et al. method), in 2 samples moderate hyperkeratosis, covering less than 50% (1 point) of the surface was noticed. While testing fattening pig stomach mucosa condition the following data was obtained: in 1 sample the mucosa was undamaged (0 points), 5 samples demonstrated moderate hyperkeratosis (1 point), and 6 samples – severe hyperkeratosis (2 points), hyperkeratosis and several small erosions (3 points) were detected in 4 samples, 3 samples revealed hyperkeratosis and extensive erosions (4 points), 1 sample – hyperkeratosis and large erosions (5 points). Stomach mucosa condition of sows was characterized by severe hyperkeratosis (2 points) in 1 sample, 2 samples demonstrated hyperkeratosis and several small erosions (3 points) and 1 sample – hyperkeratosis and extensive erosions (4 points).

Imprint smears of the stomach mucosa were prepared for primary microscopy from all the stomachs obtained under the conditions of the slaughter point. The stomach mucosa fragments of intact stomachs were taken from the cardial and fundal regions incising along the greater and the lesser curvature; from the pyloric region – along the vertexes of the imaginary equilateral triangle with pylorus in the middle (at 2–4 cm distance from it). In case of stomachs with detected pathomorphological changes – from the affected sites. The obtained biomaterial was put in tubes with thioglycollate medium and transported within 2–3 hours in thermal bag with cooling agent.

While investigating the imprint smears of suckling pig stomach mucosa no microorganisms with forms typical for *Helicobacter* were detected.

In microscope examination of imprint smears obtained from fattening pig stomach mucosa curved, spiral-shaped gram-negative bacilli (0.2–0.8 μm in diameter and 2–5 μm in length) were detected in 8 of 20 stomachs in presence of stained mucus. Microorganisms with forms characteristic of *H. suis* were found in 8 samples from the fundal region of the stomachs and in 4 samples from the pyloric region, with no similar bacteria detected in the cardial region. The II degree of contamination with microorganisms was determined in 5 samples taken from the fundal region mucosa, and the III degree – in 3 samples. In imprint smears from the pyloric region of the stomach mucosa the II degree of contamination was registered in 4 samples.

Microorganisms, bearing the forms characteristic of *H. suis* were detected in 1 of 4 stomachs in the course of examination of imprint smears, taken from sow stomach mucosa. The II contamination degree of mucosa was determined in the cardial and fundal regions of the stomach. No characteristic microorganisms were detected in the imprint smear taken from the pyloric region.

Urease activity of tested samples was determined by the CLO-test. *H. suis* contamination degree of the stomach mucosa was evaluated in the test by the speed of the indicator colour change during 24 hours. If the solution colouring changed within 1 hour it indicated significant contamination of stomach with the microorganism, from 1 to 3 hours – moderate contamination, from 3 to 24 hours – insignificant *H. suis* presence in the biopsy sample (Table 1). In case of low contamination degree of the stomach mucosa, the urease activity may be insignificant and the possibility of false-negative result achievement exists. It should be noted that CLO-test represents the indirect method because it does not detect *Helicobacter* but only the urease activity which may be demonstrated by other bacteria, for example *Proteus*.

The investigation data represented in Table 1 demonstrate high urease activity detected in stomach samples obtained from fattening pigs. In biopsy samples from suckling pig stomachs no urease activity was detected.

The biomaterial taken from different pig stomach regions was tested by PCR with *H. suis* species-specific primers – V832f and V1261r. The investigation results for *H. suis* DNA presence in the mucosa of cardial, fundal and pyloric regions of the stomach are shown in Table 2.

As Table 2 shows, *H. suis* DNA was detected in the biomaterial taken from the pyloric region of the stomach of one suckling pig. *H. suis* genome was recovered from the mucosa of 17 out of 20 fattening pig stomachs, with that in 4 cases – in the cardial region, in 15 cases – in the pyloric region and in 17 cases – in the fundal region of the stomach mucosa (36 positive samples in total). While investigating the material obtained from sows, *H. suis* DNA was detected in stomachs of all 4 animals, whilst 2 samples of the stomach mucosa from the cardial region, 4 samples – from the fundal and 1 sample from the pyloric regions were found positive (7 positive samples in total).

The results of the tests performed in order to determine the presence or absence of the pathomorphological changes in porcine stomach mucosa were compared with the results of *H. suis* identification in microscopic and biochemical tests and bacterium genome detection in PCR. For this purpose, the biomaterial obtained from pigs of each age group was divided into two groups: *H. suis*-positive (*H. suis* "+") and *H. suis*-negative (*H. suis* "–") in PCR. The data on microscopic evaluation of pig stomach mucosa, microscopy and urease test were put into the corresponding groups. The results are represented in Table 3.

Table 3 shows that moderate hyperkeratosis of the stomach mucosa covering less than 50% of the surface was observed in the pyloric region of the stomach of one suckling pig from which the *H. suis* DNA was extracted. No relevant bacteria were detected by microscopic and biochemical methods. In group representing *H. suis*-negative suckling pigs moderate hyperkeratosis of stomach mucosa was detected once, however it was impossible to detect *H. suis* by any of the test methods used.

Fattening pigs demonstrated marked hyperkeratosis and erosions of the stomach mucosa in group of *H. suis*-positive animals, whereas no marked inflammatory reactions were detected in group of *H. suis*-negative animals. In microscopy of the imprint smears of the stomach mucosa gram-negative bacilli with *Helicobacter*-characteristic forms were detected in 8 samples from *H. suis*-positive group in presence of stained mucus. The samples were urease-positive in all cases. The III degree of *H. suis* contamination of fundal region stomach mucosa was determined in 2 of 3 stomachs (which macroscopic lesions were given a 4-point mark), and the II degree – in one stomach.

H. suis DNA was detected in all tested samples in PCR of sow stomach mucosa. Hyperkeratosis of cardial, fundal and pyloric regions was observed in macroscopic evaluation of stomach mucosa condition. The II degree of *H. suis* contamination was estimated in the cardial and fundal region of the stomach affected by ulcers (with a 4-point macroscopic evaluation mark) in the area of esophageal opening (its non-glandular part). All biomaterial samples gave a positive response in CLO-test.

Table 1
Contamination degree of samples from the pyloric region of pig stomachs determined by the urease activity in CLO-test

Таблица 1
Степень обсемененности образцов из пилорического отдела желудков свиней, установленная по наличию уреазной активности в CLO-тесте

Animal age group	Number of tested stomachs	Number of positive samples during		
		1 hour	3 hours	24 hours
suckling pigs	5	0	0	0
fattening pigs	20	8	14	17
sows	4	1	2	4

Table 2
***H. suis* DNA detection in pig stomach samples by PCR**

Таблица 2
Обнаружение ДНК *H. suis* в образцах желудков свиней посредством ПЦР

Animal group (number of tested stomachs)	Number of positive samples taken from the stomach mucosa			Total number of positive samples	Number of animals with *H. suis* DNA detected in stomachs
	cardial region	fundal region	pyloric region		
suckling pigs (5)	0	0	1	1	1
fattening pigs (20)	4	17	15	36	17
sows (4)	2	4	1	7	4

CONCLUSION

The epizootological investigation data on the spread of *H. suis* bacterium in pigs given in different publications differ greatly. The number of detected cases vary from 10.8 to 90.0%. It can be explained by the following reasons: firstly, ulcer disease has a multi-factor etiology; secondly, *H. suis* represents a microorganism which is difficult to extract and it was considered to be uncultivated *in vitro* till 2008; thirdly, the material for investigations was taken from animals of different age; fourthly, the mucosa samples were obtained from different regions of animal stomachs. Nevertheless, the majority of researchers report on high (60% and more) prevalence of *H. suis* among pigs.

The conducted tests demonstrated that the results of macroscopic evaluation of the stomach mucosa lesions

Table 3
Determination of dependence between the pathomorphological changes in porcine gastric mucosa and *H. suis* detection in microscopic and biochemical tests and its genome detection in PCR

Таблица 3
Определение зависимости патоморфологических изменений СОЖ свиней от обнаружения *H. suis* в микроскопических и биохимических тестах и выявления его генома в ПЦР

Animal group (number of animals)	Macroscopic evaluation of stomach mucosa lesions, points						Microscopy +	CLO-test +
	0	1	2	3	4	5		
Group 1: *H. suis* "+" suckling pigs (1)	0	1	0	0	0	0	–	–
Group 2: *H. suis* "–" suckling pigs (4)	3	1	0	0	0	0	–	–
Group 1: *H. suis* "+" fattening pigs (17)	0	4	5	4	3	1	8	17
Group 2: *H. suis* "–" fattening pigs (3)	1	1	1	0	0	0	12	0
Group 1: *H. suis* "+" sows (4)	0	0	1	2	1	0	2	4

in each age group of pigs differed. The highest level of lesions was detected in the group of fattening pigs. In *H. suis*-positive (according the PCR data) group of fattening pigs severe hyperkeratosis and erosions in stomach mucosa were mostly observed. According to the results of microscopic investigations and urease test, high level of *Helicobacter* contamination was detected in the biomaterial taken from animals belonging to this age group. In all fattening pigs *H. suis* DNA was extracted in the fundal region of the stomach. Pathomorphological changes in the mucosa of suckling pigs were insignificant or totally absent, *H. suis* DNA was extracted in one out of five stomachs tested. Stomach mucosa condition of sows was characterized by moderate lesions, however, *Helicobacter* were detected in all mucosa samples in the course of microscopic investigations, biochemical tests and PCR.

In suckling pigs *H. suis* was found in the pyloric region of the stomach, thus, in fattening pigs – it was more often detected in the fundal region, and in sows – in fundal and cardial regions. This may indicate a shift in *Helicobacter* colonization of stomach mucosa from the pyloric to cardial region with the increase of the animal age.

The results obtained show that *H. suis* may be one of the factors playing a certain role in the development of pig stomach ulcer pathogenesis.

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