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GENOTYPING OF FN1 AND VWF GENE POLYMORPHISMS IN PROGNOSIS, PREVENTION AND TREATMENT OF PERITONEAL ADHESION DISEASE

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Adhesion disease of the peritoneum is one of the difficult and unsolved problems of surgery. The polymorphism of the FN1 and VWF genes was detected by the cytogenetics method through the cultivation of peripheral blood leukocytes and the technology of preparing chromosomal preparations with differential methods of chromosome staining, and in the presence of the FN1 and VWF gene polymorphisms, the development was predicted adhesion disease. 45 patients were classified into 3 groups: 15 people who underwent planned surgery for incisional ventral hernias; 15 people who were urgently operated on for acute adhesion intestinal obstruction; 15 people who were not operated on the organs of the abdominal cavity. The analysis of the results of the examination of genetic factors in patients with different degrees of severity and prevalence of peritoneal adhesion disease in patients with acute adhesion intestinal obstruction indicates the presence of a relationship between the pronounced polymorphism of the FN1 and VWF genes and the severity of the manifestation of the adhesion disease syndrome. In the presence of chromosomal aberrations, corresponding biochemical disorders are observed.

Key words. Adhesive disease of the peritoneum, acute adhesive intestinal obstruction, polymorphism of the FN1 and VWF genes.

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ГЕНОТИПУВАННЯ ПОЛІМОРФІЗМУ ГЕНІВ FN1 І VWF У ПРОГНОЗУВАННІ, ПРОФІЛАКТИЦІ І ЛІКУВАННІ СПАЙКОВОЇ ХВОРОБИ ОЧЕРЕВИНИ

Спайкова хвороба очеревини є однією зі складних та невирішених проблем хірургії. Поліморфізм генів FN1 та VWF був виявлений цитогенетичним методом шляхом культивування лейкоцитів периферичної крові та технології приготування хромосомних препаратів диференціальними методами фарбування хромосом, і за наявності поліморфізмів генів FN1 та VWF прогнозувався розвиток спайкової хвороби. 45 пацієнтів були класифіковані на 3 групи: 15 осіб, яким було проведено планове хірургічне втручання з приводу післяопераційних вентральних гриж; 15 осіб, яким було проведено термінову операцію з приводу гострої спайкової кишкової непрохідності; 15 осіб, яким не було проведено операцію на органах черевної порожнини. Аналіз результатів дослідження генетичних факторів у пацієнтів з різним ступенем тяжкості та поширеності перитонеальної спайкової хвороби у пацієнтів з гострою спайковою кишковою непрохідністю вказує на наявність зв'язку між вираженим поліморфізмом генів FN1 та VWF та тяжкістю прояву синдрому спайкової хвороби. За наявності хромосомних аберацій спостерігаються відповідні біохімічні порушення.

Ключові слова: спайкова хвороба очеревини, гостра спайкова кишкова непрохідність, поліморфізм генів FN1 та VWF.

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Adhesion disease of the peritoneum is one of the difficult and unsolved problems of surgery. The number of patients is constantly increasing, which is due to the increase in the number and volume of surgical interventions on the organs of the abdominal cavity. Etiological factors of formation of adhesions are diverse. These include: 1) mechanical damage to the peritoneum, 2) ingress of foreign material into the abdominal cavity, 3) infectious inflammation of the peritoneum; 4) genetic predisposition [2, 7].

Operations are and remain the main cause of adhesions. According to the authors, 10.4 % of patients develop adhesions after one laparotomy, and 70-93 % after secondary laparotomy [6].

Adhesive disease of the peritoneum causes acute intestinal obstruction in 32 % of cases, of which in 75 % of cases – acute adhesive small intestinal obstruction. In 5.0–23.2 % of cases of operations for adhesion disease, there is a need for resection of the intestine [3].

From the first minute, a serous-fibrinous exudate (fibrinogen, fibronectin and other components) appears at the site of damage to the peritoneum, in which there are various cellular elements. From the end of the second day on the peritoneum, you can observe gentle fibrous strands. Postoperative paresis of the intestine supports the direct contact of these surfaces, which makes it possible for 2-3 days for the process of the development of adhesions to develop calmly. Appearing on the 3rd day, the peristaltic movements of the intestines are no longer able to separate the glued surfaces, and adhesions become stable and strong [7, 8].

Prediction and prevention of adhesion disease are extremely important. Laparoscopic technologies are developing at a fast pace, but long surgical interventions drain the abdominal cavity, which is a pathogenetic factor for the development of adhesions

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[2, 10, 11]. That is, neither the improvement of methods of surgical treatment of diseases of the abdominal cavity, nor the emergence of new endosurgical technologies reduce the frequency of adhesions, an important aspect of solving the problem remains the development of a complex of therapeutic, diagnostic and preventive methods [4]. In the pathogenesis of the development of adhesions, the main role belongs to genetic predisposition.

The FN1 (fibronectin-1) gene in humans is located on the short arm (p) of chromosome 2. More specifically, it is located at position 2q34, encoding a protein responsible for cell adhesion, migration, and maintenance of the extracellular matrix. The FN1 gene takes an active part in the formation of fibronectin (plasma and cellular). Fibrinonectin plays a major role in the acute phase of inflammation, in the processes of cell adhesion, angiogenesis, has a collagen binding domain (joining procollagen fibrils) and 2 domains for heparin binding, two sites for interaction with fibrin. The VWF gene has domains responsible for the synthesis of a multimeric glycoprotein, which is involved in platelet adhesion during acute inflammation and damage to the vascular wall, collagen binding, and acts as a cofactor for blood coagulation factor VIII. The collagen binding domain of the VWF (located on the short arm of the XII chromosome) gene is practically not studied. In the pathogenesis of the development of adhesions, aberrations of the genes are manifested in biochemical changes in the blood, which leads to adhesion formation [6].

The purpose of the study was to improve the results of diagnosis, prevention and treatment of patients with adhesive intestinal obstruction.

Materials and methods. The study was conducted at the Department of Surgical Diseases of the Ivano-Frankivsk National Medical University, Surgical Department of the Central City Clinical Hospital for the period from May 2021 to December 2025. The polymorphism of the FN1 and VWF genes was detected by the cytogenetics method through the cultivation of peripheral blood leukocytes and the technology of preparing chromosomal preparations with differential methods of chromosome staining, and in the presence of the FN1 and VWF gene polymorphisms, the development was predicted adhesion disease. According to international rules, it is mandatory to use the standard method of differential chromosome staining with the following steps: colchicine, hypotonic KCl solution, use of “PBmax” culture mixtures, fixation with alcohol, preparation of slides.

Patient groups were selected depending on the type of surgical intervention. 45 patients of the studied population sample, depending on the detected syndrome complex, were classified into 3 groups: 1st group – 15 patients who underwent planned surgery for incisional ventral hernias (IVH) – herniolaparotomy, hernia plastic surgery was performed; 2nd group – 15 patients who were urgently operated on for acute adhesion intestinal obstruction (AAIO); The 3rd group – 15 people who were not operated on the organs of the abdominal cavity – the control group. The patients' ages ranged from 18 to 60. There were equal numbers of women and men. The study included patients with a body mass index from 17.0 to 39.9. The groups were statistically representative of the main parameters (gender, age, body mass index). Patients with severe comorbidities were not included. That is, untreated viral hepatitis, heart failure, myocardial infarction, stroke, deep vein thrombosis up to 3 months, pulmonary embolism up to 6 months, and decompensated diabetes mellitus were exclusion criteria. In accordance with international Good Clinical Practice guidelines, elderly people, prisoners, pregnant women, cognitively impaired, economically disadvantaged, ethnic minorities, and refugees were also not included in the study. The study was conducted in accordance with the expert opinion of the Ethics Commission of the Ivano-Frankivsk National Medical University regarding compliance with ethical principles in conducting the department's scientific and research work. Protocol No. 121/21 dated 13.05. 2021.

Direct chromosomal analysis involved the following sequence of actions: 1) visual quantitative analysis of preparations under a microscope (CCD video camera Kocom digital, digital camera Nikon Coolpix 5400, professional monitor Sony Trinitron HR), which means counting pro- or metaphase chromosomes within one plate and corresponding entry in the cytogenetic analysis protocol of 30 cells; 2) complete analysis of chromosomes in the plate, which means counting the chromosomes in the plate and segment-by-segment comparison of the homologues of each pair of chromosomes – 5 cells out of the 30 analyzed cells; 3) analysis of chromosomes in the plate using an ideogram obtained using a computer program or photography (image analysis software ImageTool for Windows V.3 and ImageJ open source programs, SEO ImageLab Bio program for morphometric and densitometric studies) – 4 cells out of 5 cells analyzed; 4) karyotyping by comparing the obtained layout (ideogram) with the image under a microscope – 2 cells out of 4 analyzed cells. In case of detection of mosaicism, a karyotyping procedure of at least one cell of each clone was performed.

With the help of immunoenzymatic kits Fibronectin ELISA and vWF:CBA ELISA, a study of quantitative indicators of blood fibronectin and collagen binding activity of the Willebrand factor was carried out.

The prevalence of the adhesion process was assessed according to the classification of O. I. Blinnikov: 1) stage I – a local adhesion process, limited to the area of the postoperative scar or part of the abdominal cavity, spread over no more than one

floor, in the absence of adhesions in other areas; 2) II stage – a local adhesion process in combination with single adhesions in other areas; 3) III stage – adhesion process spread over 1/3 of the abdominal cavity; 4) IV stage – a diffuse adhesion process spread over 2/3 of the abdominal cavity. For the reliability of the data, patients with the III and IV stages of the adhesion process were selected into the main and control groups.

According to the international classification RAI (Peritoneal adhesion index), patients included at least 5 out of 9 areas of the abdomen in the adhesion process.

The severity of the adhesion process was assessed according to the classification of Q. Zeng et al.: 0 degree – absence of adhesions; 1st degree – the least severe: thin, avascular, transparent, loose, easily separated by blunt means; 2nd degree – medium severity: medium thickness and transparency, partially vascularized; 3rd degree – extremely severe: very dense and highly vascularized.

The study included patients with 2 and 3 degrees of severity of adhesions.

Indications for surgical intervention of patients with AAIO: conservative treatment for more than 72 hours: pain for more than 4 days; signs of intestinal strangulation; peritonitis clinic; operation for 6 weeks before AAIO; discharge of more than 500 ml per day by nasogastric or duodenal tube; CRP more than 75 mg/l; leukocytosis more than 15,000.

Rehabilitation (Fast-track) of patients after surgery: early activation of the patient after adheolysis for 1 day after surgery; early tube electrolyte nutrition and nutrition (advantage of high intubation of the small intestine); by the end of the second day, activation of peristalsis, to achieve the release of gases; mandatory intake of a prophylactic dose of hypocoagulants (based on pathogenesis) regardless of the patient's age, even if there is no risk according to the Caprini scale); use of rectal suppositories with streptokinase and streptodornase (with risk factors according to the “severe scheme”).

Statistical analysis of the results was performed using the MedCalc program, the latest version 23.0.2.

Results of the study and their discussion. In 45 patients, the frequency of possible mutations of the genes FN1 (located on the short arm of chromosome II) and VWF (located on the short arm of chromosome XII) was studied. Out of 900 examined cells, 535 (59 % of the total number) with cell associations were found, of which 17 cells had 2 or more associations (Figs. 1, 2, 3, 4).

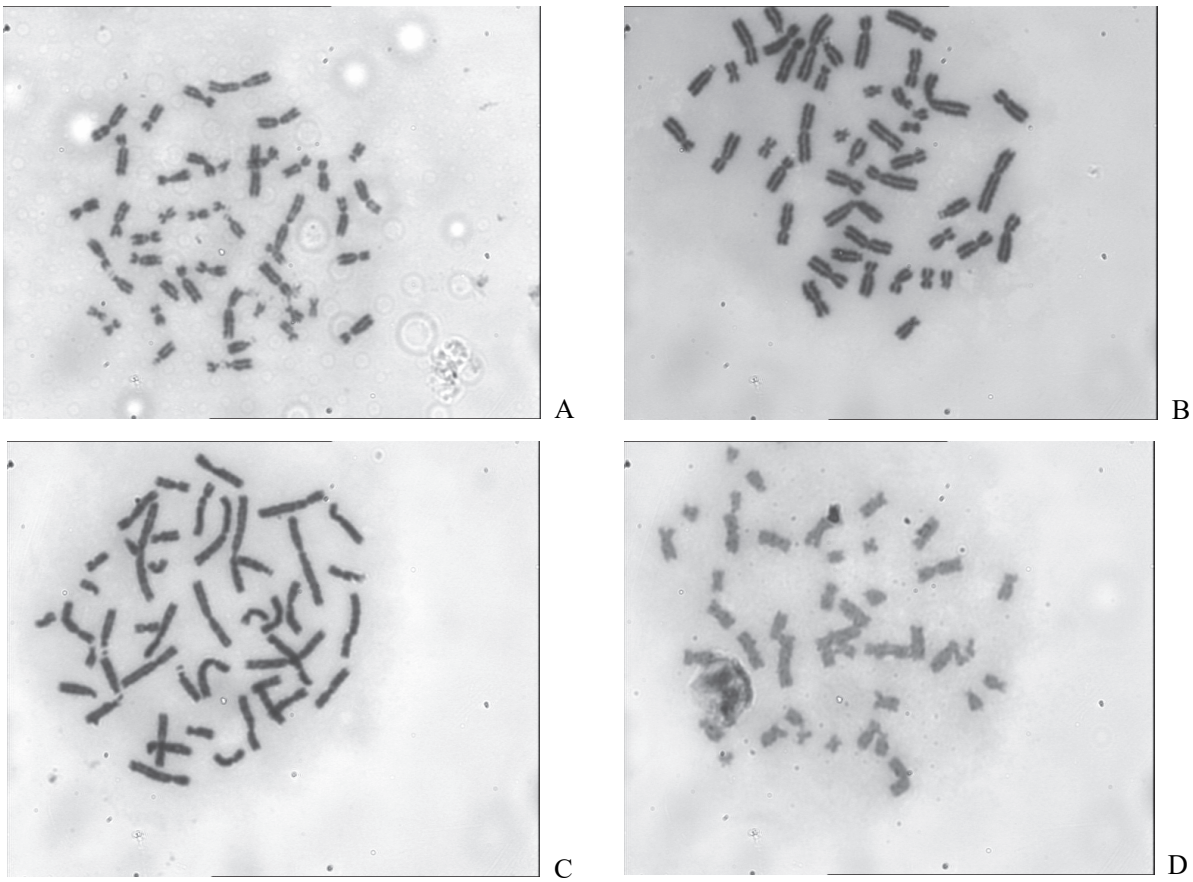

Fig. 1. Chromosomal association, aberration and breaks. A – an example of a D + chromosomal association. B – an example of an aberration of the second chromosome. C – the gap of the twelfth chromosome. D – a gap and a chromosome break.

The analysis of the results of the examination of genetic factors in patients with different degrees of severity and prevalence of peritoneal adhesion disease (PAD) in patients with AAIO indicates the presence of a relationship between the pronounced polymorphism of the FN1 and VWF genes and the severity of the manifestation of the adhesion disease syndrome (Table 1).

Table 1

Distribution of genome aberrations in different groups of patients

Group of patients	Types of genes (number of aberrations)		
	FN1	VWF	Other genomes
1 (15 patients), IVH	-	1	9
2 (15 patients), AAIO	3	3	5
3 (15 patients), control	-	1	5

Note: P=0.013. Spearman's rank correlation for the second group 0.17. Xi square 13.0. Mann-Whitney U coefficient 21.0.

Thus, in the presence of 2 mutant genes FN1 and VWF in patients with AAIO, the number of symptoms characterizing the severe course of PAD was maximal. In the IVH group, the presence of aberrations of other genomes, including ITGA 2, indicates a violation of the quality of collagen protein synthesis, especially type V. It is necessary to differentiate PAD in patients with manifest AAIO and patients with IVH (Table 2).

Table 2

Results of immune-enzyme research

Group of patients	Parameters of immune enzyme research	
	Fibronectin dilution, 200	vWF
1 (15 patients), IVH	56.72±2.01	1.2±0.41
2 (15 patients), AAIO	114.93±3.28	1.67±0.49
3 (15 patients), control	45.53±1.52	1.06±0.25

Fibronectin statistical indicators were processed. P<0.00001. Spearman's rank correlation 0.15. Xi square 42.7. Mann-Whitney coefficient 21.5. Taking into account the different data of the three groups, rank and concordance coefficients were used.

Friedman's rank coefficient 24.4. Kendapp's concordance coefficient 0.82. VWF statistical indicators were processed. P<0.00226. Spearman's rank correlation for the second group 0.19. Xi square 4.15. Mann-Whitney coefficient 22.5.

Taking into account the different data of the three groups, rank and concordance coefficients were used. Friedman's rank coefficient is 12.18. Kendapp's concordance coefficient is 0.41.

The analysis of the results of examination of genetic factors and immunoenzyme indicators clearly showed their connection. In the presence of chromosomal aberrations, corresponding biochemical disorders are observed.

One of the ways to prevent postoperative adhesions is not only the development of modern methods of surgical interventions, intact suture materials and modern implants, but also the search for new methods of preventing postoperative adhesions using anti-adhesion drugs [9].

The most famous anti-adhesion drugs are compounds based on carboxymethylcellulose and hyaluronic acid, polysaccharides that form a barrier between the abdominal organs, preventing fibrin and adhesion from getting on them. Indications for the use of anti-adhesion drugs are unclear, there are no clear algorithms and instructions for use in general surgery. Because of this, most surgeons avoid their use [15].

Some surgeons and scientific publications overestimate the role of hyaluronic acid. It has been proven that hyaluronic acid-based drugs are ineffective in patients with acute intestinal obstruction. It is necessary to find a new drug or combination of drugs for use during operations for acute intestinal obstruction [10].

There is a known method of predicting susceptibility to adhesion disease by analyzing the genetic tree and hereditary susceptibility. The disadvantage of this technique is the lack of description of the genome responsible for adhesion disease, the difficulty of predicting the transmission of specific etiopathogenetic genes from generation to generation. It is also known to predict peritoneal adhesion disease by isolating deoxyribonucleic acid from peripheral blood lymphocytes and genotyping the etiopathogenetic gene for the development of adhesion disease ITGA 2 by the polymerase chain reaction method (Denys Yevtushenko, Valery Volodymyrovych Boyko; Kharkiv National Medical University). The ITGA 2 gene is not a highly specific etiopathogenetic factor in the development of adhesion disease, but is a marker of the collagen-binding activity of platelets. It is used to detect genetic predisposition to myocardial infarction, ischemic stroke, thromboembolic complications.

The acetylation phenotype in children was studied as a risk factor for pathological adhesion formation. It was found that in patients with postoperative peritoneal adhesion disease, the rapid acetylation phenotype prevailed. The opposite results were studied regarding the slow acetylation phenotype. Many clinical studies have studied disorders of the oxidant-antioxidant system and energy metabolism in children and adults. But all these disorders are visible during the development of the pathological process [6]. Predicting the development of adhesion disease is practically impossible.

The basis of the study is the task of improving the method of predicting adhesion disease by

isolating deoxyribonucleic acid from blood and identifying polymorphisms of highly specific pathogenetic genes for the development of adhesion disease of the peritoneum.

Genotyping was carried out by cytogenetics, FN1 and VWF genes were selected as etiopathogenetic genes, their polymorphism was detected by culturing peripheral blood leukocytes and the technology of preparing chromosomal preparations with differential methods of chromosome staining, and in the presence of chromosomal mutations of FN1 and VWF genes, the development of peritoneal adhesion disease was predicted.

Treatment of peritoneal adhesions in a hospital is quite expensive, with a high incidence of complications [12]. The task of the research was to expand the arsenal of effective methods of predicting adhesion disease of the peritoneum, due to the synergism of genetic and biochemical disorders.

The preliminary results obtained stimulate a deeper study of genetic disorders in patients with acute adhesive intestinal obstruction, the severity of the manifestation of adhesive disease.

Limitations. The sample size, while balanced, was relatively small, which may limit generalizability and statistical power. Additionally, only female patients were included, which, although justified due to higher continence risk, limits the application of results to broader mixed-gender populations. A five-year period is a short period to study this pathology. Also, patients of other races may have different genetic pathologies. There are very few publications and clinical experience on the relationship between peritonitis and the severity of peritoneal adhesive disease.

Conclusion

For the first time, a mutation in the FN1 and VWF genes and a connection with biochemical disorders and the severity of the adhesion process were identified in the studied group of patients with acute adhesive intestinal obstruction. The detection of polymorphisms of these genes at a young age requires new approaches to prevention and treatment in the future. New etiopathogenetic approaches to the prevention and treatment of peritoneal adhesive disease are needed, as well as the search for new barrier agents. Further study of the severity of adhesive disease and complicated intra-abdominal infection is necessary.

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