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THE INFLUENCE OF CHRONIC NON–CALCULOUS CHOLECYSTITIS ON THE COURSE OF CORONARY HEART DISEASE

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Diseases of the gallbladder and biliary ducts, particularly, chronic non–calculous cholecystitis is a common pathology of internal organs. In addition, with chronic non-calculous cholecystitis, a reflex disorder of the coronary blood circulation, metabolic and autoimmune dystrophic lesions of the myocardium and its conduction system, which can affect the contractile function and heart rhythm, are found. Significant prevalence of these two diseases, high level of work incapacity and disability determine the relevance of the problem of the combined course of these diseases. The purpose of the work was to determine the characteristics of the course of coronary heart disease with concomitant chronic non–calculous cholecystitis, taking into account the functional state of the cardiovascular system. The total of 88 patients who were on outpatient treatment was examined. The clinical course of stable effort angina of functional classes I and II with concomitant chronic non–calculous cholecystitis is characterized by more pronounced clinical manifestations of cardiac pathology, an increase in resistance to drug treatment, and a decrease in exercise tolerance. Coronary heart disease without hronic non–calculous cholecystitis occurs as an independent disease and is not accompanied by changes in the biliary system. Lipid peroxidation enhancement plays a role in increasing the clinical manifestation of coronary heart disease with concomitant inflammation of the gallbladder. Complication of the clinical course of coronary heart disease with simultaneous chronic non–calculous cholecystitis correlates with more pronounced atherogenic lipid metabolism, activation of lipid peroxidation processes and antioxidant protection deficiency in the blood, impaired hemostasis and inhibition of the heart contractile function. Chronic non-calculous cholecystitis significantly complicates the course of coronary artery disease with stable angina of functional classes I–II: more pronounced changes in the lipid spectrum, indicating the rapid development of atherosclerosis, combination of pain in the heart and right hypochondrium, severe dyspeptic syndrome.

Key words: coronary heart disease, chronic non–calculous cholecystitis, lipid peroxidation, stable angina, antioxidant protection

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ВПЛИВ ХРОНІЧНОГО НЕКАЛЬКУЛЬОЗНОГО ХОЛЕЦИСТИТУ НА ПЕРЕБІГ ІШЕМІЧНОЇ ХВОРОБИ СЕРЦЯ

Захворювання жовчного міхура та жовчовивідних шляхів, зокрема хронічний некалькульозний холецистит є поширеною патологією внутрішніх органів. При хронічному некалькулезном холециститі встановлено рефлекторне порушення коронарного кровообігу, метаболічний і аутоімунне дистрофічні ураження міокарда і його провідної системи, що може впливати на скоротливу функцію і ритм серця. Метою роботи було визначення особливостей перебігу ішемічної хвороби серця з супутнім хронічним некалькульозним холециститом з урахуванням функціонального стану серцево–судинної системи. Обтяження клінічного перебігу ішемічної хвороби серця при супутньому хронічному некалькулезном холіцістіт корелює з більш вираженими змінами ліпідного обміну атерогенного характеру, активацією процесів перекисного окислення ліпідів і дефіцитом антиоксидантного захисту в крові, порушенням гемостазу і пригніченням скорочувальної функції серця.

Ключові слова: ішемічна хвороба серця, хронічний некалькульозний холецистит, перекисне окислення ліпідів, стабільна стенокардія, антиоксидантний захист.

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The real feature of the modern patient is comorbidity. Thus, a single patient has several diseases simultaneously. Concomitant pathology affects the course, clinical picture and the consequences of the disease as a whole. Now, despite intensive research in the field of cardiology, aimed at development and implementation of new traditional methods for diagnosis, treatment and prevention, cardiovascular disease, and first of all coronary heart disease (CHD), according to WHO remains a very common pathology and the major cause of death throughout the world (12 million every year, 50% of all deaths) [4,5].

In recent years, the processes of lipid peroxidation (LPO) and the antioxidant protection deficiency (AOD), which is an inhibitor of non-enzymatic free radical oxidation (FRO), have acqured great importance in the CHD pathogenesis In addition, atherogenic shifts in lipid metabolism contribute to acceleration of the atherosclerotic process [2, 3]. At the same time, deterioration in blood viscosity characteristics correlates with the severity of the clinical course in coronary heart disease. It is known that in CHD regional blood circulation disorder develops in different organs and systems, particularly in the hepatobiliary system [6, 9, 10].

In addition, diseases of the gallbladder and the biliary ducts, including chronic non-calculous cholecystitis (CNCC), are a common pathology of the internal organs [1]. Besides, reflex disorder of the

coronary circulation, metabolic and autoimmune dystrophic lesions of the myocardium and its conduction system, that can influence the contractile function and the cardiac rhythm, have been established with CHD [8, 12]. This correlation is confirmed by the fact that patients with CHD also experience an increase in LPO, AOP suppression, and lipid metabolism disorder. High prevalence of these two diseases, high level of work incapacity and disability make the problem of the combined course of these diseases relevant [7, 11].

The current literature does not contain complete reflection of changes in these two diseases simultaneous course.

The purpose of the work was to determine the features of the coronary heart disease course with concomitant CNCC taking into account the functional status of the cardiovascular system.

Materials and methods. The totals of 88 patients were examined on outpatient treatment in the non-profit municipal enterprise **"**City Polyclinic No. 26**"** of the Kharkiv City Council, which is the base of the General Practice-Family Medicine Department at V.N. Karazin Kharkiv National University. The control group (CG) included 20 healthy individuals. The age of the surveyed was 36 to 60 years (mean age was 47.0±1.6 years). The ratio of men and women in the groups was 3:1. All patients were examined by a cardiologist and gastroenterologist with the both diagnoses confirmation.

According to the results of complex clinical laboratory, biochemical and instrumental examination, all patients were distributed into two groups: group I – CHD patients with concomitant CNCC –48 patients, group II – 40 patients with CHD (effort angina of functional classes I and II) without CNCC.

To verify the diagnoses of CHD and CNCC, a set of clinical–laboratory, biochemical, and instrumental research methods was used. To characterize the severity of angina patients' condition a functional classification according to the Canadian Association of Cardiologists was used based on the patient's tolerance to physical exercise. CNCC was classified according to International Classification of Diseases, 10th Edition ICD–10 (1998) (K.81.1).

The state of lipid peroxidation (LPO) was assessed by the content of malondialdehyde (MDA) in the blood serum and erythrocyte membranes according to the method by M.S. Honcharenko and A.M. Latinova, the state of antioxidant protection (AOP) – by the content of catalase in the blood serum by Bach method, the content of ceruloplasmin – by Revin method. Assessment of lipid spectrum was studied by the total blood serum cholesterol (TSC), low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, serum triglyceride (TG). Ultrasound examination of the gallbladder (GB) was carried out in fasting state. The GB contractile function was assessed by the GB emptying coefficient EC=(V_0–V'/V_0x100%) and the contractility index (IC = Vmax/Vmin).

The physical activity test was performed by the method of paired cycle ergometer tests. On the day of the study, the first VEM test was performed no earlier than 2 hours after a light breakfast and no earlier than 1–1.5 hours after the last nitroglycerin intake. The studies were carried out at rest and when the patient was performing a step–by–step exercise with the "Veloergotest –Rhythm" bicycle ergometer in the patient's sitting position, with a constant pedaling velocity of 60 revolutions per minute, starting with a power of 25W. Each successive step exceeded the previous one by 25W. The studies were carried out at the stage of complete compensation in the patient.

Statistical data processing was performed using Statistica 6.0 software. Data are presented as M±m. The differences between the groups were considered reliable at $p<0.001$.

Results of the study and their discussion. In patients of group I, burning – in 20 (41.66%), compressive – in 14 (29.16%) and aching – in 14 (29,16%) pain, that occurs in the region of the heart, was observed. 20–30 minutes after the heart pain there occurs pain in the right hypochondrium. When these two diseases are combined, the pain occurs at night, similar to Prinzmetal's angina attacks. Shortness of breath was recorded in 18 (37.5%) patients.

Dyspeptic syndrome was detected in 35 (72.9%) patients. Objective examination showed positive symptoms in the gallbladder: Kerr – 9 (18.75%), Musset–Georgievsky – 6 (12.5%), Ortner – 17 (35.4%). According to the survey echolecystography, the signs of the inflammatory gall bladder (GB) impairment were more pronounced, the greatest was the initial size of the GB. Dynamic echocholecystography showed an increase in the latent period duration, a low rate of GB emptying.

A characteristic feature of patients in group I is a significantly increased blood content of TSC, LDL, TG compared to patients of group II (8.1±0.3 mmol/l and 5.8±0.5 mmol/l, $p<0.05$); (3.11 ± 0.14 mmol/l and 2.34 ± 0.06 mmol/l, $p<0.05$); (3.3±0.13 mmol/l and 2.54±0.08 mmol/l, $p<0.05$). The difference in the increase of these parameters level in patients with coronary heart disease who had CNCC and patients with coronary heart disease without biliary system diseases, indicates an earlier development of atherosclerosis, its

rapid progressing and more severe course in the patients of clinical group I compared to the patients of clinical group II .The HDL indices in patients of group II did not differ from those of the control, and in patients of group I they were somewhat reduced and amounted (1.18±0.06 and 1.06±0.02 mmol/l), respectively.

In patients of group II typical angina attacks were observed – compressive pain behind the sternum, or in the heart area with irradiation into the left arm, shoulder, lasting from 1–3 to 10 minutes. The pain was relieved with nitroglycerin. Among the patients examined, effort angina of functional class I was established in 21 (52.5%) patient and effort anginaof the functional class II was established in 19 (47.5%) patients. In 11 patients (27.5%), ECGs reported the presence of supraventricular extrasystoles (SVE) and ventricular extrasystoles (VE), not more than 2–5 in 1 minute.

Analyzing the clinical data of patients with coronary heart disease, it should be noted that in 8 patients (20%) pain occurred in the heart area, in 26 (65%) – it was retrosternal and in 6 (15%) – epigastric pain. In 18 patients (45%) the pain was compressive, 12 (30%) had burning pain and 10 (25%) had constricting pain. Pain irradiated into the left shoulder, into the left arm, under the left scapula – in 28 patients (70%) with coronary heart disease; into the both hands, under the left and right scapula –in 5 (12.5%) patients of this group. Pain duration in patients with angina ranges from 30 seconds to 10 minutes, medium intensity. In patients with coronary heart disease physical load caused pain in 32 patients (80%), and emotional stress – in 8 (20%). Shortness of breath was observed in 31 patients (77.5%) with coronary heart disease.

In the analysis of the objective features of patients with coronary heart disease, tachycardia was observed in 5 CHD patients (12.5%), bradycardia – in 9 CHD patients (22.5%). Positive GB symptoms were not observed in any patients with coronary heart disease. Blood pressure was elevated in 8 CHD patients (20%).

Dyspeptic syndrome was not characteristic of CHD patients. According to the data of dynamic cholecystosonography (DEHG) in CHD patients without concomitant CNCC, the GB contractility did not differ significantly from the similar indices of the control group (CG). The study of LPO processes in patients of group I revealed that a significant increase in the level of MDA in the erythrocyte membranes (10.29±0.48 μmol/l) ($p < 0.05$), and MDA in the blood serum increased significantly and amounted (0.90±0.03, $p > 0.05$). In these patients, a reliable decrease in serum ceruloplasmin (119.5±15.3 mg/l) ($p < 0.05$) was observed. The activity of catalase was within the normal range (2.85±0.26 units) ($p > 0.05$). Increase in the level of LPO products ($p < 0.05$) in CHD patients without CNCC was not accompanied by a significant change in antioxidant defence (AOD) activity (catalase–2.56±+0.19 units, ceruloplasmin–162.4±16.1 mg/l) ($p > 0.05$). The increased concentration of LPO products in the blood of CHD patients with concomitant CNCC, unlike patients with isolated CHD, is probably related to the inflammatory process in the gallbladder. Reduced blood serum ceruloplasmin levels in the group of patients with combined chronic pathology can be explained by the depletion of its reserves and the reduction of its synthesis by the liver, i.e., to the impaired liver response to inflammation outside it, which may be connected with the possible hepatocytes dysfunction. Analyzing the correlations between the studied parameters in CHD patients with CNCC, we found that the increase in lipid activity was manifested by an increase in the level of LPO products, accompanied by selective activation of catalase and the reduced blood serum ceruloplasmin content ($0.38 > r < 0.66$) ($p < 0.05$– 0.001). Analysis of the central hemodynamics was carried out in the patients examined at the standard load of 50 W. In all the examined patients the heart rate was increased. However, if in healthy persons it only increased by 20% and amounted (80.8±1.5) beats per minute, in patients with CHD of FC I the heart rate increased by 21.7% and amounted to (87.6±0.54) beats per minute, and in patients with CHD of FC II the heart rate increased by 24.1% and amounted to (97.3±1.2) beats per minute ($p < 0.05$). Indices of intracardiac hemodynamics at rest in healthy individuals and patients with I and II FC angina were within the generally accepted age norms and did not differ significantly.

In general, the results obtained in our study coincide with the data obtained by other researchers [6–12]. Thus, estimating the results of the studies, we can assume that the negative impact of CNCC on the clinical course of CHD has various manifestations. Clinical course of stable effort angina (FC I–II) with concomitant CNCC is characterized by more pronounced conical manifestations of cardiac pathology, increased resistance to drug treatment and reduced tolerance to physical activity. This is manifested by an increase in the frequency and intensity of angina attacks, shortness of breath and frequent cardiac rhythm disorders [6, 8].

Enhancement of LPO processes, AOP inhibition, and atherogenic shift of lipid metabolism lead to the progression of atherosclerotic damage to the coronary vessels, that potentiates the ischemic process. In CNCC there is a toxic–dystrophic effect on the myocardium, which is caused by autoimmune and metabolic disorders and the damaging effect of the increasing concentration of POL products on the membranes of myocardial

cells. Burdened clinical course in CHD with concomitant CNCC correlates with more pronounced changes in lipid metabolism [10].

In recent years, the prognostic value of certain variants of dyslypoproteidemia, including hypertriglyceridemia and decreased plasma concentrations of HDL [6, 7, 8], have been clearly defined. However, the atherogenic potential of LDL is considered to be the greatest [12]. Therefore, it is necessary to be very careful about the timely administration of antihyperlipidemic agents in these two diseases. Prospective fields are further studies of the correlation between the above diseases and prescription of timely treatment, taking into account changes identified in the comprehensive examination.

Conclusions

Based on observations, clinical and laboratory parameters, data of loading tests, daily dynamic cholecystosonography, some features of the CHD course with concomitant CNCC were revealed, namely:

1. CHD without CNCC proceeds as an independent disease and is not accompanied by changes in the biliary system.

2. LPO enhancement plays a definite role in increasing the clinical manifestation of CHD with concomitant inflammation of the gallbladder.

3. Aggravation of the CHD clinical course with concomitant CNCC correlates with more pronounced changes in atherogenic lipid metabolism, activation of LPO processes and AOP deficiency in the blood, hemostasis disturbance and suppression of contractile heart function.

4. CNCC significantly complicates the course of CHD with stable angina of functional classes I–II: more pronounced changes in the lipid spectrum, indicating a more rapid development of atherosclerosis, a combination of pain in the heart region and that in the right hypochondrium, pronounced dyspeptic syndrome.

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