Реферати

КОРЕКЦІЯ ПАРАМЕТРІВ ГУМОРАЛЬНОЇ ЛАНКИ СИСТЕМНОГО ІМУНІТЕТУ У ХВОРИХ НА ГЕНЕРАЛІЗОВАНИЙ ПАРОДОНТИТ

Савельєва Н.М., Соколова І.І.

Досліджено динаміку показників гуморальної ланки системного імунітету при застосуванні комплексної терапії з включенням імуномодуляторів у хворих на генералізований пародонтит (ГП) хронічного перебігу I і II ступеня розвитку на тлі лямбліозу. Було обстежено 180 пацієнтів з лямбліоз у віці 20-40 років, хворих на ГП хронічного перебігу I і II ступеня розвитку (основна група і група порівняння). Пацієнти основної групи отримували розроблену комплексну терапію із застосуванням імуномодуляторів, пацієнтів групи порівняння лікували за традиційною схемою. Встановлено, що розроблена схема лікування має виражену нормалізуючу дію на активність гуморального імунітету. Під її впливом нормалізується вміст в сироватці крові IgE і і циркулюючих імунних комплексів (ЦІК), підвищується спорідненість антимікробних IgG-антитіл. Отримані дані дають підставу стверджувати, що схема розробленої комплексної терапії у хворих на ГП на тлі лямбліозу виявилася більш ефективною, ніж традиційне лікування.

Ключові слова: хронічний генералізований пародонтит, лямбліоз, гуморальний імунітет.

Стаття надійшла 22.03.2019 р.

КОРРЕКЦИЯ ПАРАМЕТРОВ ГУМОРАЛЬНОГО ЗВЕНА СИСТЕМНОГО ИММУНИТЕТА У БОЛЬНЫХ ГЕНЕРАЛИЗОВАННЫМ ПАРОДОНТИТОМ

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Исследована динамика показателей гуморального звена системного иммунитета при применении комплексной терапии с включением иммуномодуляторов у больных генерализованным пародонтитом (ГП) хронического течения I и II степени развития на фоне лямблиоза. Было обследовано 180 пациентов с лямблиозом в возрасте 20-40 лет, больных ГП хронического течения I и II степени развития (основная группа и группа сравнения). Пациенты основной группы получали разработанную комплексную терапию с применением иммуномодуляторов, пациентов группы сравнения лечили по традиционной схеме. Установлено, что разработанная схема лечения обладает выраженным нормализующим действием на активность гуморального иммунитета. Под ее влиянием нормализуется содержание в сыворотке крови IgE и ЦИК, повышается сродство антимикробных IgG-антител. Полученные данные дают основание утверждать, что схема разработанной комплексной терапии у больных ГП на фоне лямблиоза оказалась более эффективной, чем традиционное лечение.

Ключевые слова: хронический генерализованный пародонтит, лямблиоз, гуморальный иммунитет.

Рецензент Аветіков Д.С.

DOI 10.26724/2079-8334-2019-4-70-151-155
UDC 616.36-006.327-036-06:616.36-002.14/2:612.6.05

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PREDICTION OF HEPATIC FIBROSIS PROGRESSION RATE IN CHRONIC HEPATITIS C ON THE BASIS OF CLINICAL AND GENETIC SIGNS

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A cross-sectional study of 166 patients with chronic hepatitis C was carried out. As a result of the analysis, among the 35 possible factors of rapid progression of hepatic fibrosis in chronic hepatitis C, 10 most informative ones were identified: male gender (p=0.005), 1 genotype of HCV (p=0.040), alanine aminotransferase above 3 upper limits of normal (p=0.015), the levels of aspartate aminotransferase, γ-glutamyltranspeptidase and total bilirubin exceeding the upper limit of normal (p=0.000, p=0.000 and p=0.001, respectively), alcohol consumption >40 g/day (p=0.033), chronic cholecystitis and/or pancreatitis (p=0.000), type II diabetes mellitus (p=0.007) and a carriage of the normal genotype (Gln/Gln, Gln/-) of the TLR7 gene (p=0.001). In order to optimize the prognostication of the affiliation of a patient with chronic hepatitis C to the risk group of rapid progression of hepatic fibrosis there were proposed the highly effective mathematical model, developed on the basis of multiple discriminant analysis, exact forecast of which was 82.5 %.

Key words: chronic hepatitis C, the rate of fibrosis progression, prognostic model, discriminant analysis.

The work is a fragment of the research project "Determination of T-like receptors polymorphism role in the pathogenesis of infectious diseases", state registration No. 0118U005006.

At present, the hepatitis C virus (HCV) is the primary cause of chronic liver diseases [7]. HCV infection remains one of the most important problems of world health care due to its high prevalence, a constant tendency to an increase in the number of patients, a high level of chronic diseases development, the risk of hepatic cirrhosis and hepatocellular carcinoma, the complexity of treatment, and the lack of specific prevention [3, 11]. According to official data, there are 130-150 million patients with chronic hepatitis C (CHC) in the world, 700 thousand annually die of complications of this disease, and in the next 20 years, a further increase in mortality is predicted [11, 13].

Continuous progress is typical of CHC and now hepatic fibrosis (HF) is considered as a process by which a certain number of external factors interact with a unique combination of host factors, which causes significant differences in the natural course of the disease. There are virus factors (genotype and HCV quasispecies, the level of viral load) and host factors (male gender, duration of disease, age over 40 years

at the time of infection, co-infection with hepatitis B virus and/or HIV, type II diabetes mellitus, iron metabolism disorders, alcohol abuse, effect of toxic substances, tobacco smoking and cannabiol derivatives) among the factors of HF progress in CHC [4, 14]. The prognosis of CHC is based on the idea about the rate of fibrosis progression (RFP), since it is patients with a rapid rate of transformation of HF into cirrhosis that require the individualization of therapeutic and diagnostic approach. Recently, there is an active search for genetic determinants, which affect RFP in CHC, in particular, the genetic polymorphism of the gene TLR7, the ligand of which is viral RNA [12, 15], is studied, and to date, the dependence of this process on the carriage of the polymorphic allele Leu is proved [1, 2]. Thus, a study, that will assess the RFP in CHC based on complex analysis and comparison of genetic markers with clinical data, is an actual scientific and practical task.

The purpose of the study was to optimize the prediction of the rate of HF formation in CHC based on a comprehensive assessment of general clinical, biochemical and molecular-genetic markers.

Materials and methods. To achieve this purpose, a cross-sectional study was conducted, which included 166 patients with CHC: men – 111 (66.9 %), women – 55 (33.1 %) who were treated at the Poltava Regional Clinical Hospital of Infectious Diseases (PRCHID) during 2011-2018 years. Complex clinical and laboratory examination of patients was conducted on the basis of this medical institution and in commercial laboratories. All diagnostic procedures were performed according to the informed consent of the patients. The criterion for inclusion in the study was the established CHC diagnosis, the formulation of which was guided by the international classification of diseases of the 10th revision and the international classification of liver diseases (Los Angeles, 1994). The diagnosis was verified by the detection of specific serological markers of HCV (anti-HCV IgM and IgG, anti-HCV core and anti-NS_3, anti-NS_4, anti-NS_5) by the method of ELISA with the obligatory detection of HCV RNA in the blood serum by PCR method in real time with genotyping and viral load detection (high counted viremia $>4.0 \cdot 10^5$ IU/ml). Exclusion criteria – co-infection with other hepatotropic viruses and/or HIV, decompensated somatic diseases, oncopathology.

The patient examination program included: assessment of complaints and anamnestic data obtained by questioning and detailed analysis of medical records, physical examination, general clinical study of peripheral blood, determination of biochemical parameters of blood serum, characterizing the functional state of the liver – alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, total bilirubin, alkaline phosphatase and γ-glutamyltranspeptidase (GGT), the stages of HF according to METAVIR and genetic studies (identification of TLR7 genotypes). The frequency of concomitant pathology was established based on the results of anamnesis analysis, outpatient cards, objective examination followed by in-depth clinical and laboratory and instrumental studies, findings of specialists in related specialties. The duration of HCV infection was determined by the results of anamnestic data analysis (indication of the transferred icteric form of acute hepatitis C, transfusion of blood and its components prior to mandatory screening of donors, initiation of systemic injecting drug use), in the absence of the anamnesis of these facts – on the basis of clinical and laboratory data (the first detection of antibodies to HCV and/or the level of hepatic transaminases exceeding the upper limit of normal (ULN), reflected in outpatient cards).

Biochemical studies were carried out on the automatic biochemical analyzer GBG STAT FAX-1904 (Japan) with Human reagents (Germany). The HF stage was assessed on the METAVIR scale using the FibroTest methods on a Cobas 6000 analyzer (with a 501 module) using the Roche Diagnostics (Switzerland) test systems of the «Synevo» medical laboratory and the transient elastometry of shear waves of the liver on the ultrasound scanning device «Ultima PA-Expert», Ukraine) on the basis of PRCHID. The RFP was calculated by T. Poynard's formula by dividing the stage of HF by METAVIR for the time, for which it was formed, and measured in units per year (units/year) [13]. Polymorphic region Gln/Leu of the gene TLR7 was genotyped by real-time allele-specific PCR on the «DT Light» amplifier («NPO DNA-Technology», LLC, Russia) on the basis of the Research Institute for Genetics and Immunological Grounds of Pathology and Pharmacogenetics of Ukrainian Medical Stomatological Academy.

Statistical processing of the findings was carried out using the IBM SPSS Statistics software version 23.0 (USA). The verification of the normality of the data distribution was analyzed by the Kolmogorov-Smirnov criterion. To determine the central trend, the value of the median (*Me*) with the upper and lower quartiles was used. As potential risk factors of the rapid progression of HF in CHC, 35 indicators (results of general clinical, biochemical and molecular genetic studies) ranked in a nominal scale (1 – sign, 0 – none) were examined and analyzed. In order to select the most informative signs ($p<0.05$), each method was evaluated by a single-factor analysis of variance. To create a mathematical model for predicting RFP, the method of stepwise multiple discriminant analysis of Fisher was used, where the binary feature served as a grouping: 1 – rapid and 0 – slow progression of HF. In the course of the analysis, Wilks's lambda

value was calculated, the informative value of each variable in the discriminant model (tolerance), the system of classification linear discriminant functions, the canonical linear discriminant function, the centroid coordinates, and the efficiency of the obtained model were estimated before and after the crosscheck. The level of difference was assumed to be statistically significant at $p<0.05$.

Results of the study and their discussion. The study found, that the age of the subjects ranged from 20 to 63 years, *Me*=40.0 (34.0-47.0), with a predominance of young and middle-aged (95.2%). According to the genotype of HCV, the patients were divided as follows: 1 genotype – have 59.6 % of people, 2 and 3 in 1.5 times less often – 40.4 %. High and low levels of viral load were determined with almost the same frequency – 48.2 % and 52.8 %, respectively. The duration of HCV infection was 1 to 46 years, and the majority (59.6 %) did not exceed 10 years: less than 5 – 39.7 %, 5 to 10 – 19.9 %, more than 10 – 40.4 %, *Me*=7.0 (2.0-19.2). At the time of the examination, different stages of HF were determined in patients on the METAVIR scale without prevailing any of them: F_0 and F_1 – by 17.5 %, F_2 and F_4 – by 25.3 %, F_3 – 16.3 %.

As a result of the genetic study, it was found out that among the patients normal carriers were registered: women – Gln/Gln (69.1 %), men – Gln/- (85.6%) and polymorphic: women – Gln/Leu (27.3 %) and Leu/Leu (3.6 %), men – Leu/- (14.4 %) of the genotypes of the TLR7 gene. Taking into account the low overall frequency of registration of Leu/Leu genotypes and Leu/- gene TLR7, which limited the possibility of statistical generalization, when comparing the characteristics, the examined were combined for the carrier of the polymorphic Leu allele. In general, the frequency of its registration was 15.1 %. Further, RFP of each of the examined was calculated and it's *Me* was determined, which was 0.185 (0.098-0.750) units/year, and afterwards there were defined groups of patients with rapid (RFP>0.185 units/year) and slow (RFP≤0.185 units/year) HF progression – 83 people from each group.

In order to select the most informative signs of rapid progression of HF, there was conducted a single-factor analysis of variance in 35 variables (general clinical, biochemical and molecular-genetic markers). As a result, it was determined that: male gender (F= 8.14, p=0.005), 1 genotype of HCV (F=4.28, p=0.040), ALT level above 3 ULN (F=6.03, p=0.015), the levels of AST, GGT and total bilirubin exceeding ULN (F=33.02, p=0.000, F=30.98, p=0.000 and F=12.42, p=0.001, respectively), alcohol consumption >40 g/day (F=4.64, p=0.033), among the concomitant pathology chronic cholecystitis and/or pancreatitis (F=32.19, p=0,000), type II diabetes mellitus (F=7.55, p=0.007) had the statistically significant effect on this process. In addition, the marker of rapid progression of HF in CHC was carriage of the normal genotype (Gln/Gln, Gln/-) of the TLR7 gene (F=11.56, p=0.001).

Thus, among the 35 possible factors of the rapid progression of HF in CHC, 10 most informative were identified, which were included in a stepwise multiple discriminant analysis, the purpose of which was to construct functions that, in an optimal set of discriminating variables, predict the assignment of a patient to a group of rapid or slow progression of HF in CHC. The final discriminant model included 5 features, each of which had a high statistical significance and a significant informative index (table).

Table

Characteristics of the variables of the final discriminant model for the prediction of rapid progression of hepatic fibrosis in chronic hepatitis C

Sign	Wilks's lambda	F	p	Tolerance
The AST level above ULN	0.832	33.02	0.000	0.913
Chronic cholecystitis and/or pancreatitis	0.739	28.73	0.000	0.952
The normal genotype (Gln/Gln, Gln/-) of the TLR7 gene	0.668	26.79	0.000	0.947
The GGT level above ULN	0.606	26.11	0.000	0.915
The level of total bilirubin above ULN	0.565	24.63	0.000	0.963

As a result, there were classification linear discriminant functions (F_r and F_s) obtained, permitting to predict rapid or slow progression of HF in CHC, by a combination of characteristics using the coefficients obtained in the course of the analysis:

$$F_r = -11.14+4.93 \cdot X_1+6.59 \cdot X_2+8.16 \cdot X_3+2.80 \cdot X_4 +3.17 \cdot X_5;$$

$$F_s = -5.00+3.06 \cdot X_1+4.15 \cdot X_2 +5.88 \cdot X_3 +1.19 \cdot X_4 +1.49 \cdot X_5,$$

where: X_1 – AST level above ULN, X_2 – chronic cholecystitis and/or pancreatitis, X_3 – the normal genotype (Gln/Gln, Gln/-) of the TLR7 gene, X_4 – GGT level above ULN, X_5 – the level of total bilirubin above ULN (if there is a characteristic, a coefficient of 1 is added, if it is absent – 0). A function, whose mathematically calculated value is larger, indicates a patient's group of belonging: in $F_r>F_s$, a rapid progression is predicted, and in $F_r<F_s$ – a slow progression of HF in CHC. In order to obtain a single formula and create a risk scale for rapid progression of HF in CHC, the results of canonical discriminant analysis were taken into account, according to which the canonical linear discriminant function (CLDF)

had the following form: CLDF = $-3.52+1.07\bullet X_1+1.39\bullet X_2+1.30\bullet X_3+0.92\bullet X_4+0.96\bullet X_5$. The risk assessment, according to the coordinates of the centroids of patient groups obtained in the course of the discriminant analysis, is carried out as follows: with a CLDF value of 0.872 and higher the risk of rapid progression of HF in CHC is high, ranging from 0.872 and lower - it is low, from 0.872 to 0.872 - it is moderate (fig.).

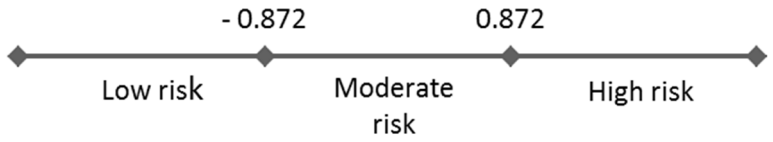

Fig. Assessment of the rapid hepatic fibrosis progression risk in chronic hepatitis C by the value of the canonical linear discriminant function.

The unmistakable forecast of the obtained models was 82.5 % (for rapid progression - 88.0 %, for slow progression - 77.1 %), while conducting a cross-check - 80.0 %, which proves the high efficiency and expediency of their practical application with the aim of optimization of predicting the rapid progression of HF in CHC. Thus, as a result of our study we have created the prognostic model of the rate of HF formation in patients with CHC. The signs included in the model are consistent with data from the scientific literature. In particular, the study confirmed the well-known fact of influence on the RFP of such factor as concomitant pathology of the gastrointestinal tract [2, 14]. There are no doubts about the data on the influence of increased levels of such functional indicators as AST, GGT and total bilirubin, because they are non-direct biochemical markers of fibrogenesis – they indicate activity of inflammation in liver tissues and disruption of its synthetic function and allow indirectly estimate a HF stage [5, 10]. However, to date, studies of the influence of polymorphic allele Leu of TLR7 gene on the RFP are limited. The results of our study are in line with a number of scientific studies [1, 2, 8], but they contradict the data of F. Z. Fakhir (2018), who describes the Leu allele as a profibrogenic factor, and E. Ascar (2010), who denies the influence of this polymorphism on fibrogenesis in CHC [6, 9]. The use of the proposed clinical and genetic prognostic model allows predicting the probability of rapid progression of HF in CHC with high accuracy and forming a group of patients who need to receive antiviral therapy in the first place on the basis of simple characteristics, most of which are used in a routine clinical practice.

Conclusions

1. Informative diagnostic signs of rapid progression of HF in CHC are: male gender (F=8.14, p=0.005), 1 genotype of HCV (F=4.28, p=0.040), ALT level above 3 ULN (F=6.03, p=0.015), the levels of AST, GGT and total bilirubin exceeding ULN (F=33.02, p=0.000, F=30.98, p=0.000 and F=12.42, p=0.001, respectively), alcohol consumption >40 g/day (F=4.64, p=0.033), chronic cholecystitis and/or pancreatitis (F=32.19, p=0.000), type II diabetes mellitus (F=7.55, p=0.007) and a carriage of the normal genotype (Gln/Gln, Gln/-) of the TLR7 gene (F=11.56, p=0.001).

2. In order to optimize the prognostication of the affiliation of a patient with CHC to the risk group of rapid progression of HF there were proposed the highly effective mathematical model, developed on the basis of multiple discriminant analysis, exact forecast of which was 82.5 %.

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Реферати

ПРОГНОЗУВАННЯ ШВИДКОСТІ ПРОГРЕСУВАННЯ ФІБРОЗУ ПЕЧІНКИ ПРИ ХРОНІЧНОМУ ГЕПАТИТІ С НА ОСНОВІ КЛІНІЧНИХ І ГЕНЕТИЧНИХ ОЗНАК

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Проведене кросс-секційне дослідження 166 пацієнтів із хронічним гепатитом С. В результаті аналізу серед 35 можливих факторів швидкого прогресування фіброзу печінки при хронічному гепатиті С виявлено 10 найбільш інформативних: чоловіча стать (p=0,005), 1 генотип ВГС (p=0,040), рівень аланін-амінотрансферази вищий за 3 верхніх межі норми (p=0,015), рівні аспартат-амінотрансферази, γ-глутамілтранспептидази та загального білірубіну, що перевищують верхню межу норми (p=0,000, p=0,000 і p=0,001 відповідно), споживання алкоголю >40 г/добу (p=0,033), хронічний холецистит та/або панкреатит (p=0,000), цукровий діабет ІІ типу (p=0,007) і носійство нормального генотипу (Gln/Gln, Gln/-) гена TLR7 (p=0,001). З метою оптимізації прогнозування віднесення пацієнта з хронічним гепатитом С до групи ризику швидкого прогресування фіброзну печінки запропонована високоефективна математична модель, розроблена на основі множинного дискримінантного аналізу, безпомилковий прогноз якої складає 82,5 %.

Ключові слова: хронічний гепатит С, швидкість прогресування фіброзу печінки, прогностична модель, дискримінантний аналіз.

Стаття надійшла 15.03.2019 р.

ПРОГНОЗИРОВАНИЕ СКОРОСТИ ПРОГРЕССИРОВАНИЯ ФИБРОЗА ПЕЧЕНИ ПРИ ХРОНИЧЕСКОМ ГЕПАТИТЕ С НА ОСНОВАНИИ КЛИНИЧЕСКИХ И ГЕНЕТИЧЕСКИХ ПРИЗНАКОВ

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Проведено кросс-секционное исследование 166 пациентов с хроническим гепатитом С. В результате анализа среди 35 возможных факторов быстрого прогрессирования фиброза печени при хроническом гепатите С выявлено 10 наиболее информативных: мужской пол (p=0,005); 1 генотип ВГС (p=0,040); уровень аланин-аминотрансферазы выше 3 верхних границ нормы (p=0,015); уровни аспартат-аминотрансферазы, γ-глутамилтранспептидазы и общего билирубина превышающие верхнюю границу нормы (p=0,000, p=0,000 и p=0,001 соответственно); употребление алкоголя >40 г/сутки (p=0,033); хронический холецистит и/или панкреатит (p=0,000); сахарный диабет II типа (p=0,007) и носительство нормального генотипа (Gln/Gln, Gln/-) гена TLR7 (p=0,001). С целью оптимизации прогнозирования принадлежности пациента с хроническим гепатитом С к группе риска быстрого прогрессирования фиброза печени предложена высокоэффективная математическая модель, разработанная на основе множественного дискриминантного анализа, безошибочный прогноз которой составил 82,5 %.

Ключевые слова: хронический гепатит С, скорость прогрессирования фиброза печени, прогностическая модель, дискриминантный анализ.

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DOI 10.26724/2079-8334-2019-4-70-155-159
UDC 614.23:37.06

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MEDICO-SOCIAL PROFILES OF PHYSICIANS IN TRAINING

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The purpose of this paper is to develop recommendations for improving the system of postgraduate medical education in the context of the overall health care reform. The survey method implemented in the form of a standardized (formalized) interview was used as the main tool for collecting social and psychological information. We have interviewed the total of 375 internship doctors after graduation including 33.60% male responders and 66.40% female ones aged 20-34 years. The results of the questionnaire indicate that internship doctors experience such polar feelings as calmness, confidence, non-contentiousness, anxiety, worry, fear, and despair. The responders suggest that health care institutions meet current requirements incompletely. Thus, there is the necessity to significantly improve the material and technical conditions as well as to review the system of medical institutions functioning while developing the strategy of health care system reform.

Keywords: interview, internship doctors, postgraduate medical education, healthcare system reform.

The work is a fragment of the research project "Determinants of rural population health and life expectancy", state registration No. 0118U000099.

The quality health care is provided for the population by means of many tools including the provision of sufficient number of highly qualified personnel. The changes in higher medical education and its integration into the European educational area demand the implementation of new approaches to medical training in the post-graduate period and to the social role and professional status of a specialized physician [6]. Another actual requirement involves organization of a qualitatively new cooperation between higher education institutions and structural health care units directed at the performance of target training, namely further professional medical training and specializing to fulfill the existing needs of practical health care [4, 7].