Changes in clinical, biochemical, immunological and integrative parameters in patients with chronic hepatitis C virus infection according to the virus genotype and the grade of activity

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The aim of this study is to determine the features of the course of chronic hepatitis C virus (CHCV) infection and the dependence of changes in integrative indicators of endogenous intoxication, nonspecific immunoreactivity and inflammation on the virus genotype and the grade of activity.

Materials and methods. In total, 287 CHCV patients were examined and their inpatient and outpatient medical cards were analyzed. The study included 55 healthy individuals. In addition to the general group, which included all the patients, the examined people were divided into groups, depending on the grade of activity (minimal activity – 210 people, moderate – 68, expressed – 9) and the virus genotype (1b – 150 people, 2 – 19, 3a – 102). Clinical and laboratory examination was performed according to the protocol. The integrative indices of severity, nonspecific reactivity, indices of inflammation and intoxication activity were also calculated. The statistical processing of the obtained results was carried out by Microsoft Office Excel 2010 and IBM SPSS Statistics 23 computer software.

Results. The groups were sex- and age-representative. The 1b genotype (52.30 %), moderate liver fibrosis (F2 – 31.25 %) and minimal activity (73.17 %) were the most frequently encountered in patients with CHCV. The most frequent clinical manifestations were asthenovegetative syndrome (81.88 %) and heaviness in the right hypochondrium (64.76 %). Patients with CHCV caused by different virus genotypes had evenly distributed clinical data (P > 0.05), with the exception of the 1b genotype patients who were diagnosed with telangiectasia 1.3 times more frequently than in the total sample; and liver enlargement was 1.5 times (P < 0.05) less frequently seen in the 2 genotype patients, there were no anemia cases (P < 0.05).

A decrease in platelet counts (1.3 times) and segmented neutrophils (1.2 times) as well as an increase in lymphocytes (1.1 times) and ESR (1.4 times) was observed in CHCV patients compared to apparently healthy individuals (P < 0.05). The changes obtained were significant in the groups with all genotypes, except for the patients with genotype 2 as the level of erythrocytes and hemoglobin was lower than in the comparison group and in the total group (1.1 times in all cases, P < 0.05), and patients with genotype 3a had a lower ESR compared to all patients (1.2 times) (P < 0.05). The groups of patients with different grades of activity were homogeneous with the exception that the leukocyte count in minimal activity (P < 0.05) was lower than in the total group, ESR was higher only in the total group in minimal activity (P < 0.05), the level of segmented neutrophils and lymphocytes in expressed activity did not differ from the comparison group, unlike other groups.

In the total group, leukopenia (15.68 %), erythrocytopenia (18.47 %), anemia (6.62 %), and thrombocytopenia (33.10 %) were more common than in the comparison group (5.45 %, 3.63 %, 0 %, 5.45 %, respectively) (P < 0.05). People with different HCV genotypes had similar changes, except for the patients with genotype 2 who did not have anemia. All CHCV patients had higher values of total protein, ALT, AST, GGT relative to the comparison group (P < 0.05), and AIP and creatinine were lower (P < 0.05). No dependence of changes in these parameters on the genotype was found, except for protein content, as it was higher in the groups with genotype 1c and 2; AIP was lower in individuals with the 1c and 3a, and creatinine – in 1c and 2 genotype patients (P < 0.05). There was also no dependence of changes in patients with CHCV on the grade of activity, except for those with expressed activity who had higher AIP, GGT and total bilirubin with reduced glucose level (P < 0.05).

In the total group of patients with CHCV, the entropy indices of leukocyte formula were higher, the indexes of nonspecific reactivity had higher values of RC (1.3 times), limph (1.3 times), IA (1.1 times), but NMRI (1.1 times) and ELRI (1.3) (P < 0.05) were lower than in the comparison group. There was a decrease (TII – 1.1 times; KI – 1.3 times) or an increase (ILG – 1.3 times; IL ESR – 1.5 times) in inflammatory parameters (P < 0.05). Indices of endogenous intoxication were decreased in patients compared with the healthy individuals (ILS – 1.2 times, NRR – 1.8 times). No dependence of changes in patients with CHCV on the genotype was found, except for IA, which was higher only in the total group and with genotype 3a (P < 0.05), and IL ESR in the patients with genotype 3a, which was lower than in the total group (P < 0.05) but did not differ from the comparison group (P > 0.05); IIS with genotype 3a was 1.7 times lower compared with all patients (P < 0.05). The ELR indicator did not change in all grades of activity and did not differ from those of healthy individuals. In patients with moderate activity, IA was higher than in the comparison group and NI was lower than in the total group (P < 0.05).

Abdominal ultrasound, regardless of the group, most frequently revealed liver enlargement (76.26 % of persons) and an increase in its echogenicity (82.35 %).

Conclusions. Chronic hepatitis C virus patients were dominated by asthenovegetative syndrome, feeling of heaviness in the right hypochondrium, liver enlargement, increase in lymphocyte count, ESR, transaminase activity. Telangiectasia in genotype 1b and liver enlargement in genotype 2 were less frequent. Laboratory changes were accompanied by leukocytopenia, erythrocytopenia, anemia and thrombocytopenia, an increase in total protein content, ALT, AST and GGT activity. In chronic hepatitis C virus, the entropy indices of leukocyte formula, RC, limph, AI, ILG and IL ESR were increased. Positive ANAs were significantly more frequently identified than AMAs.
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Мета роботи — установити особливості перебігу ХВГС і залежність змін інтегративних показників ендогенної інтоксикації, неспецифічної іммунореактивності та запалення від генотипу вірусу та ступеня активності.

Матеріали та методи. Обстежили 287 хворих на ХВГС і проаналізували їхні медичні карти стаціонарного й амбулаторного хворого. У дослідження вийшли 55 практично здорових осіб. Крім загальної групи, до якої ввійшли всі хворі, пацієнтів, яких обстежили, поділили на групи залежно від ступеня активності (мінімальна активність — 210 осіб, помірна — 68, виразна — 91) і від генотипу вірусу (1в — 150 осіб, 2 — 19, 3 а — 102). Здійснили клініко-лабораторне обстеження згідно з протоколом, розрахували інтегративні показники тяжкості, неспецифічної реактивності, індекс активності запалення та інтегративні. Статистичне опрацювання результатів здійснили у програмному забезпеченні комп’ютерних програм Microsoft Office Excel 2010 і IBM SPSS Statistic 23.

Результати. Групи за статтю та віком були репрезентативні. Найчастіше виявлялися хворі на ХВГС із 1в генотипом (52,30 %), помірним фіброзом печінки (F2 — 31,25 %) та мінімальною активністю (73,17 %). Найбільш часті клінічні вияви — астроно-вегетативний синдром (81,88 %) і тяжкість у правому підребер’ї (64,76 %). У хворих із ХВГС, що спричинено різними генотипами, клінічні дані розподілилося рівномірно (p > 0,05), крім того, в обстежених з 1в генотипом частіше, ніж у загальній вибірці діагностували телеангіектазії (в 1,3 раза); з 2 генотипом рідше — збільшення розмірів печінки (в 1,5 раза, р < 0,05), виразність анемії було менше (p < 0,05). У пацієнтів із ХВГС спостерігали зменшення кількості тромбоцитів (в 1,3 раза) та сегментоядерних лейкоцитів (в 1,2 раза), підвищення — лімфоцитів (в 1,1 раза) та ІЛГ (в 1,4 раза) порівняно з практично здоровими особами (p < 0,05). Отримані зміни були однаковими у візумі групами, на відміну від того, що у хворих із 1 в генотипом рівень еритроцитів та гемоглобіну був нижчим, ніж у групі порівняння та в загальній групі (в 1,1 раза, р < 0,05). У пацієнтів із 3 генотипом був знижений рівень еритроцитів та гемоглобіну (p < 0,05), а ЖКЛ була нижчою у хворих із 3 генотипом порівняно з усіма хворими (в 1,2 раза, р < 0,05). Групи пацієнтів із різними ступенями активності за досліджуваними показниками були однорідними за винятком того, що кількість лейкоцитів за мінімальної активності була меншою, ніж у загальній групі (p < 0,05). ІОУ була вищою тільки в загальній групі та при мінімальній активності (p < 0,05), рівень сегментоядерних лейкоцитів та лімфоцитів при виразній активності не відрізнявся від групи порівняння, на відміну від інших груп.

Серед пацієнтів загальної групи частіше виявляли лейкоцитопению (15,68 %), еритроцитопению (18,47 %), анемію (6,62 %) та тромбоцитопению (33,10 %), ніж у групі порівняння (відповідно 5,45 %, 3,63 %, 0 %, 5,45 %, р < 0,05). В іншій групі генотипами НСВ були подібні за цим показником, за винятком того, що в пацієнтів із 2 генотипом не було анемії. У всіх осіб із ХВГС були вищими значення загального білка, АЛТ, АСТ, ГГТП стосовно групи порівняння (p < 0,05), а ЛФ і креатинін були нижчими (p < 0,05). Залежності змін цих показників від генотипу не відрізнявалися від групи порівняння, на відміну від інших груп. Серед пацієнтів загальної групи порівняно зі здоровими (в 1,1 раза) і ІСЕЛ (в 1,3), (р < 0,05). Відбулося зниження (СІЗ — в 1,1 раза; ІК — в 1,3 раза; ІЛГ — в 1,3 раза; ІЛ ШОЕ — в 1,5) показників запалення (p < 0,05). Інфікції ендогенної інтоксикації зазнано у хворих із 1в генотипом з 2 і 3 генотипами (р < 0,05). Також була відсутня залежність змін у хворих на ХВГС від генотипу біля активності за виключенням того, що в іншій групі виражені активності від інфікції ендогенної інтоксикації були більшими, ніж у загальній групі (p < 0,05). ІОУ була вищою, а тромбоцитопенія більшою у пацієнтів із 1 в генотипом порівняно з усіма хворими (р < 0,05), а реєстрація була нижчою у хворих із 3 генотипом порівняно з усіма хворими (р < 0,05).

Висновки. У хворих на ХВГС переважали астено-вегетативні синдром, відсутня тяжкість у правому підребер’ї, збільшення розмірів печінки, кількість лімфоцитів, ІОУ, підвищення активності трансаміназ. При 1в генотипі частіше виявляли телеангіектазії, при 2 генотипі — збільшення розмірів печінки. Лабораторні зміни супроводжувалися лейкоцитопе- нією, еритроцитопе- нією, анемією та тромбоцитопе- нією; підвищенням мінімальної активності здорових осіб. У пацієнтів з 1в генотипом активності було вищим, ніж у групі порівняння, а ЯІ — нижчим, ніж у загальній групі (p < 0,05). Під час ультразвукового дослідження органів черевної порожнини (незалежно від генотипу) найчастіше відзначали збільшення розмірів (у 76,26 % осіб) і підвищення ехогенності печінки (у 82,35 %).

Изменения клинико-биохимических, иммунологических и интегративных показателей у больных хроническим вирусным гепатитом С в зависимости от генотипа вируса и степени активности

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Цель работы — установить особенности течения ХВГС и зависимость изменений интегративных показателей эндогенной интоксикации, неспецифической иммунореактивности и воспаления от генотипа вируса и степени активности.

Материалы и методы. Обследовано 287 больных ХВГС и проанализированы их медицинские карты стационарного и амбулаторного больного. В исследование вошли 55 практически здоровых лиц. Кроме общей группы, куда вошли все
More than 71 million people or about 1.0 % of the world’s population [1], are infected with hepatitis C virus (HCV). A predominant liver lesion characterizes hepatitis C; it has a light yellowish form in the acute period, frequent chronicity and on average, it is around 2 million IU/l. Low viral load is not very important in most clinical situations and on average, it is around 2 million IU/l. Low viral load is not very important in most clinical situations.

The fact is that only about 10 % of acute hepatitis C overlap with clear clinical signs, resulting in most of them not being timely detected. In the manifested disease, elimination of the virus is higher (up to 50 %) than among those who remain without marked symptoms of hepatitis [3]. Chronic hepatitis C virus (CHCV) is also usually clinically undetectable in the early years. Some patients complain of weakness, fatigue and malaise [4]. Compared to other viral hepatitis, arthralgia and myalgia are more commonly reported in CHCV [5]. The levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) usually range from the normal to two- to fourfold increase, rarely exceeding 200 IU / l in the absence of other concomitant liver diseases (alcohol-induced liver injury, etc.). An accurate determination of viral load is not very important in most clinical situations and on average, it is around 2 million IU/l. Low viral load is associated with faster recovery after the treatment, but is not associated with low levels of aminotransferases or less pronounced clinical symptoms. Thus, patients might not be aware of the disease for decades; diagnosis is made during screening and detection of abnormal levels of transaminites, or as a result of risk group screening [4].

Besides, HCV can cause various extrahepatic lesions that should be considered in the diagnosis of CHCV. Possible co-morbidities, including alcoholism, heart disease, renal impairment, autoimmune, genetic or metabolic liver
Оригинальные исследования

дiseases (e.g. genetic hemochromatosis, diabetes, obesity) and a possibility of drug-induced hepatotoxic effects should be evaluated [6].

The effect of the fibrosis degree on hematological and biochemical parameters has been sufficiently studied at this time [7]. But the data on the virus genotype impact on these parameters are controversial. In some previous studies, patients with CVHC did not show any association between clinical and biochemical parameters and the virus genotype [8,9], whereas other scientific papers reported on a correlation between the virus genotype and enzymatic activity of leukocytes and monocytes [10] as well as proliferative activity of lymphocytes in peripheral blood [11]. The relationship between the grade of the process activity and the hematological-biochemical data remains understudied.

In addition, it is proved that the level of ALT significantly increases with increasing degree of liver fibrosis [7], which provides a theoretical basis for studying the effect of the grade of activity on indicators that are changed in liver fibrosis progression.

Aim

The aim of this study is to determine the features of the course of CHCV infection and the dependence of changes in integrative indicators of endogenous intoxication, nonspecific immunoreactivity and inflammation on the virus genotype and the grade of activity.

Materials and methods

In the furtherance of the purpose, 287 patients with established diagnosis of CHCV who were undergoing treatment at Sumy Regional Infectious Diseases Clinical Hospital named after Z. Y. Krasovttsky from 2015 to 2019 were examined. Their inpatient and outpatient medical cards were also analyzed.

Inclusion criteria were as follows: the presence of typical clinical signs of CVHC, epidemiological data, no malignant diseases at the time of examination or in the anamnesis (including hepatocellular carcinoma), CHCV confirmed by ELISA and PCR (quality method for RNA detection).

Exclusion criteria were as follows: presence of acute conditions or major complications of decompensated pathology (decompensated cirrhosis; hepatic insufficiency III), concomitant pathology, which may affect the indicators of inflammation, endogenous intoxication and allergies (other infectious diseases, inflammatory diseases of different organs and systems, acute allergic reactions, malignancies, decompensated diabetes mellitus); not detected viral RNA by PCR, detection of hepatitis B virus DNA or antibodies to HBcor-Ag.

The comparison group included 55 apparently healthy individuals who underwent a preventive medical examination at Sumy State University Clinic in 2018–2019. The patients were divided into 3 groups depending on the virus genotype (1b – 150 people, 2 – 19, 3a – 102) and the grade of activity (minimal activity – 210 people, moderate – 68, expressed – 9). Patients with undetectable virus genotype and those who were not tested, as well as individuals with genotype 1b were included in the total sample only. General integrative indices (integral severity index – ISI, entropy of leukocyte formula), indices of nonspecific reactivity (resistance coefficient – RC, immunoreactivity index – IIR, neutrophil and monocyte ratio index – NMRI, lymphocytic index – Ilimph, eosinophils and lymphocytes ratio index ELRI, allergy index – IA, nuclear index – NI); indexes of inflammation activity (total index of inflammation – TII, Krebs index – KI, lymphocyte-granulocyte index – LG, index of leukocytes and ESR ratio – ILESR), indexes of intoxication (leukocyte index of intoxication – LII, aggression index – Iagr, hematological index of intoxication – HI, leukocyte shift index – ILS, indicator of intoxication – IIS, reactive neutrophil response – NRR) were calculated [12,13].

A clinical and laboratory examination was performed according to the protocol. Clinical blood test (CobasMicros), biochemical blood test were done at the hospital laboratory (SOBASEMira) and at the Sinevo Commercial Laboratory where serological studies – enzyme-linked immunosorbent assay for the determination of antinuclear antibody titer (ANA), antimitochondrial antibodies (AMA), thyroid peroxidase antibodies (ATPO), antibodies to thyroglobulin (ATTG), and polymerase chain reaction (PCR, detection of ribonucleic acid (RNA), virus genotype detection) were also carried out.

The grade of the process activity in the liver was determined by the generally accepted International Classification of Liver Diseases (Los Angeles, 1994), depending on the ALT level.

In terms of epidemiological and sex characteristics, age composition and degree of fibrosis, all groups were representative. Concomitant pathology in all the patients was compensated and in remission. All patients were examined prior to the start of etiotropic therapy.

The statistical processing was performed in Microsoft Office Excel 2010 and IBM SPSS Statistic 23 computer software. Data were checked for group distribution normally using the Shapiro-Wilk test. We used non-parametric methods because the data obtained did not follow a normal distribution. Mann-Whitney U-test was used to analyze the quantitative data. To determine the significance of the differences between the frequency indices in the different groups when comparing the qualitative characteristics, contingency tables using the Pearson χ² criterion were constructed. All the used tests were two-sided, P < 0.05 values were considered statistically significant. The results of the study in the text and tables are presented in the form of a median, interquartile range (25th to 75th percentiles).

Results

Among the CHCV patients examined, there were 1.96 times (66.20 %) more men than women (33.80 %). The average age of patients in the total group was 46 (36–55) years.

The vast majority of patients had a subclinical course of acute hepatitis that was detected during a preventive medical examination (97.21 %), and only 2.79 % of patients indicated previously experienced acute viral hepatitis C, while 9.04 % had acute viral hepatitis C in the past.

Among the genotype, CHCV patients were distributed as follows: the majority had genotype 1 (52.3 %), 1.5 times fewer people with 3a (35.5 %), and even fewer with 2 (6.6 %) and 1a genotypes (0.7 %) (P < 0.05). The virus genotype was not detected in 4.9 % of those infected.
The examined patients had mild F2 liver fibrosis (31.25 %), cirrhosis F4 (27.68 %), 1.7 times less fibrosis F0 (17.86 %), 2.1 times less frequently – initial F1 fibrosis (14.73 %) and 3.7 times less frequently – F3 (8.48 %).

CHCV patients showed a minimal activity (73.17 %), which was 3 times more than the moderate activity (23.69 %); 3.14 % presented with the expressed activity.

The main clinical signs revealed on the examination were as follows: asthenovigesimal syndrome (81.88 %), heaviness in the right hypochondrium (64.76 %), subicterus or yellowing of the sclera (15.58 %), feeling of a bitter taste in the mouth (14.98 %), dyspeptic syndrome (12.89 %), arthralgia and myalgia (13.58 %), itching (10.80 %), telangiectasia (6.97 %), pain in the right hypochondrium (5.92 %), the presence of skin rashes (4.18 %), jaundice (1.39 %).

On an objective examination, 74.21 % of patients showed enlarged liver and 24.39 % – enlarged spleen.

Comparing the total sample with the HCV genotype 1b patients, the latter were found to be 1.2 times more likely to have telangiectasia (8.67 % versus 6.97 %) (P < 0.05), but no significant difference was observed.

Patients with genotype 2 did not experience increased discomfort in the left hypochondrium, skin rash and jaundice, feeling of a bitter taste in the mouth was 2.9 times less frequent than in the total group (5.26 %), skin itching was twice less frequently (5.26 %), hepatomegaly – 1.6 times (47.37 %), splenomegaly – 1.5 times (15.79 %), heaviness in the right hypochondrium – 1.4 times (47.37 %) less frequently, and subicterus or yellowing of the sclera was 1.4 times more frequently (21.05 %). However, there was no significant difference in the severity of these clinical features compared to the total group except for hepatomegaly (P < 0.05).

In patients with virus genotype 3a, itching (5.88 %), telangiectasia (3.92 %) were 1.8 times less common, arthralgia and myalgia – 1.5 times less frequent (7.84 %), the presence of skin rashes – 1.4 times less frequent (2.94 %), subicterus and yellowing of the sclera (12.45 %) and feeling of a bitter taste in the mouth – 1.2 times less frequent (12.7 %), but none of the clinical signs was significantly different from the total group. Thus, the clinical features did not depend on hepatitis C virus genotype and the groups were homogeneous.

In the total group of patients, the average leukocyte count was normal (5.36 (4.27–6.49) x 10^9/l and 5.30 (4.80–6.80) x 10^9/l, respectively); ESR was significantly higher than in the comparison group (7.00 (4.00–14.00) mm/h and 5.00 (3.00–11.00) mm/h, respectively). Leukocyte formula did not differ from the norm mean values: band cells (4.00 (2.00–5.00) % and 4.00 (3.00–5.00) %, respectively); eosinophils (2.00 (1.00–3.00) % and 2.00 (1.00–4.00) %, respectively), basophils (0.00 (0.00–1.00) % and 0.00 (0.00–0.00) %, respectively), monocytes (8.00 (6.00–10.00) % and 7.00 (6.00–10.00) %, respectively). At the same time, the level of segmented neutrophils was significantly lower (48.00 (39.00–56.00) % and 55.00 (50.00–69.00) %, respectively), and the number of lymphocytes (35.00 (28.00–40.00) % and 31.00 (28.00–34.00) %, respectively) – higher than in the comparison group. Red blood counts of the CHCV patients were also within the normal range: hemoglobin (142.00 (128.00–153.00) g/l and 138.00 (130.00–146.00) g/l, respectively), erythrocytes (4.61 (4.24–5.09) x 10^12/l and 4.66 (4.32–5.05) x 10^12/l, respectively). The average platelet count was lower than that in the comparison group, 176.00 (138.00–219.00) x 10^11/l and 221.00 (195.00–265.00) x 10^11/l (P < 0.05), respectively.

CHCV patients with different genotypes (1b, 2, and 3a) had a significantly lower platelet count than those in the comparison group (183.00 (141.50–223.25) x 10^11/l; 154.00 (141.00–216.00) x 10^11/l; 173.50 (135.75–225.00) x 10^11/l, respectively); segmented neutrophils (47.00 (39.00–58.00), 47.00 (41.00–53.00), 44.00 (35.00–53.00) %, respectively), and significantly higher lymphocyte count (33.5 (26.00–42.00), 36.00 (28.00–38.00); 35.50 (28.75–39.00) %, respectively) (P < 0.05). Comparing clinical blood counts of the patients with different genotypes, a lower erythrocyte and hemoglobin level was found in patients with genotype 2 (4.34 (4.13–4.64) x 10^12/l; 128.00 (123–142) g/l) than in the comparison group (4.66 (4.32–5.05) x 10^12/l; 138.00 (130.00–146.00) g/l) and in the total group of CHCV patients (4.61 (4.24–5.09) x 10^12/l; 142.00 (128.00–153.00) g/l).

The group of patients with minimal activity showed lower leukocyte counts (5.32 (4.27–6.21) x 10^9/l) (P < 0.05), platelets (180.00 (136.00–217.25) x 10^11/l), segmented neutrophils (48.00 (40.00–58.00) %), eosinophils (2.00 (1.00–3.00) %), as well as higher lymphocyte counts (34.50 (28.00–40.00) %) and ESR (7.00 (4.25–16.00) mm/h) (P < 0.05).

Patients with moderate activity had a lower platelet count (167.50 (141.00–219.00) x 10^11/l) and higher lymphocyte counts (36.50 (31.00–45.75) %) than in the comparison group.

In the total group, leukopenia (15.68 %), erythrocytopenia (18.47 %), anemia (6.62 %) and thrombocytopenia (33.10 %) were more common compared with the healthy group (P < 0.05). People with different HCV genotypes also demonstrated these dynamics, except for the patients with 2 genotype, who did not have anemia.

Total protein levels (73.00 (69.70–76.90) g/l), ALT (61.00 (37.00–121.00) IU/l), AST (50.00 (34.00–78.00) IU/l), GGT (gamma-glutamyltranspeptidase) (48.00 (25.00–80.00) IU/l) were higher in the total group of patients (P < 0.05) than in the comparison group (71.30 (68.30–73.90) g/l, 27.70 (18.30–28.16) IU/l, 24.40 (21.40–28.00) IU/l, 26.00 (18.00–35.00) IU/l, respectively). The values of ALP (alkaline phosphatase) (79.00 (62.00–101.00) IU/l) and creatinine (77.00 (65.00–90.00) μmol/l) were normal and even lower than in the comparison group (90.00 (80.00–112.00) IU/l, 82.90 (72.90–100.70) μmol/l, respectively) (P < 0.05).

Glucose levels (5.50 ± 0.12) had no significant difference with the comparison group (5.20 (4.59–5.70)) (P < 0.05).

Total protein levels in the patients with HCV 1 and 2 genotype were higher than in the comparison group (73.20 (69.27–77.28); 74.30 (71.50–77.20) g/l, respectively) and lower in patients with genotype 1b and 3a (79.00 (61.00–97.26) IU/l, 74.00 (61.75–97.25) IU/l, respectively), creatinine was lower only in the group with genotype 1c (79.00 (72.90–100.70) μmol/l, respectively) (P < 0.05).

Besides the ALT level, groups with different activity grades had higher AST (minimal activity – 42.00 (30.75–60.00) IU/l, moderate – 78.00 (52.50–126.00) IU/l, expressed – 280.00 (207.50–370.00) IU/l), GGT (41.00 (25.00–69.00) IU/l, 66.00 (30.00–96.90) IU/l,
### Table 1. Characteristics of integrative parameters in patients with different HCV genotype

| Indicator | Group | CHCV patients | 1b genotype (n = 150) | 2 genotype (n = 19) | 3a genotype (n = 102) |
|-----------|-------|---------------|----------------------|-------------------|----------------------|
| General integrative indicators | | | | | |
| ISI | 13.83 (13.58–14.56) | 13.87 (13.45–14.60) | 13.60 (13.50–14.61) | 13.71 (10.88–14.16) |
| H | 21.05 (18.30–24.15) | 26.04 (21.64–33.32) | 24.80 (22.18–32.86) | 26.16 (20.78–32.43) |
| Non-specific reactivity indices | | | | | |
| RC | 0.74 (0.52–0.98) | 0.74 (0.47–1.01) | 0.75 (0.53–0.93) | 0.71 (0.54–1.21) |
| IIR | 4.63 (3.40–6.40) | 4.65 (3.29–7.33) | 4.95 (3.20–7.45) | 5.38 (3.84–7.65) |
| NMRI | 7.88 (5.60–10.67) | 6.88 (4.67–9.83) | 7.13 (5.00–9.80) | 6.62 (4.18–10.62) |
| LMR | 6.25 (3.00–8.83) | 6.74 (3.00–7.04) | 6.22 (3.00–7.04) | 5.00 (3.52–7.29) |
| Lymph | 0.04 (0.04–0.09) | 0.06 (0.04–0.06) | 0.07 (0.02–0.10) | 0.09 (0.05–0.10) |
| ERI | 0.08 (0.03–0.11) | 0.05 (0.03–0.10) | 0.05 (0.02–0.10) | 0.09 (0.04–0.15) |
| IA | 0.99 (0.78–1.18) | 1.11 (0.78–1.16) | 1.10 (0.80–1.56) | 1.23 (0.76–1.88) |
| NI | 0.07 (0.05–0.10) | 0.08 (0.05–0.12) | 0.08 (0.05–0.12) | 0.09 (0.05–0.13) |
| Inflammatory activity index | | | | |
| TII | 6.95 (6.33–7.69) | 6.34 (4.66–7.49) | 6.35 (4.82–7.44) | 6.13 (5.26–7.10) |
| KI | 1.85 (1.65–2.11) | 1.46 (1.10–2.03) | 1.48 (1.05–2.27) | 1.46 (0.91–2.02) |
| ILG | 5.17 (4.48–5.76) | 4.69 (4.68–6.43) | 4.63 (4.28–6.82) | 4.60 (4.85–10.27) |
| IL EST | 1.65 (0.87–2.76) | 2.40 (1.52–4.20) | 2.40 (1.40–4.25) | 1.88 (1.15–3.06) |
| Endogenous intoxication indices | | | | |
| LII | 0.45 (0.33–0.78) | 0.46 (0.25–0.68) | 0.46 (0.27–0.67) | 0.41 (0.19–0.89) |
| Iag | 0.63 (0.44–1.09) | 0.64 (0.34–1.15) | 0.65 (0.37–1.18) | 0.56 (0.28–1.20) |
| HII | 0.46 (0.30–0.70) | 0.47 (0.34–0.90) | 0.49 (0.26–0.91) | 0.47 (0.27–0.81) |
| HLS | 1.56 (1.38–1.78) | 1.27 (0.96–1.70) | 1.27 (0.90–1.77) | 1.27 (0.64–1.72) |
| IIS | 0.12 (0.06–0.31) | 0.17 (0.07–0.43) | 0.17 (0.08–0.44) | 0.10 (0.05–0.36) |
| NRR | 11.28 (7.14–16.71) | 6.28 (2.04–15.21) | 7.02 (2.04–15.65) | 6.86 (2.65–11.49) |

Significant difference in the indicator relative to: *: comparison groups; **: total group (P < 0.05, calculated according to the Mann–Whitney criterion).

In the total group of CHCV patients, the entropy indices of leukocyte formula were higher; the indexes of nonspecific reactivity had higher values of RC (1.3 times), IIR (1.3), IA (1.1), and lower than in the comparison group were NMRI (1.1) and ERI/ (1.3). There was a decrease in inflammation indicators: TII by 1.1 times, KI – by 1.3 times and an increase in ILG by 1.3, ESR – by 1.5 times. Indices of endogenous intoxication were decreased in patients, compared with healthy individuals (ILS – by 1.2 times, NRR – by 1.8) (Table 1).

In groups with different genotypes, the changes corresponded to the overall sample, except AI that was higher only in the total group and with 3a genotype; ESR in patients with 3a genotype was lower than in the total group but did not differ from the comparison group: IIS was higher in the group with 1b genotype of HCV than in the comparison group, and it was 1.7 times lower in 3a genotype compared with the group with 1b genotype of HCV.
Table 2. Features of integrative parameters in patients with different grade of the liver process activity

| Indicator | Group | Comparison (n = 55) | Total (n = 287) | Minimal activity (n = 210) | Moderate activity (n = 65) |Expressed activity (n = 9) |
|-----------|-------|--------------------|----------------|---------------------------|---------------------------|--------------------------|
| General integrative indices | ISI | 13.83 (13.58–14.56) | 13.87 (13.45–14.60) | 14.00 (13.55–14.94) | 13.69 (2.88–14.20) | 13.55 (2.60–13.95) |
| | H | 21.05 (18.30–24.15) | 26.04 (21.49–33.32) | 26.68 (21.49–33.33) | 24.80 (21.07–30.31) | 27.42 (23.08–32.03) |
| Non-specific activity indices | RC | 0.57 (0.49–0.66) | 0.74 (0.52–0.98) | 0.72 (0.50–0.95) | 0.78 (0.59–1.24) | 0.69 (0.57–0.78) |
| | IIR | 4.63 (3.40–6.40) | 4.86 (3.28–7.33) | 5.00 (3.22–7.50) | 4.75 (3.64–6.67) | 3.70 (2.75–5.65) |
| | MNRI | 7.88 (5.60–10.67) | 6.88 (4.67–9.83) | 7.11 (5.00–10.25) | 6.13 (4.47–8.43) | 6.25 (4.58–6.88) |
| | LIR | 4.25 (3.00–5.83) | 4.50 (3.08–7.00) | 4.71 (3.00–7.00) | 4.50 (3.27–6.28) | 3.50 (2.63–5.79) |
| | I Emb | 0.54 (0.47–0.60) | 0.69 (0.49–0.91) | 0.68 (0.47–0.88) | 0.73 (0.54–1.14) | 0.62 (0.51–0.71) |
| | ELRI | 0.08 (0.04–0.11) | 0.06 (0.03–0.11) | 0.05 (0.02–0.10) | 0.07 (0.03–0.13) | 0.03 (0.01–0.08) |
| | AI | 0.99 (0.78–1.18) | 1.11 (0.78–1.58) | 1.05 (0.75–1.50) | 1.32 (0.93–1.83) | 0.92 (0.61–1.04) |
| | NI | 0.07 (0.05–0.10) | 0.08 (0.05–0.12) | 0.08 (0.05–0.12) | 0.06 (0.04–0.11) | 0.09 (0.05–0.12) |
| | | | | | | |
| | | | | | |
| Inflammatory activity index | TII | 6.95 (6.33–7.69) | 6.34 (4.66–7.49) | 6.41 (4.91–7.60) | 6.19 (5.00–6.93) | 6.58 (5.00–7.32) |
| | KI | 1.85 (1.65–2.11) | 1.46 (1.10–2.03) | 1.48 (1.14–2.11) | 1.36 (0.88–1.86) | 1.61 (1.39–1.95) |
| | LGI | 5.17 (4.46–5.76) | 6.49 (4.68–8.43) | 6.40 (4.46–8.13) | 6.65 (5.00–10.53) | 6.10 (5.01–6.85) |
| | IR ESR | 1.65 (0.87–2.76) | 2.40 (1.52–4.20) | 2.48 (1.59–4.56) | 2.16 (1.33–3.84) | 1.98 (1.40–3.28) |
| Endogenous intoxication indices | LII | 0.45 (0.33–0.78) | 0.46 (0.25–0.85) | 0.50 (0.28–0.86) | 0.30 (0.19–0.69) | 0.64 (0.41–1.13) |
| | Iag | 0.83 (0.66–1.09) | 0.64 (0.34–1.15) | 0.69 (0.39–1.17) | 0.44 (0.25–0.84) | 0.44 (0.26–1.03) |
| | HII | 0.46 (0.30–0.70) | 0.47 (0.24–0.90) | 0.50 (0.27–0.94) | 0.30 (0.19–0.70) | 0.31 (0.19–0.64) |
| | HLS | 1.56 (1.38–1.78) | 1.27 (0.96–1.70) | 1.28 (1.00–1.72) | 1.17 (0.85–1.63) | 1.22 (0.87–1.60) |
| | IOS | 0.12 (0.06–0.31) | 0.17 (0.07–0.43) | 0.19 (0.08–0.44) | 0.10 (0.05–0.34) | 0.10 (0.06–0.41) |
| | NRR | 11.28 (7.14–16.71) | 6.28 (1.92–15.21) | 6.22 (1.77–14.33) | 5.16 (2.02–20.05) | 5.74 (2.02–9.09) |

Significant difference in the indicator relative to: * comparison groups; ** total group (P < 0.05, calculated according to the Mann–Whitney criterion.

to all patients. In contrast to the total group, in patients with 2 genotype, the TII was decreased even more, but NMRI, IA, and ELRI were not changed compared with the healthy subjects (Table 1).

Among individuals with minimal activity, endogenous intoxication indices (Iag, HII, IIS, ILS) were higher than in the comparison group. Differences from the comparison group were observed in the distribution of leucocyte formula entropy values, RC, I Emb, ELRI, TII, KI, ILG, IL ESR, ILS, HII, IIS and NRR (Table 2).

In patients with moderate activity, in addition to the previous group, IA was increased, NMRI, LII were decreased, and ELRI, HII, IIS – without changes. Compared to the total group, LII, Iag, HII had lower values.

The values of the integrative indicators of the sample with expressed activity differed from the total group lage, and from the comparison group – in the value of ISI, entropy, KI, ILG, ILS (Table 2).

We studied the features of autoimmune reactions and immunological features in 84 patients, and it was found that the values of ATPO (14.46 (10.52–21.48) IU/ml), ATTrG (22.59 (15.54–29.50) IU/ml), were normal. Negative values of ANA (<1:100) among the examined were 54.76 %, values at the limit of norm (1: 100) – 20.24%, positive (> 1:100) – 25.00 %. In this group patients, the AMA level had the following features: negative values (<1:100) were 79.76 %, values at the limit of norm (1: 100) – 20.24%, positive (> 1:100) – 25.00 %. In this group patients, the AMA level had the following features: negative values (<1:100) were 79.76 %, values at the limit of norm (1: 100) – 20.24%, positive (> 1:100) – 25.00 %. In this group patients, the AMA level had the following features: negative values (<1:100) were 79.76 %, values at the limit of norm (1: 100) – 20.24%, positive (> 1:100) – 25.00 %. In this group patients, the AMA level had the following features: negative values (<1:100) were 79.76 %, values at the limit of norm (1: 100) – 20.24%, positive (> 1:100) – 25.00 %.
It is known that CHCV can cause various extrahepatic lesions that need to be considered for diagnosis. This implies the need for examinations on the presence of comorbidities (alcoholism, heart disease, impaired renal function, autoimmune, genetic or metabolic diseases of the liver) [6]. The examination of CHCV patients found an autoimmune component in the disease pathogenesis: cryoglobulinemia, psoriasis, autoimmune thyroiditis, glomerulonephritis, rheumatic heart disease, Recklinghausen disease, although they are rare. According to a systematic review and meta-analysis, the nine most common diseases associated with HCV infection are known. These include mixed cryoglobulinemia, chronic kidney or end-stage renal disease, type 2 diabetes mellitus, B-cell lymphoma, Sjogren's syndrome, late-stage porphyria, rheumatoid arthritis. The authors reported that type 2 diabetes mellitus (15 %) and depression (25 %) had the highest incidence among HCV-infected patients. In addition, 4.9 % of patients could develop symptomatic mixed cryoglobulinemia, and 30 % had true cryoglobulinemia. In fact, CHCV patients had a 12-fold higher risk of mixed cryoglobulinemia than healthy patients did. Other researchers also found that CHCV patients had an increased risk of developing kidney disease and / or end-stage kidney disease by 23 %, an increased risk of type 2 diabetes mellitus, and a 60 % higher risk of developing lymphoma. In addition, HCV-infected patients were twice as likely to develop flat lichen, Sjogren's syndrome, rheumatoid arthritis, and depression, with an 8-fold increased risk of late-onset porphyria [17]. The mechanisms by which extrahepatic lesions develop include immunological disorders when chronic virus persistence results in the circulation of immune complexes and other autoimmune phenomena that are directly caused by the virus and associated with its tropism to other tissues [18].

Cardiovascular disorders (from 4.18 % to 37.63 %) had a significant role in patients. Other researchers also evaluated the impact of HCV on the incidence of cardiovascular and cerebrovascular lesions and found that cardiovascular disease was more frequent in CHCV patients by 20 % and cerebrovascular – by 35 % compared to those without HCV [19]. However, some European studies showed very different features of concomitant pathology in CHCV, when the most common disease was diabetes mellitus (20.8 %), metabolic syndrome (15.5 %), and coronary heart disease in a small number of patients (6.2 %) [15], the majority of HCV-positive patients also had diabetes mellitus (18.7 %), chronic kidney disease (4.4 %), and end-stage renal insufficiency requiring hemodialysis (2.6 %) [20]. These differences are explained by the peculiarities of different nosologies incidence in the population of some countries. It is well-known fact that the highest level of metabolic disorders (including diabetes mellitus) among US residents is related to their lifestyle and diet. According to the WHO, the relative mortality rate from cardiovascular pathology in Ukraine is 68 %, and in the USA – 31 %, while the death rate from diabetes mellitus in Ukraine is 1 %, and in the USA – 3 % [21].

Typical signs were observed in patients with CVHC: thrombocytopenia, erythrocritocytopenia, leukocytopenia, which was confirmed by the literature data. However, according to the previous studies, the mean count of erythrocytes, leukocytes and platelets did not differ from the values of the control group [22,23], while in our study, platelet count...

Discussion

Hepatitis C virus is a common disease. Only 10 % of acute hepatitis C overlap with clinical signs [3]. Among the patients examined, the majority were detected during preventive medical examination (97.21 %). Most of the patients had 1c (52.30 %) and 3a (35.50 %) HCV genotype, which corresponds to the situation in Central Asia (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan; 1 genotype – 52.60 % and 3 genotype – 38.00 %) [14], and is partly in line with studies carried out in Italy where the most common virus genotypes were 1b (47.4 %) and 2 (16.5 %). Most patients had a moderate degree of fibrosis (F2 – 31.25 %). The number of our patients with cirrhosis (27.68 %) was not significantly different from the data obtained in other studies, where 32.8 % of the whole group had cirrhosis [15]. However, more than half of the examined patients with CHCV in Brazil (54.4 %) had F4 [16].

Among all the patients, the vast majority had a clear asthenovegetative syndrome (81.88 %) and a feeling of heaviness in the right hypochondrium (64.76 %). Other authors' publications also state that chronic HCV infection in the early years does not have a clear manifestation. Only some patients complain of weakness, fatigue and malaise [4].

echogenicity (minimal activity – in 79.27 %, moderate – in 86.27 %, expressed – in 83.33 %; 1b genotype – in 84.62 %, 2 genotype – in 84.00 %, 3a genotype – in 87.84 %). In 42.08 % of the examined, the liver vascular pattern was increased (minimal activity – in 43.90 %, moderate – in 49.02 %, expressed – in 33.33 %; 1b genotype – in 46.22 %, 2 genotype – in 46.67 %, 3a genotype – in 42.67 %).

An increased diameter of the portal vein was diagnosed in 2.73 % of patients (minimal activity – in 4.27 %, moderate – in 3.92 %, expressed – in 0.00 %; 1b genotype – in 4.24 %, 2 genotype – in 0.00 %, 3a genotype – in 2.70 %).

72.47 % of patients had gallbladder wall compression (minimal activity – in 71.34 %, moderate – in 62.75 %, expressed – in 83.33 %; 1b genotype – in 70.94 %, 2 genotype – in 71.43 %, 3a genotype – in 76.81 %).

37.98 % of patients had a mural layer of inspissated bile, 33.48 % had an altered gallbladder shape (G, S-shaped with constriction, which could disrupt bile flow); minimal activity – in 34.76 %, moderate – in 33.33 %, expressed – in 33.33 %; 1b genotype – in 29.52 %, 2 genotype – in 35.71 %, 3a genotype – in 43.66 %). In 6.68 % of patients were determined concrements in the gallbladder cavity (minimal activity – in 12.20 %, moderate – in 7.84 %, expressed – in 0.00 %; 1b genotype – in 14.41 %, 2 genotype – in 6.67 %, 3a genotype – in 8.57 %). The gallbladder diameter (4.00 (3.00–4.00)) was enlarged in 3.79 % of patients (minimal activity – in 3.66 %, moderate – in 3.92 %, expressed – in 0.00 %; 1b genotype – in 5.93 %, 2 genotype – in 0.00 %, 3a genotype – in 1.41 %). In 31.31 % of the patients, spleen enlargement found (minimal activity – in 39.02 %, moderate – in 21.57 %, expressed – in 33.33 %; 1b genotype – in 44.23 %, 2 genotype – in 26.67 %, 3a genotype – in 27.03 %), the spleen vein diameter was enlarged in 9.71 % (minimal activity – in 8.57 %, moderate – in 3.92 %, expressed – in 0.00 %; 1b genotype – in 43.66 %). In 6,68 % of patients were determined gallbladder wall compression (minimal activity – in 71.34 %, moderate – in 62.75 %, expressed – in 83.33 %; 1b genotype – in 70.94 %, 2 genotype – in 71.43 %, 3a genotype – in 76.81 %).

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we have demonstrated a significantly lower incidence of anemia in patients with 2 genotype, and other studies have shown a higher incidence of hemoglobin reduction in patients with 1 genotype [22], which is not contradictory but complementary.

Among the examined CHCV patients, the values of liver enzymes (AST, ALT, GGT) were significantly higher. The increase in ALT and AST activity is in line with other studies where their levels were higher than normal [4,7,9,23].

As the study shows, changes in the integrative indices were found, with indices of nonspecific reactivity and inflammation predominantly changing, whereas among the indexes of endogenous intoxication, the ILS and NRR were mostly changed. According to other authors, laboratory signs of endogenous intoxication syndrome were recorded during the acute pathological process and after the end of it, in chronic course of viral hepatitis without clinical signs and in the formation of liver cirrhosis, confirming the severe and profound changes in the liver as the main organ of the regulation and detoxification system [18]. Quantitative and qualitative immune imbalance in viral hepatitis leads to dysfunction of immune cells and humoral immunity factors, which causes activation of endogenous flora and increase in its metabolism products, which further increases endotoxins [24]. The increase in entropy in all groups is explained by worsening disorder in leukocyte formula in CHCV patients. It is well known that entropy increases as the process is directed toward increasing chaos in the system. The increase in RC was due to the increase in the adaptive body reactions in HCV infected, lillmph – increased cellular immunity compared to humoral given to viral etiology of the disease. The decrease in NMR1, ELRI and IK in patients was due to a decrease in the ratio of microphage-macrophage system components and the lymphocyte prevalence, which is a typical sign of reactivity in viral infection. An increase in ILG and IL ESR indicated the prevalence of the autoimmune inflammatory component in patients compared to infectious, and the decrease in TII – the absence of inflammation or its mild activity [25].

Conclusions

1. Young people, male, with HCV 1 genotype, moderate hepatic fibrosis (F2), and minimal process activity (P < 0.05) predominated in CHCV. The most pronounced were asthenovegetative syndrome and heaviness in the right hypochondrium with objective findings – hepatomegaly (P < 0.05). The disease was accompanied by leukocytopenia, erythrocytopenia, decrease in hemoglobin content, thrombocytopenia, increase in lymphocyte count and ESR, hyperfermentemia.

2. The groups with different genotypes were homogenous in most features, except that telangiectasia, glomerulonephritis were more frequently found in the examined with 1 genotype with higher protein and lower AIP and creatinine levels; hepatomegaly was less frequent and creatinine was lower (P < 0.05) in 2 genotype. Patients with 3a genotype had higher total protein level (P < 0.05).

3. Among the examined with varying degrees of activity, most indicators were in the total group. However, in those with minimal activity, the level of segmented neutrophils and ESR was higher, and that of lymphocytes and platelets was lower (P < 0.05). Among patients with moderate activity, hemoglobin and segmented neutrophils were higher and lymphocytes and platelets were lower (P < 0.05). Patients with expressed activity had higher AIP, GGT and total bilirubin, and lower glucose levels (P < 0.05).

4. In the total group of patients with CHCV, the entropy indices of leukocyte formula were higher as well as the indices of nonspecific reactivity – RC, Ilimph, IA, and lower – NMRI and ELRI (P < 0.05). In addition, all indicators of inflammation were changed: decreased TII and KI, and increased ILG and IL ESR (P < 0.05). Patients with 2 genotype had lower values of TII, with 3a genotype – ISI, IL ESR, and IIS (P < 0.05). Among those with minimal activity, higher values of endogenous intoxication (Iagr, HII, IIS) were observed, lower levels of NI, LII, Iag, IIS – in patients with moderate activity, and lagr (P < 0.05) – in patients with expressed activity.

Conflicts of Interest: authors have no conflict of interest to declare.

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