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Hepatocellular Carcinoma in Patients with Chronic Hepatitis C

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Abstract

The purpose of the study was to examine the clinical and epidemiological data in patients with chronic hepatitis C (CHC) and hepatocellular carcinoma (HCC) before they sought specialized medical care.

The study included 92 patients with CHC. All patients were divided into 2 groups: Group 1 consisted of CHC patients with HCC (n=45), and Group 2 (n=47) consisted of CHC patients without HCC.

With the development of HCC in CHC patients, clinical manifestations were absent only in 2.2% of patients. Determining factors in HCC development are male sex, mature age, the maintained HCV replication, moderate and severe fibrosis, disease duration of more than 10 years, and the lack of effect of antiviral treatment. **Int J Biomed. 2016;6(3):195-198.)**.

Key Words: chronic hepatitis C • hepatocellular carcinoma • risk factors • clinical manifestations.

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide.[1] In most countries, HCC accounts for 70%–85% of primary liver cancer cases,[2] with the burden of disease expected to increase in coming years.[3] HCC causes ~600,000 deaths worldwide per year.[1]

HCC is a complex disease associated with many risk factors and cofactors.[4,5] Most cases of HCC are secondary to chronic infection with HBV or HCV. About 10% to 25% of HCC cases worldwide are thought to be a result of HCV infection.[6,7]

There is a need for further investigation of the clinical and pharmacological aspects of this disease. Algorithms for HCC treatment depend on the stage of the disease at diagnosis and the availability of complex therapies.[8] However, the disease is incurable in advanced stages, when its management is very expensive and effective only in terms of quality adjusted life years (QALY).[9] According to Bolondi et al.[10] the cost per treatable HCC was $17,934 with a cost per life year saved of $112,993.

The rating and ranking of risk factors (RFs) for the formation of cirrhosis and primary liver cancer in patients with chronic hepatitis C (CHC) is a serious health problem. Its relevance is unquestionable and requires immediate development of organizational models of treatment and prevention of viral hepatitis and primary liver cancer, because this pathology is one of the threats to national security.

The purpose of the study was to examine the clinical and epidemiological data in patients with CHC and HCC before they sought specialized medical care.

Materials and Methods

Diagnosis was established based on the clinical-laboratory data as well as the results of the PCR (RNA-HCV) and IEA (anti-HCV). The expression of the hepatic cytolysis syndrome was determined according to the International Classification (Los-Angeles, 1994). Viral loading and the genotype of the C virus were defined by PCR. A percutaneous liver biopsy was performed to confirm HCC diagnosis and to grade and stage histological disease. Liver biopsies that were at least 1.5 cm in length and had 3-5 portal tracts were considered as informative. Coded histological sections of liver biopsies were scored independently by two different histopathologists using the Knodell Histology Activity Index (HAI)[11] and Metavir system.[12] A consensus score was calculated after discussion on the points of differences for comparison of various classification and statistical calculations. Patients with PCC were distributed in stages of the disease according to AJCC TNM 6th edition.[13]

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The study included 92 patients with CHC. All patients were divided into 2 groups: Group 1 consisted of CHC patients with HCC (n=45), and Group 2 (n=47) consisted of CHC patients without HCC (Table 1).

Table 1.

Baseline characteristics of patients

Variable		Group 1 n=45	Group 2 n=47	*P*
Male, n(%)		29 (64.4)	26 (55.3)	*0.3723*
Female, n(%)		16 (35.6)	21 (44.7)	
Age, y		56.0±2.5	32.1±2.1	*0.0000*
Weight, kg		66.1±3.2	72.8±2.9	*0.1237*
Duration of disease, y		17.5±2.7	7.9±2.1	*0.0059*
HCV genotype, n(%)	1b	33 (73.3)	27 (57.4)	*0.1097*
	3a	7 (15.6)	12 (25.5)	*0.2374*
	2	5 (11.1)	8 (17.0)	*0.4158*
METAVIR stage F3		19 (42.2)	6 (12.8)	*0.0015*

In accordance with the purpose of the study, we designed a specific observation card, which included demographic data, duration of HCV infection, routes of HCV transmission, alcohol consumption, smoking status, and the results of physical examination and laboratory/instrumental investigations.

The study was approved by the local Ethics Committee. Written informed consent was obtained from each patient.

Statistical analysis was performed using the statistical software «Statistica» (v6.0, StatSoft, USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean ± SEM for continuous variables. The Mann-Whitney (U Test) was used to compare the differences between groups. Group comparisons with respect to categorical variables are performed using chi-square test. A probability value of $P<0.05$ was considered statistically significant.

Results and Discussion

Among CHC patients with HCC, 29(64.4%) were male and 16(35.6%) female. The average age of patients at the first examination ranged from 40 to 72 years (mean age 56.0±2.5 years), with no significant differences between men and women.

A history of icteric forms of acute viral hepatitis (AVH) was found in 5(11.1%) patients. The presence of HCV infection RFs was found in 39(86.7%) patients. These patients were those with the following conditions: earlier acute surgical diseases, which were a reason for blood transfusion and surgical interventions (30.8%); a combination of RFs for infection (professional risk and blood transfusion) (12.8%); elective surgical operation and parenteral manipulations in hospital (28.2%); occupational exposure to blood (12.8%); drug use by injection (10.3%); and tattoos (5.1%).

The duration of HCV infection was determined in 42 patients of Group 1: up to 10 years in 14.3% of patients, from 10 to 15 years in 33.3% of patients, and more than 15 years in 52.4% of patients.

In Group 1, the characteristic clinical signs of the disease (by the frequency of their appearance) were asthenovegetative syndrome(fatigue, irritability, sleep disturbances, a decreased performance, and general weakness, malaise, mood instability, headache), dyspeptic syndrome(loss of appetite, abdominal discomfort, nausea, bloating, belching and vomiting in some patients), and dull aching pain in the epigastric zone or right upper quadrant. Almost all patients of Group 1 had complaints (Table 2); the difference was only in the degree of the severity and various combinations of the complaints.

Table 2.

Clinical syndromes and symptoms in patients of both groups

Clinical manifestations	Group 1 n (%)	Group 2 n (%)	*P*
Asthenovegetative syndrome	44 (97.8)	28 (59.6)	*0.000*
Dyspeptic syndrome	31 (68.9)	27 (57.4)	*0.2557*
Hepatomegaly	37 (82.2)	29 (61.7)	*0.0289*
Splenomegaly	23 (51.1)	10 (21.3)	*0.0028*
Hemorrhagic syndrome	16 (35.6)	4 (8.5)	*0.0017*
Right hypochondrium syndrome	43 (95.6)	30 (63.8)	*0.0002*
Icteric skin/sclera	12 (26.7)	2 (4.3)	*0.0028*
Weight loss	27 (60.0)	2 (4.3)	*0.0000*
Arthralgia	28 (62.2)	12 (25.5)	*0.0004*
Myalgia	26 (57.8)	15 (31.9)	*0.0126*
Depression	19 (42.2)	6 (12.8)	*0.0015*
Skin rashes	5 (11.1)	2 (4.3)	*0.397**

**- Yates' p-value*

In Group 1, the first clinical manifestations of the disease in 36(80%) patients were the hepatic manifestations (hepatomegaly, jaundice, an enlarged spleen), whereas in Group 2, these manifestations were found only in 10(21.3%) patients. In early disease, extrahepatic manifestations were detected in 27(60%) patients in Group 1 and 12(25.5%) patients in Group 2. The combination of the hepatic and extrahepatic manifestations occurred in 29 (64.4%) patients in Group 1 and 9 (19.1%) patients in Group 2.The absence of the hepatic and extrahepatic manifestations was noted only in 3(6.7%) patients of Group 1 and 19(40.4%) patients of Group 2. Disease debut with hepatic manifestations was found in 21(74./2%) men and 7(43.7%) women, whereas disease debut with extrahepatic manifestations was in 8(50%) women and 6(20.6%) men ($p<0.001$).

In Group 1, the nonspecific complaints were also frequent: fatigue (weakness and decreased performance) (97.8%), headache (61.1%), heaviness (88.2%) and pain

in the right upper quadrant (47.2%), poor appetite(57.6%), epigastric pain (45.1%), nausea (42.4%), flatulence (61.1%), and abdominal discomfort (63.2%). In addition, itchy skin was found in 4 patients. Among the objective data from the physical examination, we found enlargement of the liver and spleen in 82.2% and 51.4% of patients, respectively; hemorrhagic syndrome in 35.6% of patients; and extrahepatic signs of liver disease as a palmar erythema and vascular "sprockets" in 68% of patients.

In general, the combination of CHC and HCC has no strictly specific clinical symptoms that can help to distinguish this concomitant pathology from other liver diseases. However, the comparative analysis shows the predominance of the asthenovegetative and hemorrhagic syndromes, hepatosplenomegaly, arthralgia, myalgia, depression, and weight loss in patients of Group 1. Clinical manifestations of the disease often did not meet the severity of liver injury; to evaluate the activity and prognosis, we used laboratory, instrumental, and morphological methods of diagnosis.

In Group 1, the degree of inflammatory activity by HAI was as follows: minimal (score 1-3) - 5(11.1%), mild (score 4-7) - 10(22.2%), moderate (score 8-12) - 14(31.1%), and marked (score 13-18) - 16(35.6%). Distribution of patients by METAVIR stage of liver fibrosis is shown in Fig. 1.

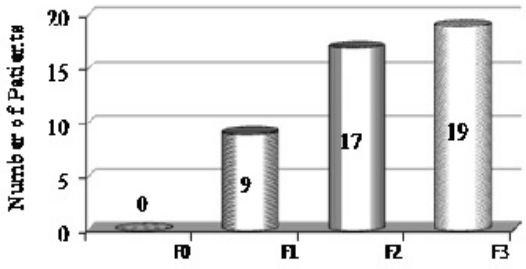

Fig. 1. *Distribution of patients by METAVIR stage of liver fibrosis*

The distribution of Group 1 patients according to the HCV genotypes was as follows: genotype 1b - 33(73.3%), genotype 3a - 7(15.6%), and genotype 2 - 5(11.1%). HCV RNA was detected in 41(91.1%) patients. The average viral load was $2.3x10^6$ IU/ml.

In Group 1, 18(40%) patients received the combined antiviral treatment: peginterferon-alpha2a plus ribavirin. However, antiviral treatment did not lead to a sustained virologic response. On the background of antiviral treatment, virological relapse and virological breakthrough were noted in 6 and 12 patients, respectively; 22 people refused to initiate antiviral treatment, and one patient did not receive antiviral treatment due to the presence of contraindications.

Indicators of alpha-fetoprotein (AFP) remained within the normal range (from 0.5 to 2.5 MoM) in 50% of patients. In 24% of patients, AFP increased from 5 to 30 MoM, and 26% of patients had AFP from 170 to 12000 MoM. According to MRI results, the left lobe of the liver was moderately enlarged in 40% of patient, the right lobe in 10% of patients, and both lobes in 10% of patients. The liver size within the age norm was found in 40% of patients. We found the following localization of the pathological process: S7-60%, S8-40%, and the combination of 3 or more segments in 30% of patients.

The presence of concomitant diseases was noted in 38(84.4%) patients in Group 1: gastrointestinal disease in 71% of cases, including 15(33.3%) patients with two or more comorbidities.

Conclusion

The clinical picture of CHC without HCC was low symptomatic, and clinical signs were absent in 36% of patients. With the development of HCC in CHC patients, clinical manifestations were absent only in 2.2% of patients. In some patients, the disease was diagnosed in connection with the "accidental" discovery of elevated levels of serum transaminases and/or detection of anti-HCV. Often, especially in women, the first clinical signs of the disease were extrahepatic signs. Determining factors in HCC development are male sex, mature age, the maintained HCV replication, moderate and severe fibrosis, disease duration of more than 10 years, and the lack of effect of AVT.

Competing interests

The authors declare that they have no competing interests.

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