

LIVER DAMAGE FROM HEROIN MISUSE, COMBINED WITH HCV INFECTION: CLINICAL AND MORPHOLOGICAL CHANGES

Dessislava Lubomirova
Pavlova,
Reni Ivanova¹,
Ivan N. Ivanov¹,
Ivanka P. Marinova,
Angelika S. Velkova²,
Elena S. Markova¹,
Pavlina Iordanova Laleva³,
Ivan A. Lalev⁴,
Margarita D. Vlachova⁴

*Clinic of Gastroenterology and
Hepatology,*

University Hospital, Pleven

¹*Department of Clinical Pathology,
University Hospital, Pleven*

²*Department of Social and
Preventive Medicine,
Pedagogy and Psychology,
Medical University, Pleven*

³*Department of Clinical Laboratory,
Clinical Immunology and
Allergology,
Medical University, Pleven*

⁴*Gastrodiagnostics Department,
University Hospital, Pleven*

Corresponding Author:

Dessislava Lubomirova
Clinic of Gastroenterology and
Hepatology
UMHAT "Dr G.Stranski"
5800, Pleven
Bulgaria
e-mail: Dr_lubomirova@abv.bg

Received: July 15, 2011

Revision received: October 04, 2011

Accepted: December 22, 2011

Summary

The aim of the study was to assess more data on the severity of liver damage in heroin addicts (HA) with proved hepatitis C viral (HCV) infection. The study included 20 patients with chronic viral hepatitis C (CHC), of which ten had a documented history of intravenous heroin misuse. The two groups of patients were compared according to biochemical changes, characterising the liver damage (serum levels of ASAT, ALAT, GGT, APH and total bilirubin), serum level of HCV RNA, ultrasound images visualizing grades of steatosis, histological changes assessed by METAVIR and histochemical changes, evaluated using PAS, Gomori and Van Gieson reactions. Our study confirmed the presence of liver damages in both groups but the role of heroin as an independent damaging factor could not be elicited.

Key words: heroin abuse, chronic hepatitis C, liver

Introduction

Heroin (diacetylmorphine, diamorphine, morphin diacetate) is a semi-synthetic drug from the opioid group. It is a product of morphine - one of the major alkaloids, obtained from opium poppy. It was first synthesised by the English chemist Wright in 1874. Dresser, who introduced the acethyl-salicylic acid too, introduced heroin in medical practice 23 years later [1, 2]. The major locus of action of heroin is the brain, which is reached extremely fast after parenteral use. Heroin is metabolised to the inactive 3-monoacetylmorphine and the active 6-monoacetylmorphine and then to morphine, which binds to the μ -receptors in brain tissue. The result of this reaction is the specific action of heroin - narcotic euphoria, powerful analgesia and anxiolysis [1].

Numerous studies on humans and experimental animals have proved that intravenous heroin misuse leads to various morphological changes in the liver tissue, the intensity of which increases with the length of heroin abuse, including vesicular degeneration, fatty changes, reduction of glycogen content in hepatocytes, vascular changes [2-10]. The following changes are specific for the action of heroin on the liver:

- fibrosis (group of hepatocellular changes);
- vascular damages (sinusoidal dilatation);

- hepatic vein changes (phlebosclerosis) [7, 8, 9].

Heroin itself leads to liver injury but is also one of the major risk factors for transmission of the virus of chronic hepatitis C. [11]. Hepatitis C becomes chronic in about 80 % of the cases. When it is not treated, it leads to progressive liver damage, and eventually to liver cirrhosis and clinical manifestation of the whole spectrum of symptoms of liver insufficiency.

The aim of the study was to evaluate combined liver damage in HA with CHC and to find out if there is a significant difference in the severity of liver damage in patients with CHC with and without intravenous heroin abuse.

Matherial and Methods

We investigated 20 patients with chronic viral hepatitis C (CHC). The patients were divided into two groups: 10 with a reliable history of intravenous heroin use (cases), and 10 non-users (control group). All the patients were consulted by a psychiatrist.

Biochemical changes were evaluated through testing serum levels of ASAT, ALAT, GGT, APH and total bilirubin (Roche reagents, Integra 400 analyser).

Serological analysis included testing for anti HCV antibodies (ELISA). Quantitative analysis of viremia was carried out using polymerase chain reaction (PCR).

Ultrasound examination was done using ALOKA (USA), and steatosis was evaluated as slight, moderate and marked.

Histomorphological diagnosis: blind liver biopsy was performed on all the patients. The histological diagnosis was made based on METAVIR, with staining of hematoxylin eosin. Severity of fibrosis was evaluated with 0-4 points, and the inflammatory changes as follows: periportal/bridging necrosis – 0-10 points, intralobular degeneration – 0-4 points, portal inflammation reaction – 0-4 points.

Grade of steatosis was histologically evaluated with the help of Brunt's classification, according to which the patients were divided into three groups: 1 – absence of steatosis; 2 – mild steatosis (5-30% of the hepatocytes affected); 3 – severe steatosis (>60% of the hepatocytes affected) [12].

Histochemical analysis included PAS, Gomori and Van Gieson reactions. The changes in the glycogen content were evaluated with the

PAS reaction. Gomori reaction was used to provide information on reticulin fibres, and the Van Gieson staining was applied to prove the presence of collagen. The severity of the changes was evaluated in 3 degrees: slight, moderate and marked.

Statistical analysis

Repetitive variables were grouped as mean and standard deviation. Categorized variables were calculated using frequencies and percentages. To explore the effect of heroin abuse on the severity of biochemical, serological, ultrasound and histological changes, ANOVA analysis was applied. The non-parametric distributed variables were analysed using the Mann-Whitney test.

Results

The 20 patients – 13 males (65%) and 7 females (35%) were divided into two groups, each of 10 patients according to history of intravenous heroin abuse. In the group of the HA 9 were the men and only one was female. In the control group 4 of the patients were men and 6 were women.

The average age of drug abusers was 24.2 ± 3.26 years. The average age of the non-users was 42.2 ± 10.37 years.

The duration of heroin abuse in the drug addicted persons was between 3 and 8 years (average 6 years).

Ultrasound examination revealed absent or slight steatosis in 50 % of the HA group, while in the group of CHC patients without drug abuse no steatosis was found in 30%, and the remaining 70% had moderate steatotic changes in the liver parenchyma (borderline p-value of 0.051).

Biochemical changes: We used the test of Mann-Whitney to evaluate the changes in the levels of ASAT, ALAT, GGT, as well as for the level of HCV RNA because of the non-parametrical distribution of the data (Table 1). The comparison of the average values of alkaline phosphatase and total bilirubin was made using ANOVA (Table 2). Comparison showed no significant differences between the groups with/without heroin abuse.

Table 1. Serum levels of ASAT, ALAT, GGT, and HCV RNA (medians) in the two groups

Parameter	Cases n=10	Control group n=10	p value
ASAT IU/l	42.55	66.50	0.39
ALAT IU/l	104.00	111.50	0.91
GGT IU/L	40.20	57.95	0.97
HCV RNA IU/ml	428 500.00	1 600 000.00	0.06

Table 2. Serum levels of APH and total bilirubin (M±SD) in the two groups

Parameter	Cases n=10	Control group n=10	p value
APH IU/l	72.9±26.36	62.6±20.81	0.37
BIL-T IU/l	13.19±6.36	11.67±4.59	0.55

Histological changes: Histological evaluation of the studied patients found 9 variants. The variants with highest frequency, accounting for 50% of the patients in the studied group were A2F2 (n=6) and A1F2 (n=4). More severe changes were found in the control group (in 4 cases the METAVIR score was A2F2), while in the HA group the score A1F2 was the one with highest frequency. (Figure 1; Figure 2.)

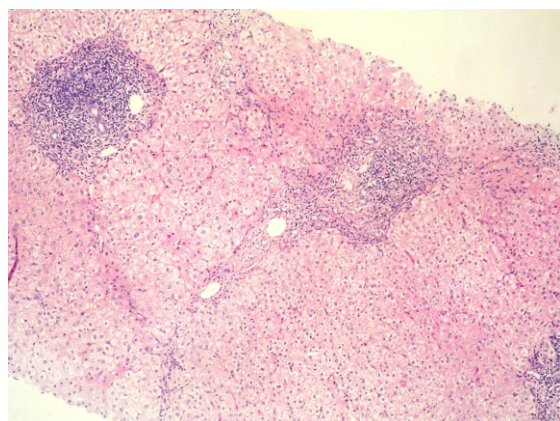


Figure 1. Chronic hepatitis C without heroin misuse. Chronic viral hepatitis with septal fibrosis without cirrhosis, high activity – A3F3 – HE x 100

Analogical results were obtained by the evaluation of grade of steatosis: No steatosis was found in 60% of the cases in both studied groups. Slight grade of steatosis was found by 4 of the cases in group 1, and 3 cases in group 2. Heavy steatosis was found in 1 case from the group of the non-addicted patients with CHC. Comparison

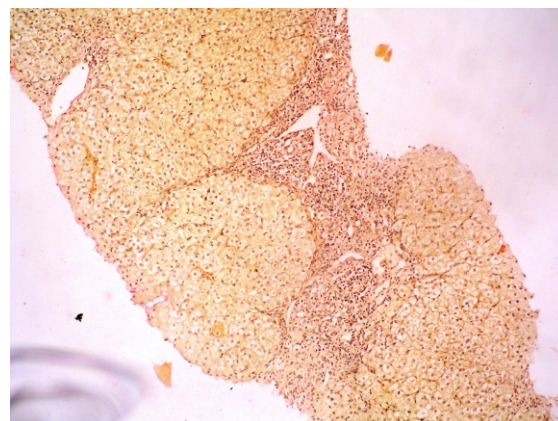


Figure 2. Chronic hepatitis C combined with heroin misuse. Chronic viral hepatitis with septal fibrosis without cirrhosis, moderate activity A₃F₂ – Van Gieson x 100

showed no significant differences between the studied groups of patients (p=0.56).

Histochemical analysis: The liver damages, reported in the literature and typical for heroin users were confirmed using the histochemical methods of staining.

Diminished glycogen content, as well as expansion of reticulin fibres was found in both groups (Table 3), without significant changes between them. (Figure 3; Figure 4; Figure 5; Figure 6).

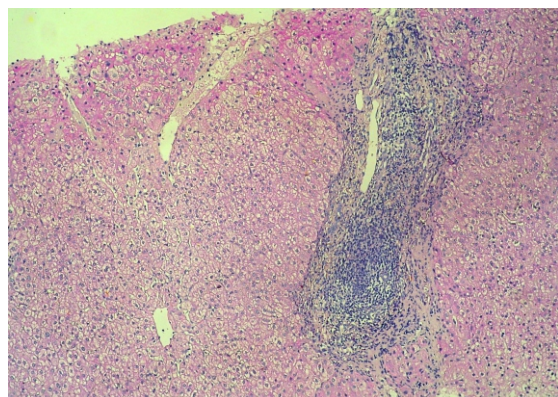


Figure 3. Chronic hepatitis C without heroin misuse. Moderate loss of glycogen in the hepatocytes – PAS x 100.

Regarding phlebosclerosis (Table 4), the severe changes were more frequent in the patients with CHC without DA, p=0.047 (Figure 2; Figure 7).

Table 3. Distribution of the patients with/without heroin abuse according to qualitative characteristics: diminished glycogen content and expansion of reticuline fibres

Histological criterium (histochemical method)	Degree of changes	Cases (n=10)	Control group (n=10)
Diminished glycogen content (PAS)	slight	8	4
	moderate	2	5
	severe	0	1
Expansion of reticuline fibres (Gomori)	slight	4	2
	moderate	5	7
	severe	1	1

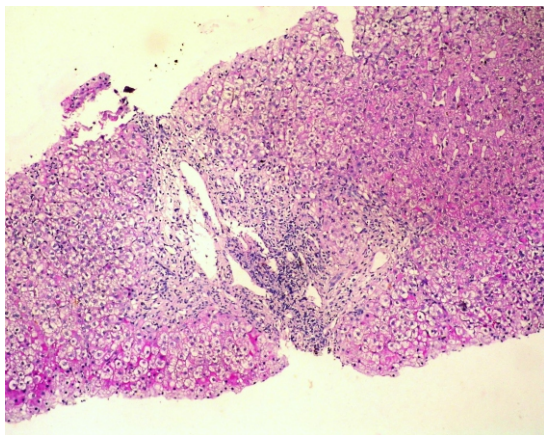


Figure 4. Chronic Hepatitis C, combined with heroin misuse. Moderate loss of glycogen PAS x 100.

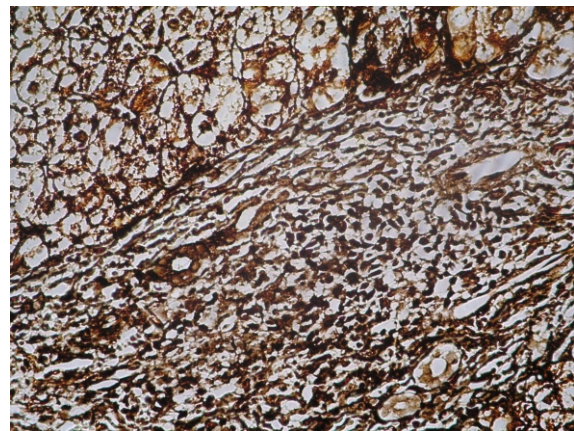


Figure 5. Chronic hepatitis C without heroin misuse. Well manifested portal and – periportal fibrosis – Gomori x 400

Table 4. Distribution of the patients according to the presence of phlebosclerosis.

Presence of phlebosclerosis (Van Gieson)	Patients with CHC and heroin (n=10)	Patients with CHC without heroin abuse (n=10)
Absent	8	2
Slight	1	2
Moderate	0	3
Severe	1	3

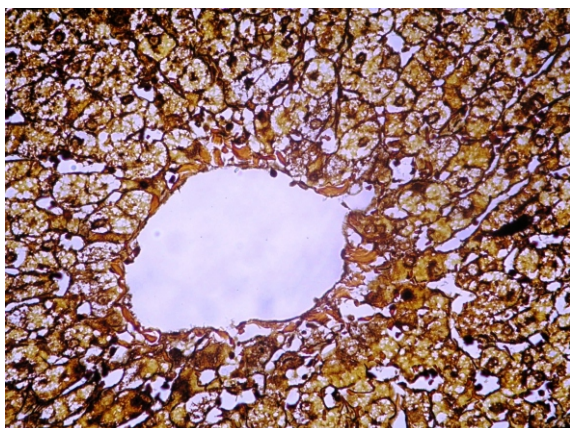


Figure 6. Chronic hepatitis C with heroin misuse. V. centralis with slight fibrosis Gomori x 400

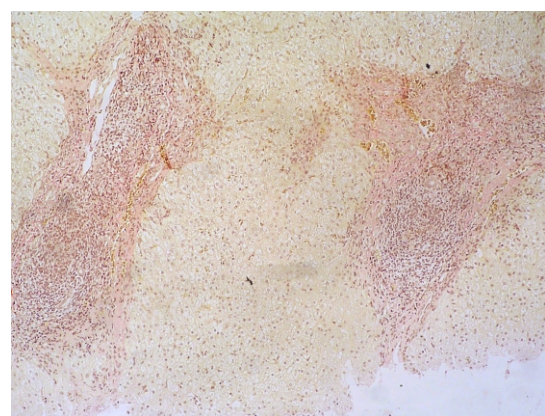


Figure 7. Chronic hepatitis C without heroin misuse. Well manifested portal and periportal fibrosis – Van Gison x 100

Discussion

Liver damage from heroin has been proved in numerous studies worldwide [2-10]. A big amount of data is obtained from forensic departments on autopsies [2, 5, 6]. Our study presents data about a relatively small group of patients – 10 HA with chronic viral hepatitis C, with ongoing drug use during the period of the study. Investigations on drug-addicted subjects are extremely difficult, as drug addiction is, in the first place, a major social and psychological problem.

Our data ascertained the presence of liver damage as a result of intravenous heroin abuse. The damage was proved by biochemical changes – higher values of ASAT, ALAT, GGT, APH and total bilirubin, as well as presence of chronic viral hepatitis C in all 10 heroin addicted patients and the histological changes, discussed above.

The lack of significant changes in the heaviness of the liver changes between the group of heroin addicted and the patients with CHC without data about HA can be explained only with the duration of liver disease. In the group of patients with CHC without data about HA the average age of the persons is 42.2 years and unclear duration of the chronic viral infection. (no history about acute hepatitis C, fixed in the time). In the group of the drug addicted, the average age is 24.2 years. The duration of the heroin abuse is clear for all of them and the duration of the chronic infection is suspected (not longer than 8 years).

What will be the effect of the ongoing heroin abuse and the simultaneous action of the infection of CHC (as well as proved from many studies occult hepatitis B with high incidence) on the liver function of the young people, included in our study (and a lot, like them, not included in such studies) will be shown in further investigations.

Conclusion

No significant differences in the severity of liver damage between the heroin users with CHC and non-users with CHC were found. The latter, however, does not diminish the leading role of heroin abuse for the transmission of hepatitis C virus and all the risks for the development of progressive liver damage, liver cirrhosis and liver cancer, as well as for the transmission of HBV and HIV.

References

1. Klous M, Brink W, Ree J, Beijnen J. Development of pharmaceutical heroin preparations for medical co-prescription to opioid dependent patients. *Drug Alcohol Depen.* 2005;80(3):283-95.
2. Ilic G, Karadzic R, Kostic Banovic L, Stioanovic J. Chronic intravenous heroin abuse: impact on the liver. *Facta Universitatis Series: Medicine and Biology.* 2005;12(3):1503.
3. Fazelpour S, Kiaei SB, Tootian Z, Dashnavard H. Histomorphometric study of hepatocytes of mice after using heroin. *International Journal of Pharmacology.* 2008;4(6):496-9.
4. Atici S, Cinel I, Cynel L, Doruk N, Escandari G, Oral U. Liver and kidney toxicity in chronic use of opioids: An experimental long term model. *J Biosci.* 2005;30(2):245-52.
5. Ilic G, Karadzic R, Kostic Banovic L, Antonovic A. Amiloidosis, change in macrophage number and dysplasia in the liver of intravenous heroin users. *Rom J Leg Med.* 2011;19:27-32.
6. Ilic G, Karadzic R, Kostic Banovic L, Stioanovic J. Influence of heroin on the hepatocyte glycogen content. *Acta Fac Med Naiss.* 2006;23(1):9-12.
7. Trigueiro De Araujo MS, Gerard F, Chossegross P, Barlet P, Grimaud JA. Vascular hepatotoxicity related to heroin addiction. *Virchows Arch A Pathol Anat.* 1990;417:497-503.
8. Trigueiro De Araujo MS, Gerard F, Chossegross P, Guerret S, Barbt P, Adeline P, Grimand JA. Cellular and matrix changes in drug abusers liver sinusoids: a semi-quantitative and morphometric ultrastructural study. *Virchows Arch A Pathol Anat Histopathol.* 1993;422(2):145-52.
9. Korolenko TA, Goncharova IA, Anterejkina LI, Levina OA, Korolenko CP. Influence of opiate addiction on liver cell damage of patients with viral hepatitis C. *Alaska Med.* 2007;49(2 Suppl):75-8. [In Russian]
10. Wasmuth JC. Epidemiology, trasmission and natural history. In: Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H, editors. *Short Guide to Hepatitis C.* Flying Publisher; 2011. p. 13-18.
11. Krustev N. Chronic hepatitis C. In: *Clinical Hepatology.* 2008. p. 52-76. [In Bulgarian]
12. Assy N, Bekirov I, Merjitski Y, Solomon L, Szvalb S, Hussein O. Association between thrombotic risk factors and extent of fibrosis in patients with non-alcoholic fatty liver diseases. *World J Gastroenterol.* 2005;11(37):5834-9.