CLINICAL PHASES OF CHRONIC HEPATITIS B AMONG GEORGIAN PATIENTS

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Hepatitis B virus (HBV) infection remains a global public health problem with changing epidemiology due to several factors including vaccination policies and migration [8]. All patients with chronic HBV infection are at increased risk of progression to cirrhosis and hepatocellular carcinoma (HCC), depending on host and viral factors [4].

Hepatitis B virus infection is one of the major healthcare problems in Georgia. Prevalence of exposure to HBV is 25.9% and hepatitis B surface antigen (HBsAg) is 2.9%, which estimates 80 000 chronic HBV infection and 20 000 – 30 000 at risk of liver cirrhosis and/or HCC [1].

There are progress and challenges in different directions of managing HBV infected patients in Georgia. The progress is especially visible in prevention. There is limited data about clinical management of those patients, on the prevalence of liver cirrhosis and HCC in HBV infected patients and viral characteristics of HBV infection and correlation to host factors, potentially related to disease progression [2,7,9].

Chronic HBV infection can be classified into five phases: (I) hepatitis B envelope antigen (HBeAg) positive chronic infection, (II) HBeAg-positive chronic hepatitis, (III) HBeAg-negative chronic infection, (IV) HBeAg-negative chronic hepatitis and (V) HBsAg-negative phase [2,10].

The specific aim of our study was to collect data on clinical characteristics of HBV infected patients and clinical phases of chronic HBV infection in Georgian population.

Material and methods. We have randomly selected chronic HBV infected patients from database of medical center Mrcheveli. Demographic, epidemiological and clinical characteristics were collected from patients' medical records. HBsAg and HBeAg tests were performed with electro-chemiluminescence immunoassay (ECLIA). HBV RealTime Viral Load assessment was performed with Roche COBAS 6800 HBV Test, and Aptima HBV Quantitative assays. Genotyping was performed with INNO-LiPA methodology. The degree of liver damage was assessed by non-invasive methods such as liver stiffness measurement with transient elastography (FibroScan®, Echosens™) and FIB-4 score [3]. For statistical analysis of associations between basic demographic, clinical and laboratory characteristics and genotypes, statistical software SPSS v.23 was used.

The European Association for the Study of the Liver (EASL) clinical practice guideline was used for new classification of phases of HBV infection [2,10] (Table 1).

Results and discussion. A total number of 111 chronic HBV infected patient from database of medical center Mrcheveli. 71 were males (64%) and 40 females (36%). The mean age was 35. The mean BMI was 25. HBeAg test was available in 70 out of 111 patients, from which 68 (98%) were negative and 2 (1.8%) were positive. The mean alanine aminotransferase (ALT) level was 33.

The mean FIB4 score was 0.88. Liver fibroses results was available only in 74/111 (67%) patients, assessed by Fibroscan and majority of patients 72/74 (97%) had no signs of advanced liver fibrosis. From total 94 patients were viral load data were available, 70/94 (75%) had HBV-DNA level less than 2000 IU/ml, while 18/94 (19%) HBV-DNA level between 2000 and 20000 IU/ml and 18/94 (19%) more than 20000 IU/ml. (Table 2)

ALT, alanine aminotransferase; BMI, body mass index; HBV, hepatitis B virus.

The full data for assessment of clinical phase of chronic HBV infection (HBeAg, HBV DNA, ALT and FIB4 or liver stiffness by elastography) were available among 54% (60/111) of patients. From these 60 patients 28.2% (17/60) had HBV-DNA level above the threshold which might be recognized as active infection based on international guidelines (EASL, Association for the Study of the Disease (AASLD), The Asian Pacific Association for the Study of the Liver (APASL)) - >2000 IU/ml [2,10].

Surprisingly, only 3.3% (2/60) of patients had completely undetectable HBV-DNA and 75% (45/60) had viral load from <2000 IU/ml. 2 patients were HBeAg positive, both having HBV-DNA > 2000 IU/ml (3231 and 803768 IU/ml). According to AASLD criteria of normal ALT level (<25 U/L women, <35 U/L men) both patients had abnormal ALT [10]. But according to EASL criteria (normal ALT level for both men and women <40), one patient had normal ALT (32 U/L) and another one - abnormal (116 U/L) [2]. Neither of them had significant liver damage based on FIB4 (<1.45). 3/60 patients (5%) by EASL and 6/50 patients (10% by AASLD normal ALT criteria classified as HBeAg negative chronic hepatitis and therefore, 11/60 (18.5%) and 8/60 (13.5%) of patients had HBV-DNA >2000 IU/ml, but normal ALT (Table 3).

Chronic HBV infection is a dynamic process reflecting the interaction between HBV replication and the host immune response and not all patients with chronic HBV infection have chronic hepatitis. The new nomenclature is based on the description of the two main characteristics of chronicity: infection vs. hepatitis. The assessment of the severity of liver disease is important to identify patients for treatment and HCC surveillance [7].

Measurement of HBV virological parameters such as HBV DNA serum level and HBeAg is essential for the diagnosis, establishment of the phase of the infection, the decision to treat and subsequent monitoring of patients. However, despite this nomenclature, in a significant number of patients, a single determination of HBV replication markers as well as disease activity markers does not allow an immediate classification to one of the phases.

Table 1: Phases of chronic HBV infection

	HBeAg positive		**HBeAg negative**	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBeAg	positive	positive	negative	negative
HBV-DNA	>2000	>2000	<2000	>2000
ALT	Normal	Elevated	Normal	Elevated

Table 2: Patient characteristics

Patient characteristics	Total number of Patients (N=111)
Gender, n/N (%)	
Male	71/111 (64)
Female	40/111 (36)
HBeAg, n/N (%) Positive Negative	70/111 (63) 2/70 (2) 68/70 (98)
HBV DNA n/N (%) <2000 2000 – 20000 >20000	94/111 (94.5) 70/94 (75) 18/94 (19) 6/94 (6)
HBV Genotypes n/N (%) A D Not available	91/111 (82) 35/91 (38.5) 51/91 (56) 5/91 (5.5)
Mean ALT level, n (range)	33 (10-179)
Liver damage	
Mean FIB-4 score n (range)	0.88 (0.3 – 8.2)
Fibrosis by Fibroscan n/N (%) F 0-1 (<7 KPa) F 1-2 (7-9 KPa) F 3 (9-12 KPa) F4 (>12 KPa)	74/111 (67) 63/74 (85) 8/74 (11) 2/74 (3) 1/74 (1) 71/74 (96)
Mean age, n (range)	35 (17-60)
Mean BMI, n (range)	25 (18-42)

Table 3: Distribution of patients with chronic HBV infection in different clinical phases

Phase	Patients total n=60 n (%)	Description
HBeAg-positive chronic infection	1 (1.5)	HBV DNA >2000 and normal ALT
HBeAg-positive chronic hepatitis	1 (1.5)	HBV DNA >2000 and abnormal ALT
HBeAg-negative chronic infection	44 (73.5)	HBV DNA <2000 and normal ALT
HBeAg-negative chronic hepatitis	3 (5) 6 (10)*	HBV DNA >2000 and abnormal ALT
Not elsewhere classified	11 (18.5) 8* (13.5)	HBV DNA >2000 and normal ALT

** If we take normal ALT according to the AASLD criteria (<25 U/L women, <35 U/L men), 3 patients can be classified as chronic active infection*

In our study we observed that up to 13 to 19% of chronic HBV patients in Georgia is not classified in any phase, who had HBV DNA >2000 IU/ml, but normal ALT.

The 2000 and 20000 IU/mL HBV DNA cutoff is an arbitrary value. Mild ALT elevations are often observed in patients with HBeAg-negative chronic HBV, who may sometimes have HBV DNA between 2,000 and 20,000 IU/mL or transiently <2,000 IU/mL. In study by Papatheodoridis GV et at, 35 out of 399 (8.7%) HBeAg negative patients with chronic hepatitis B found to have persistently normal ALT and HBV DNA >2,000 IU/mL [5]. In a systemic review, a total 246 patients met criteria of persistently normal ALT and HBV DNA >2000 IU/ml. On liver biopsy minimal/mild necro-inflammatory activity was observed in 10% and more than mild fibrosis in 8% of all patients (moderate fibrosis: 7%, severe fibrosis: 1%, cirrhosis: 0%) [6].

Monitoring of serum HBeAg, HBV DNA and ALT levels is required in most cases but even after a complete assessment, some subjects fall into an indeterminate grey area and management needs to be individualized.

This is the first study of patients with chronic HBV infection in Georgia, who were evaluated according to modern updated clinical phases. Despite the small number of patients, we can conclude that the majority of patients 45/60 (75%) had HBeAg positive or negative chronic HBV infection, without hepatitis. However, in up to 19% (11/60) of patients it was not possible to classify in any of the phases.

These data provide an opportunity to further evaluate the reason of high viral load in HBeAg negative patients with normal

ALT. It will be interesting to evaluate long-term sequelae of HBV infection among these patients (liver fibroses and/or HCC development).

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SUMMARY

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Hepatitis B virus infection remains one of the major healthcare problems in Georgia with an exposure prevalence of 25.9% (Positive Anti-HBc) and chronic HBV infection (Positive HBsAg) 2.9%. Determination of clinical phase of chronic HBV infection is crucial for evaluation prognosis and accordingly, initiation of antiviral treatment, which might be lifelong.

The specific aim of our study was to collect data on clinical characteristics of HBV-infected patients and determine the clinical phases of chronic HBV infection in the Georgian population.

We randomly selected 111 chronic HBV-infected patients from the database of the medical center Mrcheveli. Liver fibrosis was assessed by Fibroscan, and viral load data were computed by the Real Time polymerase chain reaction (PCR) methodology.

Liver fibrosis results were available for 74 of the patients (67%), and a majority of patients (72 of the 74, 97%) had no signs of advanced liver fibrosis. Viral load data were available for 94 patients, of whom 70 (74.5%) had an HBV-DNA level less than 2000 IU/ml, while 18 (19.1%) had an HBV-DNA level between 2000 and 20000 IU/ml and 6 (6.4%) were higher than 20000 IU/ml. Data for the assessment of the clinical phase of chronic HBV infection were available for 54% of patients (60 of the 111). Only 3.3% (2/60) of patients had undetectable HBV-DNA and 75% (45/60) had a viral load <2000 IU/ml. Two patients were HBeAg-positive, one of them with hepatitis and another with normal ALT. A few patients classified as HBeAg-negative with chronic hepatitis given normal ALT criteria: 3/60 (5%) by EASL and 6/50 (10%) patients by AASLD. In summary, 11/60 (18.5%) and 8/60 (13.5%) patients had HBV-DNA >2000 IU/ml but a normal ALT.

Given the small number of patients, we cautiously conclude that most patients (75%) had HBeAg-positive or -negative chronic HBV infection without hepatitis. However, up to 19% of patients were not possible to classify in any of the internationally recognized phases of HBV infection. Patients within this indeterminate grey area, should be evaluated cautiously and management needs to be individualized.

It will be interesting to evaluate the reason high viral load in HBeAg negative patients with normal ALT and long-term outcome among these patients (liver fibroses and/or HCC development).

Keywords: Hepatitis B virus, viral load, HBV-DNA, fibrosis.

РЕЗЮМЕ

КЛИНИЧЕСКИЕ ФАЗЫ ХРОНИЧЕСКОГО ГЕПАТИТА В СРЕДИ ПАЦИЕНТОВ ГРУЗИИ

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Вирус гепатита В (HBV) - одна из основных проблем здравоохранения в Грузии. Распространенность бывшего контакта с HBV (анти-HBc-положительного, HBsAg-отрицательного варианта) составляет 25,9%, а хронической HBV инфекции (HBsAg-положительного варианта) - 2,9%.

Целью исследования явился анализ клинических характеристик пациентов, инфицированных HBV, и определение клинических фаз хронической HBV-инфекции среди населения Грузии.

Из базы данных медицинского центра Мрчевели случайным образом было отобрано 111 пациентов с хронической HBV-инфекцией. Фиброз печени оценивали с помощью аппарата Fibroscan, вирусную нагрузку определяли методом полимеразной цепной реакции (ПЦР) в реальном времени. Показатели фиброза печени были доступны в даннх 74 пациентов (67%), и у большинства из них (у 72 из 74, 97%) не было признаков выраженного фиброза печени. Данные о вирусной нагрузке были доступны для 94 пациентов, из которых 70 (74.5%) имели уровень ДНК ВГВ менее 2000 МЕ/

мл, у 18 (19.1%) уровень ДНК ВГВ был между 2000 и 20000 МЕ/мл и у 6 (6.4%) превышал 20000 МЕ/мл.

Данные для оценки клинической фазы хронической HBV инфекции были доступны для 60 из 111 пациентов (54%). Двое пациентов были HBeAg-положительными, один из них с гепатитом, а другой с нормальным уровнем аланин аминотрансферазы (ALT). У большинства (у 44) пациентов была HBeAg-отрицательная форма хронической инфекции (73,5%). При этом, 11 из 60 (18,5%) имели высокую вирусную нагрузку (> 2000 МЕ / мл) и нормальный уровень ALT в крови.

Несмотря на небольшое количество пациентов, мы можем сделать вывод, что большинство пациентов 45/60 (75%) имели HBeAg-положительную или отрицательную хроническую инфекцию HBV без гепатита. Однако, почти у 19% (11/60) пациентов не определялся международно признанная фаза HBV инфекции.

რეზიუმე

ქრონიკული B ჰეპატიტის კლინიკური ფაზები პაციენტთა შორის საქართველოში

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B ჰეპატიტის ვირუსით (HBV) გამოწვეული ინფექცია წარმოადგენს ჯანდაცვის ერთ-ერთ მთავარ პრობლემას საქართველოში. 18 წლის ზემოთ მოსახლეობის 25.9%-თან ფიქსირდება წარსულში გადატანილი HBV ინფექცია (anti-HBcAb - დადებითი, HBsAg - უარყოფითი), ხოლო 2.9% - ქრონიკული HBV ინფექცია (HBsAg-დადებითი).

კვლევის მიზანს წარმოადგენდა კლინიკური ფაზების შეფასება ქრონიკული HBV ინფექციით პაციენტებში საქართველოში.

სამედიცინო ცენტრი მრჩეველის მონაცემთა ბაზიდან შემთხვევითი გზით შეირჩა 111 ქონიკული HBV ინფექცის მქონე პაციენტის კლინიკური მონაცემები. ღვიძლის ფიბროზი შეფასდა "ფიბროსკანის" აპარატით, ვირუსული დატვირთვის განსაზღვრა განხორციელდა პოლიმერიზაციის ჯაჭვური რეაქციის (პჯრ) მეთოდით რეალურ დროში. ღვიძლის ფირბოზი გამოუვლინდა 74 (67%) პაციენტს, მათგან უმრავლესობას (72, 97%) არ აღმოაჩნდა ღვიძლის მძიმე ფობროზის ნიშნები. ვირუსული დატვირთვის მონაცემები ხელმისაწვდომი იყო 94 პაციენტისთვის, საიდანაც 70 შემთხვევაში (74.5%) HBV-DNA დონე სისხლში იყო <2000 ს.ე./მლ., 18 შემთხვევაში (19.1%) 2000-დან 20000-მდე ს.ე./მლ, ხოლო 6 შემთხვევაში (6.4%) 20000-ზე მეტი ს.ე./მლ.

პაციენტების 54%-ში (60/111) ხელმისაწვდომი იყო კლინიკური ფაზის შესაფასებელი ყველა მაჩვენებელი (HBeAg, ვირუსული დატვირთვა, ALT-ს დონე სისხლში, ღვიძლის დაზიანების ხარისხი). აღნიშნული მონაცემების ანალიზის შედეგად აღმოჩნდა, რომ 2 პაციენტს ქონდა ქრონიკული, HBeAg დადებითი, HBV ინფექცია, ერთს ჰეპატიტით, ხოლო მეორეს - ჰეპატიტის გარეშე. პაციენტების უმრავლესობას აღენიშნებოდა HBeAg-უარყოფითი ქრონიკული HBV ინფექცია ჰეპატიტის გარეშე (44/60, 73.5%). 11 შემთხვევაში 60-დან (18.5%) გამოვლინდა მაღალი ვირუსული დატვირთვა (HBV DNA>2000 ს.ე./მლ) და ნორმალური ALT-ს დონე.

მიუხედავად პაციენტების მცირე რაოდენობისა, შეგვიძლია დავასკვნათ, რომ პაციენტების უმრავლესობა 45/60 (75%) კლასიფიცირდა როგორც HBeAg-დადებითი ან უარყოფითი ინფექცია ჰეპატიტის გარეშე, თუმცა პაციენტების დაახლოებით 19%-ში (11/60), არსებული საერთასორისო კლასიფიკაციის შესაბამისი კლინიკური ფაზის განსაზღვრა შეუძლებელი იყო.

DISTRIBUTION OF HBV GENOTYPES AMONG GEORGIAN PATIENTS OF DIFFERENT AGE GROUPS

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Chronic hepatitis B virus (HBV) infection is a leading risk factor for deaths from cirrhosis and liver cancer worldwide. It is estimated that approximately two billion people have evidence of past or present infection with HBV infection and 248 million individuals are chronically infected [1]. The overall prevalence of hepatitis B Surface Antigen (HBsAg) is reported to be 3.6%; however, it varies depending the geographic area. The prevalence of chronic HBV ranges from <2% in low-prevalence areas to 2% to 7% in intermediate-prevalence and ≥8% in high-prevalence areas [2]. The wide range in the prevalence of patients with chronic HBV in different parts of the world is largely related to differences in the age at infection, which is inversely related to the risk of chronicity. The rate of progression from acute to chronic HBV infection is approximately 90 percent for perinatally acquired infection, 20 to 50 percent for infections between the age of one and five years, and less than 5 percent for adult-acquired infection [3]. A cross-sectional, nationwide survey to assess hepatitis B prevalence among the general adult Georgian population (age ≥18 years) was conducted in 2015. The national prevalence of anti-HBc and HBsAg positivity among adults were 25.9% and 2.9%, respectively [4].