World Journal of Medical Sciences 9 (4): 235-238, 2013
ISSN 1817-3055
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DOI: 10.5829/idosi.wjms.2013.9.4.1135

HBsAg Quantitative Analysis Value for Dynamic Monitoring of Inactive Chronic Carriers of Hepatitis B Virus Infection

E.V. Garagulya, N.V. Mazurchik, O.I. Tarasova and P.P. Ogurtsov

Centre for the liver researches and hospital medicine department school of medicine faculty People's Friendship University of Russia (Russia, 117198, Moscow, Mikluho-Maklaya st

Abstract: Role of HBsAg level for monitoring hepatitis B inactive carriers is not clear. 66 patients-hepatitis B inactive carriers-were followed (21 patient during 1 year, 25 patient-2years, 30 patient-3 years), the average time 161 person-years. Median follow-up was 2.4 years. During the follow-up in 15 people reactivation of infection (transition from the category of inactive carriers in HBe antigen negative hepatitis B occurred. Thus, the reactivation of the virus was 9.3% per year. In patients who become reactivated HBV-infection the HBsAg level was 3393.2 lU/ml, it was significantly higher than in the group of patients with "stable values" in which theHBsAg level was 647.29 lU/ml ($p < 0.05$). The obtained data has great practical significance for dynamic monitoring of inactive carriers.

Key words:

INTRODUCTION

Clinical conditions associated with chronic infection with hepatitis B virus (HBV) various from the inactive carrier (IC) to chronic hepatitis B (CHB) [1].Determination of transaminase (TA),DNA HBV, HBeAg, the lack of or a minimal histological activity are a key factors in the diagnosis of IC. According to the EASL 2012criteria "inactive HBsAg carriers" considered HBe-negative patients with normal transaminase levels (TA) (not more than 40 IU / ml), [2] and low level DNA HBV-less than 2000 IU / ml. Monitoring indicators for the diagnosis should be carried out within 1 year, every 3 to 4 months. IC does not need antiviral therapy, these patients require follow-up.

Some patients in the inactive hepatitis B phase eventually clear HBsAg at a rate of about 0.5% per year; most of them achieved HBsAg to anti HBsAgseroconversion.

IC lifespan iscomparable touninfected persons (at least for Western countries) [4]. About 20% of the IC can develop acute hepatitis, which confirmed by increased levels of ALT and increasing serum DNA HBV with / without reversion of anti-HBe in HBeAg [5]. Virus relapse and reactivation may contributeliver fibrosis progression.

The development by company AbbottLaboratories (USA) fully automated chemiluminescentmicroparticle immunoassay (Architect HBsAg QT) to measure the level of HBsAg (HBsAglevel) wasinnovation in identifying HBV-infection markers in the early 2000s [6]. Currently, diagnostic test systems-enzyme-linked immunosorbent assay (ELISA) of the third generation are used for the detection of serum HBsAg level. This test has high sensitivity (0.1 to 0.05 IU / ml) and suitable for a wide population screening. Now two commercial test systems to determine the quantitative level of HBsAg («Architect HBsAg QT», Abbott Laboratories, Abbott Park, IL, USA and «ElecsysHBsAg II», Roche Diagnostics, Indianapolis, IN, USA) areavailable for practical public health [3].

Technique is relatively simple, its cost is considerably lower than the DNA HBV definition. Studies conducted in various countries have shown a wide range of quantitative characteristics of HBsAg in patients with chronic HBV-infection [7,8]. Modern standard of antiviral therapy involves HBsAglevelmonitoring to assess its effectiveness.

Corresponding Author: E.V. Garagulya, Centre for the liver researches and hospital medicine department school of medicine faculty People's Friendship University of Russia (Russia, 117198, Moscow, Mikluho-Maklaya st. 10. Tel: +7-916-820-01-65.

Over the past few years, several studies on the value of the HBsAg levelfor clarification the clinical variant of chronic HBV-infection and its monitoring were published. Thus, Brunetto *et al.* [10] in a prospective study of a large cohort HBeAg-negative patients showed HbsAg serum level were significantly lower in 56 inactive carriers (IC) than 153 active carriers (AC): median, 62.12 (range, 0.1-4068) vs median, 3029 (range, 0.5-82,480) IU/mL; P <. 001. However, a small amount of work require additional studies to clarify the role of quantitative determination of HbsAg for dynamic monitoring of inactive chronic carriers of hepatitis B virus infection Aim. To evaluate the role of HbsAglevel in IC follow up. 187 HbsAg positive patients attending to Centre for the liver researches of RPFU (Russia, Moscow) from 2010 to March 2013 were studied. The age of patients was from 20 to 75 years, the average age was 46 years. All patients were performed: biochemical blood analyses (ALT, AST, glucose, insulin, cholesterol, HDL, LDL, triglycerides, iron, transferrin, ferritin), the definition of BMI, HOMA index, DNA HBV qualitatively, DNA HBV quantitative analysis, hepatitis Delta RNA (RNA HDV), quantification of HBsAglevel, HBeAg, anti-HBe, liver elastography (FibroScan). We excluded patients who had additional etiological factors of liver damage: coinfection with HCV, Wilson's disease, autoimmune hepatitis, patients with HIV infection, hypothyroidism and patients who previously received antivirals.

IC criteria were the HBsAg presence, normal TA level during one year at a 3-fold measurement, DNA HBV level is not more than 2,000 IU /ml,elastography result is not more than 7 kPa. Genotype of hepatitis B virus was not investigated.

The inactive carriers were the major part-104 people (55%), patients with HBe-negative chronic hepatitis B were 52 (28 %), patients with hepatitis D-22 (12%), patients with HBe positive chronic hepatitis B-7 (4 %); immunotolerant patients-2 (1 %).

66 patients-hepatitis B inactive carriers-were followed (21 patient during 1 year, 25 patient-2years, 30 patient-3 years), the average time 161 person-years. The survey was conducted every 6-12 months.Median follow-up was 2.4 years.

During the follow-up in 15 people reactivation of infection (transition from the category of inactive carriers in HBV e antigen negative hepatitis B) occurred. Thus, the reactivation of the virus was 9.3 % per year. However, 8 patients with reactivation returned to the inactive carrier state in a period of 3 to 6 months. 7 patients are now regarded as patients with possible HBeAg-negative hepatitis B and are following-up.

Patients with TA and DNA HBV remained within criteria of IC were provisionally designated as "stable patients"; patients who were identified DNA HBV fluctuations (sometimes accompanied by the rise of TA) exceeding the criteria of IC were conventionally called "patients with reactivation of HBV infection".

The median level of ALT in "stable patients" group was 19 U / l (min 10 U/l, max 37 U/l) and in "patients with reactivation of HBV infection " group was 17.85 U /l (min 14 U/l, max 25 U/l) (p> 0.05) (Tab. No 1). The median level of DNAin "stable patients"group was 166 IU/ml (min 0 IU/ml, max 2000 IU/ml) and 455 IU/ml (min 23,4 IU/ml, max 1202 IU/ml)in "patients with reactivation of HBV infection" group (p> 0.05). Levels of fibrosis did not differ and were 5.35 kPa (min 2,7 kPa, max 6, 8 kPa) in"patients with reactivation of HBV infection " and 4.5 kPa (min 0 kPa,max6,6kPa) in "stable patients" group (p> 0.05).

Table 1: Main values of«stable patients» group and«patients with reactivation of HBV infection» group

		«Stable patients» (n-51)	«Patients with reactivation of HBV infection»(n-15)
ALT U/l	Median	19	17,85
	Min	10	14
	Max	37	25
DNA HBV (IU/ml)	Median	166	455
	Min	0	23,4
	Max	2000	1202
HbsAg (U/ml)	Median	647,29	3393,215
	Min	0,01	454,45
	Max	11624,33	13046,79
F (kPa)	Median	5,35	4,5
	Min	2,7	0
	Max	6,8	6,6

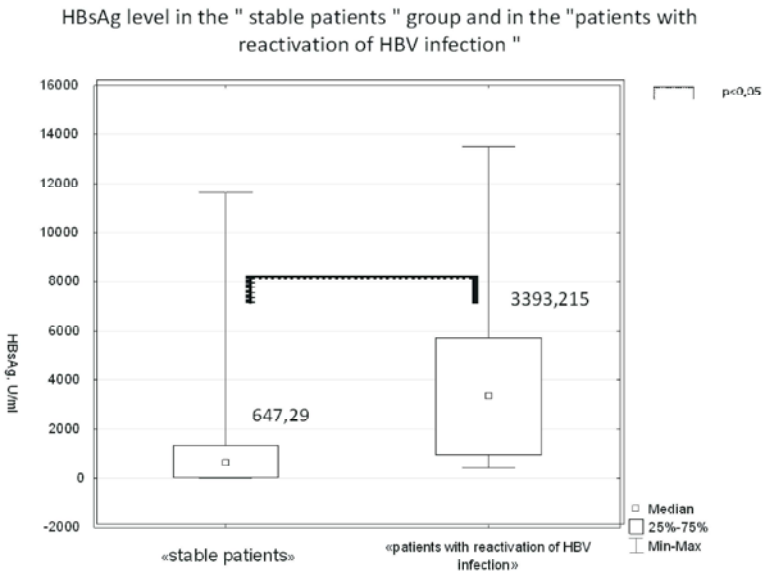

Fig. 1:

HbsAglevel in the "stable patients " group was 647.29 U/ml (min 0,01 U/ml, max11624, 33U/ml) and in the "patients with reactivation of HBV infection" was 3393.215 U/ml (min 454.45 U/ml, max13046, 79U/ml) ($p < 0.05$) (Fig. No 1).

CONCLUSIONS

The findings suggest that IC group is heterogeneous. Some of the patients are "stable carriers" without the risk of liver disease progression. However, about a quarter of patients can lose the status of "inactive carrier" in the observation periods of 2-3 years because the threshold of viral load exceeded. TA levels and DNA HBV ofthese groups were not significantly different at the beginning of follow-up. The only marker that has prognostic value in relation to the IC "stability" wasHBsAg level.

According to numerous reports, up to a third of patients with a viral load in the range of 2 000-20 000 IU / ml have an inflammatory process in the liver according to histological studies and have the risks of disease progression. Such patients are recommended a liver biopsy. However, according to our data, more than half of these patients regain their status during IC dynamic observation. Consequently, early liver biopsy on loss of IC status is hardly advisable. These patients are needdynamic monitoring with annual liverelastography as for antiviral therapy of primary it is importance the rate of fibrosis progression, but not the intensity of inflammation.

Small number of patients and the short period of observation does not allow us to evaluate the sensitivity and specificity of different thresholds for HBsAg level assessment for risk of HBV-infection reactivation. But these data can be used to estimate the intensity of dynamic monitoring of inactive carriers. In patients who become reactivated HBV-infection HBsAg level was 3393.2 lU/ml, it was significantly higher than in the group of patients with "stable values" in which the of HBsAg level was 647.29 lU/ml ($p <0.05$). It can be assumed that patients with baseline HBsAglevel less than 1000 U/ml may occur less frequently than once per year. Patients with HBsAglevel over 2000 U/ml requires enhanced dynamic observation, because of risk of a possible reactivation of chronic HBV-infection. Accumulation of statistical data probably will differentiate approach to dynamic observation and clarify prognosis of HBV-infection in inactive carriers.

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