

The Incidence and the Clinical Significance of the Gray Zone in the Clinical Phases of Chronic Hepatitis B Virus Infection

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Abstract

Background: five clinical phases were described in patients with chronic (HBV) infection: HBeAg- positive HBV infection, HBeAg- positive chronic HB, HBeAg negative HBV infection, HBeAg-negative CHB and occult HBV infection.

Aim: This study aimed to determine the incidence of the unclassified phase (gray zone) in chronic hepatitis B patients and its significant in the clinical practice.

Patients and methods: The study was conducted retrospectively on 109 patients' who have HBsAg positive for more than 6 months. The data recorded include; HbeAg and anti-HBe Ab, ultrasound of the abdomen, HBV DNA load and alanine aminotransferase (ALT), accordingly; we classify the patients to known clinical phases. Patients who were unfit one of these phases considered to be in the gray zone and subsequently sent for liver fibroscan to determine the fibrosis stage.

Results: The mean age of our patients was 34.25 (± 13.93) years with 54.12% being males. The mean viral load was 5,885,490 IU/ml and mean ALT was 56.22 (± 89.88) U/L. eight patients (7.3%) were in the HBeAg+ve HBV infection, 13 patients (11.9%) were in HBeAg+ve CHB. Thirty four patients (31.1%) were in the HBeAg-ve HBV infection and 23 (21.1%) were in HBeAg-ve CHB phase, both were showed a higher occurrence with age > 35 years. Thirty one (28.4%) further patients failed to identify with any of the four phases (normal ALT with HBV load > 2000 IU/ml), this group also showed significant relation to age above 35 years and 12 patients (38.8%) had significant fibrosis on fibroscan.

Conclusions: A considerable number of patients with chronic HBV infection have persistently normal ALT levels, despite elevated levels of viral load; this is known as the "grey zone" phase. These patients merit close follow up with short-interval measurement of liver enzymes, liver fibroscan and biopsy may be considered.

Keywords: Chronic hepatitis B, HBe Ag, HBV carrier, clinical phases.

Introduction

About 350 million people worldwide are chronically infected with hepatitis B virus (HBV). (1) The two major complications of chronic infection are cirrhosis and hepatocellular carcinoma (HCC), both of which can lead to liver-related death. The natural history of chronic HBV infection is complex, and viral replication and therefore the host's immune response can allow the infected person to go through several stages. (2) Phase 1: is called also Hepatitis B e antigen (HBeAg)-positive chronic HBV infection, characterized by high serum HBV DNA levels, persistently normal serum alanine aminotransferase (ALT) values, and little change in liver biopsy. (3) This stage, which predominantly affects people who contracted HBV during after delivery or youth and

typically lasts 10 to 30 years, has a very low rate of spontaneous HBeAg clearance. The majority of the patient in this phase will spontaneously clear HBeAg after three years and 15% after 20 years of infection. (4) Phase 2: Serum HBe Ag positive chronic hepatitis B (CHB), characterized by raised ALT levels, and a high level of HBV DNA exceeding 2000 IU/mL which are signs of chronic hepatitis B. Liver fibrosis or active liver inflammation is typically present (5). During this stage, the immune system of the host detects HBV as a foreign substance and launches an immunological reaction that damages the hepatocytes. It happens several years after the first phase and is frequently and quickly reached by people who catch the infection in adult age. (6) The majority of patients in this stage achieved HBeAg seroconversion, suppressed their HBV DNA, and moved on to the HBeAg-negative infection stage. Others might have struggled for years to control their HBV and advance to CHB with no detectable HBeAg. Phase 3: formerly known as the "inactive carrier" phase, is characterized by the presence of anti-HBe antibodies (anti-HBe Ab) and at least 3 normal ALT levels and HBV DNA levels < 2000

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IU/ml. (7) In individuals who remain in the inactive phase, liver fibrosis is either absent or mild in this stage, and there is little evidence that it will worsen over time. (8). Meta-analysis found that severe liver disease was uncommon in people with an HBV DNA level under 20,000 IU/mL and a persistently normal ALT (9, 10). Patients should not be classified as inactive carriers unless there are at least three ALT levels and two to three HBV DNA values over a period of time due to the fluctuating nature of chronic HBV infection. Phase 4: is the chronic hepatitis with HBe-Ag negative is characterized by the absence of serum HBeAg, typically with detectable anti-HBe, and by persistent or fluctuating moderate to high levels of serum HBV DNA as well as persistently increased ALT readings. Necroinflammation and fibrosis are visible in the liver histology (11). In the second phase after seroconverting from HBeAg to anti-HBe Ab, about 10%–20% of patients will still have hepatitis activity, although the majority of cases are brought on by one or more episodes of reactivation while they are in the third phase.(12). Compared to those who have chronic hepatitis B with HBeAg positivity, these individuals typically have lower amounts of HBV DNA. (13). they still carry wild-type virus or variants, but they are unable to create HBeAg because of genetic changes in the precore or core promoter. (14) Phase 5: is The HBsAg-negative phase is characterized by negative serum HBsAg and anti-HBc antibodies (IgG) that are positive with or without the presence of (anti-HBs) Ab, also called as (occult HBV infection),and characterize by the presence of the HBV DNA (cccDNA) in the liver. According to estimates, the annual rate of HBsAg delayed clearance in Western patients ranges from 0.5 to 2 percent, while it is substantially lowers (0.1 to 0.8 percent) in Asian nations. (15) Patients with HBsAg clearance appeared to have a positive prognosis in the majority of cases. (16, 17) There have been few researches done to examine the unclassified stage of clinical practice. Understanding the stage of chronic HBV infection is crucial since it can help the clinician decide when to start treatment. (2)

Patients and Methods:

A retrospective study was conducted at the gastroenterology tertiary clinic that included the recorded data of patients from 2 consecutive years (from January 2019 to November 2020). A total number of 109 patients were included. The inclusion criteria: patients were eligible for inclusion in this study, if they have a confirmed state of chronic HBV infection as suggested by the presence of HBsAg for more than 6 months. The data included in this study, HBeAg and anti-HBe antibody, in addition to serial HBV DNA load and alanine aminotransferase (ALT) in the last 12 months; in addition, abdominal US for the liver were also recorded.

After analyzing the serological and biochemical data of all patients, we categorized the patients to one of the clinical phases that mentioned in the literature.

Patients who have HBeAg-negative HBV infection with persistently normal ALT values and HBV viral load > 2000 IU/ml were considered as unclassified phase(gray zone) of HBV infection, those patients were sent for liver elastography FibroScan System (Echosens SAS, Paris, France) to determine the stage of the hepatic fibrosis in this group.

Statistical analyses were performed using IBM SPSS, The variables described using their number and percentage, chi square test was used to do analysis of these variables. T test used to do analyze of the differences in means between two groups. P value < 0.05 is considered to be significant..

Results:

In this study, data of 109 patients were reported. Of which, 59 patients (54.12%) were males and 50 (45.87%) patients were females. The population age ranged from 11-80 years with a mean of 34.32 (\pm 13.82). The mean value of ALT for the whole sample was (56.22 ± 89.88) U/L (Range= 3-637 U/L).

Serological profile

Twenty one patients (19.26%) were HBeAg positive and 88 patients (80.73%) were HBeAg negative. The mean age of HBeAg positive patients were (20.47 ± 13.3 , 31.00 ± 15.0 , respectively), while the mean age of HBeAg negative patients are (42.36 ± 13.6 , 39.91 ± 13.1), p value is significant ($P=0.005$). In addition, HBeAg-positive patients have ($P=0.017$) higher viral loads compared with HBeAg-negative patients. (Table 1)

The clinical phases

The majority of the patients (78) can be categorized to one of the classical phases of the chronic HB infection. 8 Patients (7.3%) were in HBeAg-positive chronic HBV infection phase (HBe Ag positive with normal serial ALT level) and 13 patients (11.9%) were in the HBe Ag- positive CHB phase (with elevated serial ALT level). The majority of the patients, 34 patients (31.1%) patients were in the HBeAg-negative chronic HBV infection phase (HBe Ag negative and normal serial ALT), and 23 (21.1%) patients were in HBe-Ag negative CHB phase (with elevated serial ALT), both were showed a statistically significant rate with age > 35 years (P value are 0.005).(Table 1) Furthermore, 31 (28.4%) patients had viral load >2000 IU/mL, but were positive for anti-HBe antibody and had persistently normal ALT levels, which can't be classified to specific phase, (Table 2). The fibrosis stages in these patients were as follows: F0, 13 patients (41.9%); F1, 6 patients (19.3%); F2, 9 patients (29.2%); F3, 2 patients (6.4%); and F4, 1 patient (3.2%).

Table 1: comparison of HBeAg +ve and -ve groups in relation to age and viral load

	HBeAg	N	Mean	P value
age of participant (year)	Negative	88	37.28	0.005 (significant)
	Positive	21	28.10	
viral load (IU/ml)	Negative	88	1.68 ⁶⁶	0.017 (significant)
	Positive	21	1.26 ⁶⁷	
ALT value (IU/ml)	Negative	88	68.43	0.63
	Positive	21	53.30	

P value > 0.05 is considered as level of significant

Table 2. The clinical Phases of chronic HB infection according to the age

Clinical Phase	Number of patient	Percentage	Mean (years)	Age	P value
Phase I HBeAg +ve HBV infection	8	7.3%	20.47+13.34		0.497
Phase II HBe Ag +ve CHB	13	11.9%	31.00+15.0		0.474
Phase III HBeAg-ve HBV infection	34	31.1%	42.36+13.6		0.002
Phase IV HBe Ag -ve CHB	23	21.1%	39.91+13.1		0.013
Unclassified	31	28.4%	38.92+16.6		0.016

P value > 0.05 is considered as level of significant

Discussion:

This collection of data from a cohort of chronic HBsAg positive patients highlights some expected characteristics of chronic HBV infection as well as some interesting erratic behaviors of the disease. Since the viral load is best predictor of progression to the cirrhosis, studying the fibrosis stage of patient with high viral load but normal liver enzymes is important in in the clinical practice.(3) In this study, the patients who were classified as HBeAg- negative HBV infection and CHB phases displayed a statistically significant relationship with age > 35 years, in concordance with what was found in the international study by (Hoofangle et al.)(18). In addition, patients who have HBeAg positive, they have high viral load in comparison to patients who have HBeAg negative, this finding is expected as HBeAg is indicator of active replication of the virus. A considerable proportion of our sample (28.4%) does not fit the mentioned phases, 31 patients had normal serial ALT levels and were positive for anti-HBe antibody, and negative HBe Ag but had serial viral load >2000 IU/mL. A possible explanation of these conditions is the possibility of episodic reactivation of HB infection that sometimes happens in patients in the chronic inactive phase as noted by Kumar, Manog et al (19). This finding has also been observed by Ormeci et al during their investigation

of a similar pattern (20), which has been termed the "grey zone" of chronic HBV infection. Second explanation for this discrepancy is the presence of significant liver fibrosis (F2-4) which can be responsible for the persistently normal ALT, according to international studies (21, 22) (Yuen et al., Hsu et al.), this is may not be applicable to our patients (in the unclassified group) as19 patients (61.2%) had non significant liver fibrosis (F0-F1) and while 12 patients (38.8%) had significant hepatic fibrosis (F2-4), only three of them had advanced hepatic fibrosis (F3 or F4) depending on fibro- scan results . Histologic examination may also be appropriate for this group of patients but liver stiffness measurement (LSM) by fibroscan was also shown to be a reliable noninvasive examination for the diagnosis of liver fibrosis in HBV infected patients with high HBVDNA (>2000 IU/ml), HBe Ag negative and normal serial ALT levels. 23 This pattern is aberrant when examined under the light of the classical outcomes of chronic HBV infection, and they do align with the clinical experience of the practicing physicians in this tertiary care center.

Conclusion:

Based on the study findings, we can conclude patients with chronic HBV infections who have persistently normal ALT levels despite elevated levels of viral DNA load; this is known as the "grey zone" phase, is a common finding in clinical phases of chronic HBV infection. Significant proportion of this group has advanced fibrosis, therefore, they merit close follow up with short-interval measurement of liver enzymes and liver fibro- scan and liver biopsy may be considered.

Author’s Contributions: Both authors contributed to design this research, acquisition and analysis of data, drafting and revising it critically and approval of the final version for publication.

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نسبة الحدوث والاهمية السريرية للمرحلة الغير مصنفة في مرضى الكبد الفيروس B

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الخلاصة:

المقدمة : خمسة مراحل سريرية تم تصنيفها لمرضى التهاب الكبد الفيروسي المزمن من مرحله الاولى يكون فيها المستضد HBe موجب ,المرحلة الثانية يكزن فيه المستضد HBe موجب مع وجود التهاب في الكبد ,مرحلة الثالثة يكون المستضد HBe سالب ,المرحلة الرابعة يكون فيها المستضد HBe سالب مع وجود التهاب في الكبد والمرحلة المخفية للفيروس

هدف الدراسة : هذه الدراسة كانت تهدف لغرض تعيين نسبة حدوث مرحلة الغير مصنفة من مراحل التهاب الكبد الفيروسي السريرية واهميتها السريرية **طرق العمل :** هذه الدراسة اجريت على 109 مريض الذين يحملون فيروس نوع B لاكثر من ست اشهر المعلومات التي دونت من ملفات المرضى تشمل : سونار الكبد نسبة , كثافة الفيروس مع انزيمات الكبد تم تقسيم المرضى بعدها الى مراحل سريرية اربعة المرضى الذين لا يمكن وضعهم في مرحلة معينة تم اعتبارهم في مرحلة غير مصنفة يتم فحص نسبة تليف الكبد لهذه المجموعة عن طريق جهاز الفيروسكان

النتائج : معدل العمر للمرضى 34 سنة منهم 54 بالمئة ذكور , معدل كثافة الفيروس 5885490 وحدة دولية ومعدل انزيم الكبد 56 وحدة دولية . 8 مرضى ضمن المرحلة الاولى , 13 مريض ضمن المرحلة الثانية . 34 مريض ضمن المرحلة الثالثة و 23 مريض ضمن المرحلة الرابعة وكلاهما يلاحظ نسبة حدوث مرتفعة فوق عمر ال35 سنة . 31 مريض لم يتم تصنيفهم الى اي من المراحل المعروفة سريريا وغالبية اعماهم فوق ال35 سنة و 38 بالمئة منهم مصابين بتليف متقدم في الكبد

الاستنتاج : نسبة شائعة من المرضى المصابين بالتهاب الكبد الفيروسي المزمن لديهم انزيمات الكبد ضمن الحدود الطبيعية بالرغم من ارتفاع كثافة الفيروس والذي يعتبر مرحلة غير مصنفة سريريا وجزء كبير من المرضى في هذه المجموعة مصابين بتليف متقدم بالكبد يحتاجون هولاء المرضى متابعة دورية واجراء خزعة الكبد او الفيروسكانز.

مفتاح الكلمات: التهاب الكبد المزمن B , الناقل HBV , HBe Ag , المراحل السريرية.