Dissociation of alanine aminotransferase values in acute hepatitis A patients with and without past experience to the hepatitis B virus

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SUMMARY

Serological markers and peak serum alanine aminotransferase (ALT) values of 140 in-patients with acute hepatitis, either type A ($n = 90$), or type B ($n = 50$) were prospectively assessed. In 23 out of the 90 patients with acute hepatitis A, evidence of previous experience with hepatitis B virus (HBV) was found, whereas 35 out of the 50 patients with acute hepatitis B had past contact with hepatitis A virus (HAV). The mean peak ALT values [s.d.] were significantly higher in hepatitis A patients with previous experience with HBV (1413 [704] i.u./l), when compared to those without such experience (842 [464] i.u./l, $P < 0.001$). Such a difference was not evident between acute hepatitis B patients, whether or not they had previous contact with HAV. We conclude that when acute hepatitis A is superimposed on past HBV infection an augmented transaminaemia, indicative of enhanced liver cell necrosis, takes place although a definite explanation is lacking. We suggest that individuals with markers of HBV infection should be early candidates for HAV immunization.

INTRODUCTION

Hepatitis B virus (HBV) infection continues to be a major public health problem in Greece. On the other hand, hepatitis A (HA), although having a milder course than hepatitis B (HB), has a high morbidity. The likelihood of an individual in this country being infected simultaneously or in succession by both viruses is not negligible [1], but so far the data concerning the course of such an infection by the two viruses are controversial. In cases of concurrent infection by hepatitis A virus (HAV) and HBV, described both in men [2–4] and in the experimental animal [5], the course of the ensuing disease seemed somewhat aggravated. Other papers refer to the course of acute HA in groups of institutionalized persons with past contact with HBV as being either milder [6] or

aggravated [7]. More recently it has been concluded that HAV superinfection in HBsAg carriers neither causes a more severe illness, nor affects the course of chronic HB [8-10].

The above observations prompted us to investigate the clinical and biochemical course of HA in patients with past experience of HBV including, in addition to HBsAg carriers, persons already immune to HBV. We also examined the reverse case to determine if past contact with HAV could affect the severity of acute HB.

MATERIALS AND METHODS

Patients. Ninety adults (mean age 20.9 [s.d. 4.8] years), with acute HA who were in-patients of our Clinic from 1 January 1987 to 31 December 1989 were studied prospectively. Twenty-three of these patients were also positive for at least one of the serological markers of HBV. Because of its heterogeneity, this latter group was subdivided into two. The first ($n = 14$), comprised the HBsAg carriers. The second ($n = 9$), included the 'cured' or 'immune' persons, i.e. those who had developed antibodies to HBsAg, HBcAg and HBeAg. The above two groups were compared to each other and to the remaining 67 patients, who had acute HA (positive IgM anti-HAV) alone, without any marker of HB infection (group 3).

Fifty further adult in-patients (mean age 22.1 [s.d. 5.5] years), with acute HB (positive IgM anti-HBc plus HBsAg) were also examined during the same period. Thirty-five of these, positive to total anti-HAV but negative to IgM anti-HAV, were considered to have had previous exposure to HAV. A comparison similar to the above was made between them and the remaining 15 patients without experience of HAV as indicated by negative HAV markers. Sera from all patients with experience of HBV were also tested for the presence of antibody to hepatitis D (delta) virus, in order to study the possible influence of coinfection with this virus.

Methods. The serological markers were assayed by ELISA, by the use of commercially available kits (Abbott). The biochemical parameters (Alanine aminotransferase [ALT], alkaline phosphatase [AP] and bilirubin) were measured immediately after withdrawal of blood by the commonly approved methods, employing International Units.

F-test, *t*-test and Mann-Whitney test were used for statistical analysis [11].

RESULTS

The distribution of HBV serological markers and anti- δ in the 23 individuals with acute HA and 'past experience' of HBV is shown in Table 1. All were positive for anti-HBc. Fourteen were positive for HBsAg, eight had anti-HBs, six had HBeAg and seven anti-HBe. In 4 out of the 14 HBsAg carriers, HBsAg was, along with total anti-HBc, the sole marker identified. In five other patients, HBsAg was found in association with HBeAg, in three with anti-HBe, in one with HBeAg plus anti-HBs and in one case with anti-HBs. Three patients had only total anti-HBc, two had only anti-HBs and, finally, anti-HBe was the only marker in two persons. IgM anti-HBc and anti- δ antibodies were not found in any individual.

Among the three groups of patients with acute HA a comparison was made of

Table 1. Serological HBV profile and anti- δ in 23 patients with acute hepatitis A and previous contact with HBV

Patient	anti-HBc IgM	anti-HBc	HBsAg	anti-HBs	HBeAg	anti-HBe	anti- δ
1	—	+	—	+	—	+	—
2	—	+	+	—	—	+	—
3	—	+	+	—	+	—	—
4	—	+	+	—	—	—	—
5	—	+	+	—	—	+	—
6	—	+	—	+	—	+	—
7	—	+	—	—	—	—	—
8	—	+	—	—	—	—	—
9	—	+	—	—	—	—	—
10	—	+	+	—	—	—	—
11	—	+	—	+	—	+	—
12	—	+	+	—	+	—	—
13	—	+	+	—	+	—	—
14	—	+	+	—	—	—	—
15	—	+	+	—	+	—	—
16	—	+	—	+	—	—	—
17	—	+	—	+	—	+	—
18	—	+	+	+	—	—	—
19	—	+	—	+	—	—	—
20	—	+	+	—	+	—	—
21	—	+	+	+	+	—	—
22	—	+	+	—	—	—	—
23	—	+	+	—	—	+	—
Total	0	23	14	8	6	7	0

Table 2. Mean peak values of alanine aminotransferase (ALT), alkaline phosphatase (AP) and bilirubin in patients with acute hepatitis A with and without past experience of HBV

Parameter	Previous contact with HBV		No previous contact with HBV Group 3 (n = 67) x $\pm$ S.D. (S.E.)	P values of groups		
	Group 1 (n = 14) (carriers of HBV) x $\pm$ S.D. (S.E.)	Group 2 (n = 9) (‘immune’ to HBV) x $\pm$ S.D. (S.E.)				
				1-2	1-3	2-3
ALT	1442 $\pm$ 650 (174)*	1369 $\pm$ 742 (247)*	842 $\pm$ 464 (57)	NS	< 0.001	< 0.05
AP	117 $\pm$ 120 (32)	149 $\pm$ 87 (29)	171 $\pm$ 82 (10)	NS	NS	< 0.01
Bilirubin	7.3 $\pm$ 3.4 (0.9)	8.2 $\pm$ 3.2 (1.1)	7.3 $\pm$ 4.6 (0.6)	NS	NS	NS

* ALT 1 + 2 = 1413 $\pm$ 704 (147), $P(1+2)-3 < 0.001$.

the mean peak values of ALT, AP and bilirubin (Table 2). From these results it is clear that: (a) The mean peak ALT values were higher in the patients of group 1 ($P < 0.001$), whereas there was no difference in AP and bilirubin between groups 1 and 3; (b) no difference was seen between groups 1 and 2 with any of the above parameters; (c) ALT values were higher in group 2 than group 3, but without statistical significance. Groups 1 and 2, taken together demonstrated significant differences in the peak ALT values compared with group 3 (1413 [s.d. 704] i.u./l, versus 842 [s.d. 464] i.u./l, $P < 0.001$).

Table 3. *Mean peak values of alanine aminotransferase (ALT), alkaline phosphatase (AP) and bilirubin in patients with acute hepatitis B with and without past experience of HAV*

Parameters	Contact with HAV (<i>n</i> = 35)	No contact with HAV (<i>n</i> = 15)
	$\bar{x} \pm \text{s.d. (S.E.)}$	$\bar{x} \pm \text{s.d. (S.E.)}$
ALT	1634 $\pm$ 731 (123)	1463 $\pm$ 762 (197)*
AP	135 $\pm$ 40 (6.7)	123 $\pm$ 42 (11)*
Bilirubin	11.6 $\pm$ 11 (1.9)	10.5 $\pm$ 5.9 (1.5)*

* $P > 0.1$.

In patients with acute HB (Table 3), no significant difference was obtained between groups with and without past experience to HAV in ALT values (1634 [s.d. 731], versus 1463 [s.d. 762], $P > 0.1$).

DISCUSSION

In this study, significantly higher peak ALT values were found during the course of acute HA in patients with past experience to HBV. Previous studies on either concurrent HAV and HBV infections or HAV superinfection of HBsAg carriers, provide no definite conclusion on the effects of one infection on the other. Thus, Zachoval and colleagues [9] and Tassopoulos and colleagues [10] did not find higher transaminase values in HBsAg carriers suffering acute HA. In the first report the values were compared with reference data, whilst, in the second, the small number of the sample was perhaps responsible for the lack of significant differences. Hindman and colleagues [7], on the other hand, reported increased transaminase levels in HBsAg carriers, but their sample population was also too small to demonstrate clear differences.

In our study the number of patients with acute HA who had previous experience of HBV was high enough to permit a statistical confirmation of the differences in ALT values. In addition, the absence of a similar difference in the reverse situation (i.r. between acute HB patients with and without past experiences of HAV) indicates that double infection *per se* is not able to produce higher transaminaemia, for which the preexistence of HBV infection is a prerequisite.

Elevation of ALT values as a result of extensive (confluent) liver cell necrosis has been reported on several occasions. This reflects the host's attempt to eradicate the virus and is associated with HBeAg seroconversion and disappearance of DNA polymerase [12-14]. Such a seroconversion was also noted in HBsAg carriers during HAV [10, 15, 16], Delta [17] and Non-A, Non-B viruses superinfection [18]. All these findings are consistent with the increase in ALT levels, seen in our patients.

The finding that mean peak ALT values were not lower in patients whose serological status indicated prior infection with HBV and 'cure' (group 2), when compared to the HBsAg carriers (group 1), seems at first difficult to explain. However, it is not unlikely, that at least some of the members of group 2 continued to harbour HBV in their liver cells, as this has been reported even in cases where

HBV markers were totally absent from the serum [19–21]. In addition, during the phase of HBV genome integration, HBsAg continued to occur alone in the serum [22]. On the other hand, the presence of anti-HBc alone is not always indicative of immunity; it is occasionally compatible with HBV replication, with intrahepatic nuclear HBcAg, and membrane IgG. Seroconversion to anti-HBe is not always believed to be synonymous with cessation of HBV replication, at least in certain racial groups, such as Mediterranean people, including Greeks [22]. The above data suggest that the persistence of HBV in the liver and not the patient's serological profile determines the results of viral interference. Such a suggestion is compatible with our findings.

All our patients, despite their high transaminaemia, had an uncomplicated recovery during their follow-up period, although in case of concurrent infection by both viruses fulminant hepatitis has been described [4]. All our patients were asymptomatic before their current illness, and remained quite well thereafter. Consequently liver biopsies were not done, so we do not know the spectrum of their hepatic histological lesions.

From the above results we conclude that individuals who have had previous contact with HBV risk a more serious illness should superinfection with HAV occur. Therefore, we suggest that they should be considered as candidates for anti-HAV vaccine, as soon as the latter becomes commercially available.

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