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OCCURRENCE OF HEPATITIS-ASSOCIATED-ANTIGEN (HAA) SUBDETERMINANTS ad AND ay IN BLOOD DONORS, ACUTE AND CHRONIC LIVER DISEASE

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SUMMARY

The sera of 120 individuals were examined for ad and ay subdeterminants of Australia antigen. Twenty out of 33 patients with acute viral hepatitis, not identified as post-transfusion cases, were ay positive (60.6%); in a group of 76 blood donors the predominant subdeterminant was ad (80.3%). Three out of 4 cases of chronic aggressive hepatitis had an antigen-positive status and all were ad positive; all patients with chronic persistent hepatitis had an antigen-negative status. In 5 cases of postnecrotic cirrhosis, only two were positive for Australia antigen with an ad specificity. In addition, it was studied the occurrence of antinuclear factor (ANF), smooth muscle antibodies (SMA), mitochondrial antibodies (MA) and Australia antigen in cases of chronic aggressive hepatitis and postnecrotic cirrhosis.

INTRODUCTION

The hepatitis-associated-antigen or Australia antigen was discovered by BLUMGERG [3] as a result of a study on multiple antigen specificities of serum proteins. Subsequent studies confirmed the association of this antigen with acute viral hepatitis and a variety of other conditions [4, 5, 15, 19, 22, 23]. Also some apparently normal individuals carry this antigen and the data obtained seem to be consistent with the hypothesis that there is a genetic susceptibility to persistent infection with Australia antigen [6, 8, 20]. In relation to chronic hepatic conditions it is probable that other etiological factors than the antigen are responsible for the development of the disease. Autoimmune processes induced by unknown factors are believed to play a part in their pathogenesis as the presence of various autoantibodies seem to suggest [24].

In addition to the subdeterminant a, common to all antigens [12] there are three other subdeterminants, d, x and y. The d and y are mutually exclusive and, possibly, with the a subdeterminant reflect the genotype of the virus; the x subdeterminant is a possible component of the host [14]. BANCROFT et al. [2] described two additional antigenic subdeterminants w and r. MAGNIUS & ESPMARK [17] proposed the designation of e to another subdeterminant.

The present report includes the result of a study on the occurrence of Australia antigen subdeterminants ad and ay in serum

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TABLE I

Australia antigen subdeterminants in acute serum hepatitis patients and in normal blood donors

Group Disease	Number	ad		ay	
		No.	%	No.	%
Acute viral hepatitis	33	13	39.4	20	60.6
Normal blood donors	76	61	80.3	15	19.7
Totals	109	74	68.9	35	31.1

specimes collected from various groups of individuals. In some groups the presence of autoantibodies is studied.

MATERIALS AND METHODS

Australian antigen-positive sera from 120 individuals were examined for ad and ay subdeterminants. The major group includes 33 individuals with acute viral hepatitis and 76 normal blood donors. Another group of 11 individuals, 4 with chronic aggressive hepatitis, 2 with chronic persistent hepatitis and 5 with postnecrotic cirrhosis was included in this study. All sera were concentrated, before use, by polyacrylamide gel (*) in order to improve the sensitivity of the test [1].

The immunodiffusion test used follows the procedures described by SCHMIDT & LENNETTE [21] with some modifications: the gel contained 0.8% agarose in 0.01 M tris (hydroxymethyl), aminomethane buffer, 0.1 M NaCL, 0.001 M ethylenediaminetetraacetate and 0.05% sodium azide, with a final pH of 7,6.

Human sera containing anti-HAA and reference Australia antigen with specificities ad and ay were kindly suplied by Drs. J. W. Mosley and Y. Cossart. Our antisera to Australia antigen gave reactions of immunologic identity with those standard antisera.

(*) Lyphogel, Gelman Instrument Co., Ann Arbor, Michigan

RESULTS

In Table I is shown the distribution of ad and ay subdeterminants in 33 cases of acute viral hepatitis and in 76 normal blood donors. The first group shows a higher proportion of ay subdeterminants (60.6%) compared to the blood donor group (19.7%).

The ad subdeterminants had, as well, an unbalanced distribution in these groups, being the blood donor group predominantly ad in its specificity (80.3%), in relation to the acute viral hepatitis group (39.4%).

Table II presents pertinent data concerning the distribution of Australia antigen and its specificities in cases of chronic aggressive hepatitis and postnecrotic cirrhosis. In three patients with chronic aggressive hepatitis it was possible to detect the Australia antigen and all were ad positive. In 5 cases of postnecrotic cirrhosis, only 2 were Australia antigen-positive and in the characterization of the subdeterminant all two cases were ad positive.

Table III presents the average values for some conventional liver tests in the patients with chronic aggressive hepatitis, chronic persistent hepatitis and postnecrotic cirrhosis. Raised total serum bilirubin was noted in 2 patients with chronic persistent hepatitis Australia antigen-negative, and in 5 patients with postnecrotic cirrhosis. The transaminases were raised in all patients. The albuminaemia had normal values; the gammaglobulinaemia had normal or slightly increased values.

TABLE II

Australia antigen subdeterminants in chronic aggressive hepatitis and postnecrotic cirrhosis patients

Group Disease	Number	Number with Au antigen	Number with antigenic subdeterminants	
			ad	ay
Chronic aggressive hepatitis	4	3	3	0
Postnecrotic cirrhosis	5	2	2	0
Totals	9	5	5	0

TABLE III

Biochemical findings in chronic aggressive hepatitis, chronic persistent hepatitis and postnecrotic cirrhosis patients

Group Disease	Australia antigen	Number	SB mg %	SGOT u/ml	SGPT u/ml	ALB g%	GAMM g%
Chronic aggressive hepatitis	+	3	0.75	144	154	4.16	1.50
	—	1	0.50	120	240	4.40	1.99
Chronic persistent hepatitis	+	0	—	—	—	—	—
	—	2	1.25	50	50	4.16	1.90
Postnecrotic cirrhosis	+	2	3.75	254	227	3.18	2.10
	—	3	1.70	74	108	3.06	2.63

SB = serum bilirubin

Finally, the incidence of smooth muscle antibodies, mitochondrial antibodies, antinuclear factor, Australia antigen and antibodies is presented in Table IV.

None of the cases presented Australia antibodies and the Australia antigen-positive patients, which include three cases of chronic aggressive hepatitis and two cases of postnecrotic cirrhosis were negative to mitochondrial antibodies and antinuclear factor. The smooth muscle antibodies were absent in all cases of chronic aggressive hepatitis and in one of the two cases of postnecrotic cirrhosis, above mentioned; the other case of postnecrotic cirrhosis had smooth muscle antibodies in a titer of $> 1:250$.

DISCUSSION

The results of our study largely confirm the different distribution of ad and ay subdeterminants in acute viral hepatitis and in blood donors, as it has previously been shown [11, 13].

The group of chronic aggressive hepatitis, chronic persistent hepatitis and postnecrotic

TABLE IV

Immunological findings in chronic aggressive hepatitis and postnecrotic cirrhosis Australia antigen-positive patients

Patient	Group Disease	Australia antigen	Australia antibodies	SMA	MA	ANF
L.S.S.	Chronic aggressive hepatitis	+	—	—	—	—
W.G.	" " "	+	—	—	—	—
P.L.	" " "	+	—	—	—	—
C.L.N.	Postnecrotic cirrhosis	+	—	+	—	—
N.M.	" "	+	—	—	—	—

SMA = smooth muscle antibodies

MA = mitochondrial antibodies

ANF = antinuclear factor

cirrhosis comprises too small a number of patients in which to base any conclusions. It should be mentioned, however, some peculiar findings obtained. The cases of chronic persistent hepatitis were all Australia antigen-negative and of the 4 patients with chronic aggressive hepatitis, 3 had Australia antigen in their serum; two cases of postnecrotic cirrhosis were Australia antigen-positive. This is an observation not in aggrement with data obtained in other studies [16, 25], but the limited number of cases studied do not allow any conclusion. In the characterization of the subdeterminants, all these five patients were identified as ad positive. Our data are probably a consequence of the limited number of observations or they might as well reflect the prevalence of that viral genotype at the moment the patients were infected. MOSLEY [18] in a group of 32 patients with "unresolved hepatitis" found 66% ad positive and 34% ay positive. GORDON et al. [10] found in 19 cases of chronic persistent hepatitis 13 ad positive and 6 ay positive; in 23 cases of chronic active hepatitis the occurrence was 19 ad positive and 4 ay positive. The terms "unresolved hepatitis" and chronic persistent hepatitis are frequently used to describle the same condition, however the term chronic persistent hepatitis, as originally used by DEGROOT et al. [9], was a histologic term related to a nonspecific hepatic inflammatory reaction. This reaction could be the result of an anicteric viral hepatitis, an hepatitis in a subsiding stage or any reticuloendothelial inflammatory response to different infections in which the liver participates.

In VISCHER's report [24] on Australia antigen and auto-antibodies in chronic hepatitis the mutual exclusion between M and SM antibodies and Australia antigen is mentioned. Our findings tend to support this study and the study of BULKLEY et al. [7] in cases of chronic aggressive hepatitis. However it is interesting to refer our data in relation to one case of postnecrotic cirrhosis, Australia antigen-positive and at the same time with a titer of SM antibodies of > 1.250. LOPES [16] in a study about the diagnostic value of auto-antibodies and Australia antigen in chronic hepatic conditions considers three different groups, comprising group I, prolonged forms of acute hepatitis, group II, chronic persistent hepatitis and group III, chronic aggressive hepatitis of intense activity and chronic active hepatitis in a cirrhotic phase. In 19 cases belonging to the group III he found a proportion of 94.7% with an Australia antigen-negative status

associated to the presence of auto-antibodies. Although evidence is limited, our observation, inconsistent with those results, may confirm the possible role of the persistent viral infection and autoimmune processes as inducing elements of a selfperpetuating inflammatory reaction of the liver. A more detailed study including a significant number of cases is presently being developed.

RESUMO

Identificação dos subdeterminantes ad e ay do antígeno associado à hepatite (AAH) em doadores de sangue e casos de doenças infecciosas aguda e crônica do fígado

Examinaram-se 120 soros de diversos indivíduos para a identificação dos subdeterminantes ad e ay do antígeno Australia. De 33 casos de hepatite aguda não relacionados com transfusões de sangue, 20 foram ay positivos (60,6%); em 76 doadores o subdeterminante predominante foi ad (80,3%). Em 4 casos de hepatite crônica agressiva, 3 positivos para o antígeno Australia foram identificados como ad. De 5 casos de cirrose pós-necrótica somente dois foram positivos para o antígeno Australia e também estes foram ad positivos. Estudou-se, igualmente, a ocorrência de fator anti-nuclear (FAN), anticorpos anti-músculo liso (AML), anticorpos anti-mitocôndria (AM) e antígeno Australia nos casos de hepatite crônica agressiva e cirrose pós-necrótica.

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